FEMALE REPRODUCTIVE SYSTEM AND WOMEN'S HEALTH THROUGH A MULTIDISCIPLINARY LENS



Samar Hegazy, Margaret Burnette and Judith Thorn
University of Illinois

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Female Reproductive System and Women's Health through a Multidisciplinary Lens

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Margaret (Peg) Burnette is Associate Professor Emerita of the University of Illinois at Urbana-Champaign. Peg spent her entire career supporting medical education, first at the UIC College of Medicine and then at the University of Illinois at Urbana. Since 2012, Peg served as Medical and Biomedicine Librarian at the University of Illinois where she helped to build library services and resources for the Carle Illinois College of Medicine, which welcomed its first class in 2015. As a faculty member of the new medical school, Peg continued to build programming and provide instruction and research support for faculty and students until her retirement in October 2123. Peg's research sits as the intersection of Knowledge Management, Librarianship, and Medicine, focusing on tacit knowledge (TC) and how TC impacts knowledge sharing and its influence on the evidence base. Peg continues to be engaged with Carle Illinois and the University Library in retirement.



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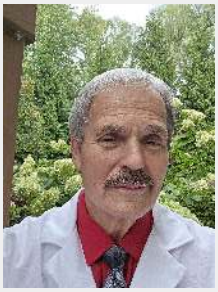
Chapter 1



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Wessam Ibrahim is a Teaching Assistant Professor and serves as the Anatomy & Embryology Discipline Lead at Carle Illinois College of Medicine, University of Illinois Urbana-Champaign. She brings a robust background in medical education, having earned her Medical degree, Master's, and Doctoral degrees in Basic Sciences, Anatomy, and Embryology from Ain-Shams University Faculty of Medicine, Cairo, Egypt. Further enhancing her expertise in educational leadership, she completed a Master of Education in Health Professions (MEHP) at the Johns Hopkins School of Education.

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		continued to build programming and provide instruction and research support for faculty and students until her retirement in October 2123. Peg's research sits as the intersection of Knowledge Management, Librarianship, and Medicine, focusing on tacit knowledge (TC) and how TC impacts knowledge sharing and its influence on the evidence base. Peg continues to be engaged with Carle Illinois and the University Library in retirement.
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Sol's educational background includes a doctorate in educational policy and organizational leadership from the University of Illinois at Urbana-Champaign with a specialization in differentiated instruction and organizational change, a master's in technology impact and assessment from the University of Illinois at Springfield with a concentration in liberal and integrative studies, and a bachelor's in chemistry from Illinois College.



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3D Model Designer

Janet Sinn-Hanlon, MAMS, earned a master’s degree in Biomedical Visualization from the University of Illinois at Chicago. Her many years of experience in data visualization and 3D modeling and animation for scientific research journals and educational applications has laid the foundation for her role as Lead Modeler for the project. In this role, Janet created the original polygonal meshes for the normal human female anatomy and a number of pathology models, and optimized them for 3D printing. Janet currently works for iLearning@VetMed where she works with a team of educators, multimedia and CG

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Preface

Acknowledgement

This open educational resource project to support women's health education nationally and globally under the title "The Female Reproductive System and Women's Health Through a Multidisciplinary Lens." is created by a multidisciplinary team from CIMED and Knox College https://medicine.illinois.edu/news/carle-illinois-led-team-advances-instruction-on-womens-health-issues-with-federal-funding. The contents of this resource, including the Textbook and 3D printed models, were developed under grant P116T210005 from the Open Textbook Pilot Program, Fund for the Improvement of Postsecondary Education (FIPSE), U.S. Department of Education. Grant name: Illinois SCOERs (Support for the Creation of Open Education Resources), facilitated by the Consortium of Academic and Research Libraries in Illinois (CARLI). However, those contents do not necessarily represent the policy of the U.S. Department of Education, and you should not assume endorsement by the Federal Government. The grant was awarded to Dr. Samar Hegazy, project PI

Introduction

Welcome to “The Female Reproductive System and Women’s Health Through a Multidisciplinary Lens”. This Open Education Resrouce (OER) project began in 2023 as a collaboration of faculty from the Carle Illinois College of Medicine, Urbana Illinois, and Knox College, Galesburg Illinois.

> Carle Illinois College of Medicine (CI MED) was founded in 2015 as the world’s first accredited engineering-based medical school and represents a new concept in the field of healthcare education. Innovation is the cornerstone of the curriculum, with emphasis on human factors, design thinking, medical technologies, and entrepreneurship.
>
> Knox College was founded on a commitment to fairness and diversity from its beginning in 1837, and that commitment continues to the present. Knox College welcomes first generation students from all different backgrounds and ethnicities.

The goal of this Open Education Resource (OER) is to provide open learning opportunities related to the female reproductive system through the lens of science and humanities. The OER provides flexibility for various audience levels so that content that can be adapted for multiple learners, from undergraduate STEM students, to graduate students in health professions or social sciences, to medical students.

Learning units are enhanced with opportunities for 3D printing of anatomical models of normal female reproductive organs, embryonic models, pregnant uteri, and female reproductive organs with different abnormal pathologies. These models can be sued for both demonstration and hands-on simulation activities, and activities and materials can be adapted to a variety of levels of STEM courses.

Chapters

Each chapter is comprised of multiple units that address aspects of the main topic. The chapter homepage provides overall learning objectives for the chapter.

> Chapter components may include:

- Text (Open Access content and authors’ original)
- Illustration Objects (Images, Diagrams, Videos)
- 3D Models for 3D printing
- Interactive Learning Activities
- Assignments
- Assessments
- Glossary

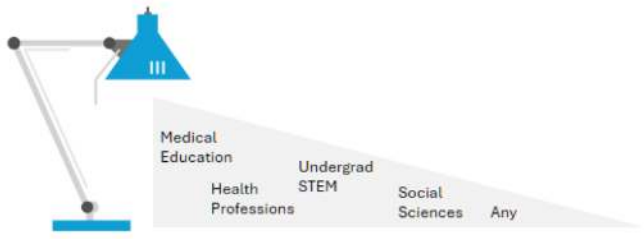
Text/Course Objectives

Students who complete this course will....

- Learn biological structures & processes involved in female reproductive health, pregnancy and early human development
- Describe and explain applications and societal implications of female reproductive health, and pregnancy related science outside of the classroom
- Identify and compare gender constructions in female reproductive health and pregnancy related situations
- Apply scientific investigative skills to answer questions related to female reproductive health, pregnancy and early human development issues

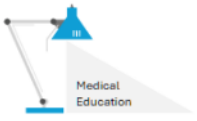
Audience Levels

The visual scale below provides indicators of appropriate audience for chapter and unit content. Material may be easily adapted for more than one audience level.

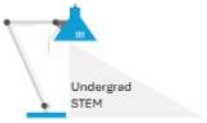


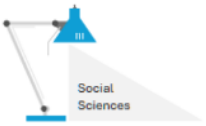
Chapter units will include one or more graphics indicating the level of audience for that content.

The content of this chapter is appropriate for, or easily adapted for the following audiences:









CHAPTER OVERVIEW

1: Anatomy of the Female Reproductive System

1.1: The Pelvis
1.2: Female Reproductive Organs
1.3: Female Mammary Glands
1.4: The Perineum
1.5: Glossary

Chapter Authors:

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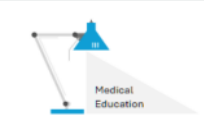
Michael Dauzvardis, Ph.D.

About this Chapter

This chapter addresses the foundational anatomical knowledge of the female pelvis and perineum. It covers the anatomy of the female reproductive system, including the bony pelvis, joints, muscles, ligaments, internal pelvic and perineal organs, vasculature, innervation, and relevant clinical applications.

The chapter will include mnemonics that should help the learner to remember complex anatomical relations.

The content of this chapter is appropriate for, or easily adapted for the following audiences:





Learning Objectives

By the end of this chapter, learners will be able to

- Describe the anatomical arrangement of the female pelvis, including bones, ligaments, muscles, joints, vasculature, and innervation (lumbar and sacral plexus).
- Recall the female urinary system components while classifying the importance of the peritoneal arrangement concerning female reproductive organs.
- Explain the anatomical description, important relations, blood supply, venous drainage, innervations, ligaments, and clinical applications of female reproductive organs, including the ovary, fallopian tube, uterus, and vagina.

- Describe the anatomical arrangement, muscles, blood supply, venous drainage, innervation, and clinical correlations of the female perineum, including the boundaries and contents of anal and urogenital triangles.
- Recognize the anatomical structure and function of the female breast, describing the importance of lymphatic drainage and blood supply in the spread of breast cancer.

Common anatomical terms

Each chapter in this textbook has a corresponding Glossary section. The terms listed below are commonly used anatomical regional and directional terminology that appear throughout the entire textbook.

Regional Terms

- **Coxal** – hip
- **Femoral** – thigh
- **Gluteal** – butt
- **Inguinal** – groin (junction of trunk and thigh)
- **Lumbar** – lower back
- **Pelvic** – pelvis - anterior/interior
- **Pubic** – anterior, inferior pelvis
- **Sacral** – triangular region of the base of the spine
- **Spinal cavity** – division of the dorsal cavity that houses the spinal cord; also referred to as vertebral cavity

Directional Terms

- **Anterior** (or **ventral**) describes the front or direction toward the front of the body. The toes are anterior to the foot.
- **Caudal** describes position below or lower than another part of the body proper; near or toward the tail (in humans, the coccyx, or lowest part of the spinal column); also referred to as inferior.
- **Deep** describes a position farther from the surface of the body. The brain is deep to the skull.
- **Distal** describes a position farther from the point of attachment or the trunk of the body.
- **Dorsal** describes the back or direction toward the back of the body; also referred to as posterior.
- **Parietal** refers to the wall of a body cavity or hollow structure.
- **Posterior** (or **dorsal**) describes the back or direction toward the back of the body. The popliteus is posterior to the patella.
- **Superior** (or **cranial**) describes a position above or higher than another part of the body proper. The orbits are superior to the oris.
- **Inferior** (or **caudal**) describes a position below or lower than another part of the body proper; near or toward the tail (in humans, the coccyx, or lowest part of the spinal column). The pelvis is inferior to the abdomen.
- **Lateral** describes the side or direction toward the side of the body. The pollex (thumb) is lateral to the digits.
- **Medial** describes the middle or direction toward the middle of the body. The hallux (big toe) is the medial toe.
- **Posterior** describes the back or direction toward the back of the body; also referred to as dorsal.
- **Proximal** describes a position in a limb that is nearer to the point of attachment or the trunk of the body. The brachium is proximal to the antebrachium.
- **Distal** describes a position in a limb that is farther from the point of attachment or the trunk of the body. The crus is distal to the femur.
- **Superficial** describes a position closer to the surface of the body. The skin is superficial to the bones.
- **Superior** describes a position above or higher than another part of the body proper; also referred to as cranial.

- **Ventral** describes the front or direction toward the front of the body; also referred to as anterior.
- **Visceral** refers to internal organs.

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Chapter 1 Bibliography

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apter 1 Acknowledgements

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Jose Beltran, Class of 2026 - Carle Illinois College of Medicine

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1.1: The Pelvis

Think of the number four when you visualize the pelvis:

- Four bones; two hip bones (right & left), sacrum and coccyx.
- Four joints: two sacroiliac joints, symphysis pubis, and sacrococcygeal joint.
- Four ligaments support the bony pelvis: iliolumbar, lumbosacral, sacrotuberous, and sacrospinous ligaments.
- Four muscles; piriformis, obturator internus, levator ani and coccygeus muscles.

1.1.1 Bones of the Pelvis

The **pelvic girdle** consists of a pair of hip bones, also known as the coxal bones (Figure 1.1). Each bone is made up of three individual bones that fuse together over the first 20 years of life. These bones are known as the **ilium** (IL-e-um; plural, ilia), **ischium** (ISH-e-um, ischia), and **pubis** (PU-bis). The ilium is the most superior and largest portion of the coxal bone. It is firmly connected to the sacrum by the **sacroiliac** joint. The ischium forms the most inferior and posterior portion of the coxal bone; It is the portion of the pelvic girdle that supports the body when seated and is commonly known as the “sits bone”. The pubis forms the most anterior portion of the pelvic girdle and joins the two coxal bones together at the **pubic symphysis** joint.[1]

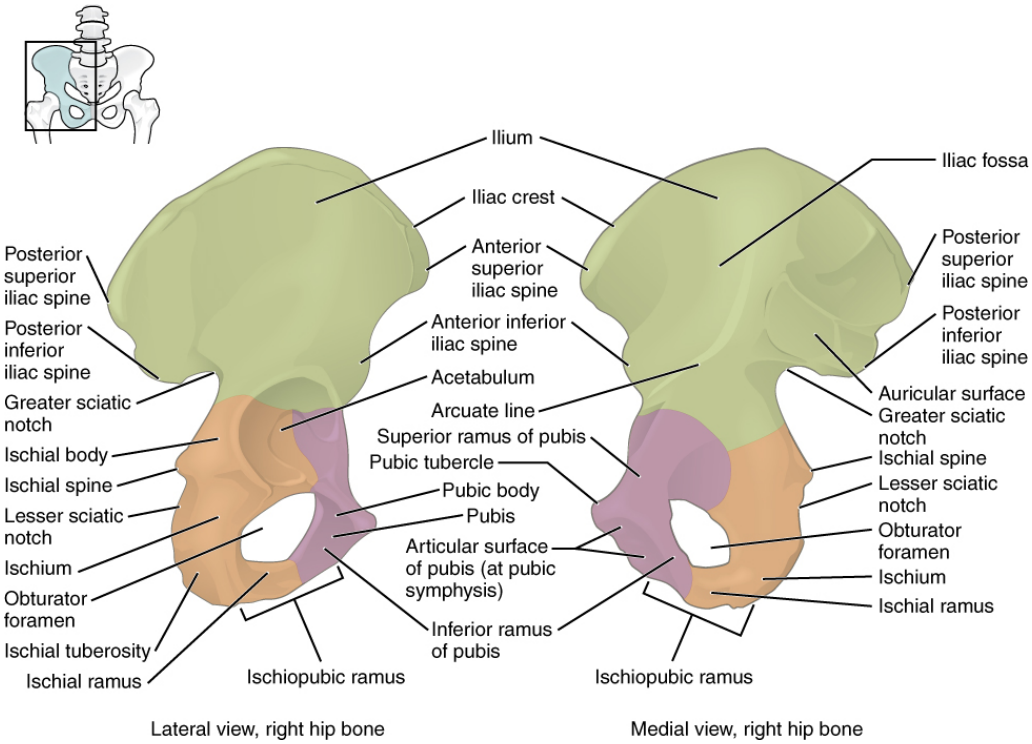


Figure 1.1 Diagram demonstrating the coxal bone’s three regions. These regions are made up of individual bones that were fused together over the first 20 years of human life. The ilium forms the large, fan-shaped superior portion, the ischium forms the posteroinferior portion, and the pubis forms the anteromedial portion.

Image Source: PHED 301 Students. *Advanced Anatomy 2nd. Ed.* (2018) This work is made available under a CC BY-NC-ND 4.0, except where otherwise noted. Available from Pressbooks.

The **sacrum** (SAY-crum) forms the posterior aspect of the pelvis (Figure 1.2). It is a triangular shaped bone comprised of five sacral vertebrae (S1-S5), which begins to fuse during adolescence and finishes fusing by early adulthood. It contains four pairs of anterior and posterior foramen, which decrease in size inferiorly. The sacrum transmits the weight of the body and helps stabilize the pelvis. The sacrum articulates on its superior aspect (the base of the sacrum) with the lumbar vertebrae (L5) at the lumbosacral joint; on its lateral aspects

with the iliac bones at the sacroiliac joint; and on its posterior aspect (the apex of the sacrum) with the coccyx at the sacrococcygeal joint.

The **coccyx** (cocs-ICKS), or tailbone (Figure 1.2), is the most inferior portion of the human vertebral column. It is comprised of two to four fused bones (Co1-Co4) and is the remnant of a vestigial tail. The base of the coccyx has a pair of transverse processes and cornua and articulates with the sacrum at the sacrococcygeal joint.[3]

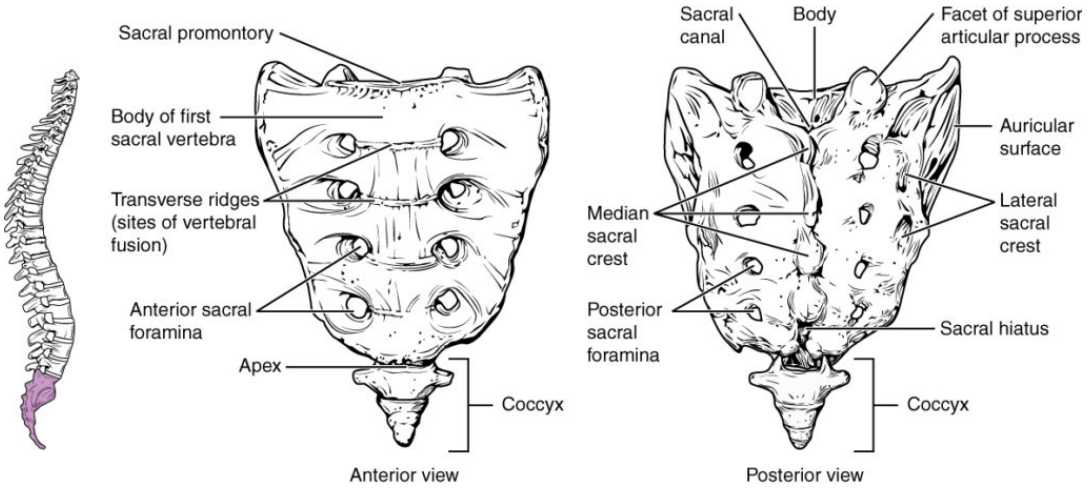


Figure 1.2 Diagram summarizing the anterior (left) and posterior (right) of the sacrum and coccyx bony features and landmarks.
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The pelvis is generally classified as the greater and lesser pelvis. The greater pelvis is a part of the abdomen, while the lesser pelvis is the true pelvis.

The true pelvis has an inlet, outlet, and pelvic cavity:

- The pelvic inlet (or pelvic brim) is oval-shaped in females, and it is formed by the promontory of the sacrum, sacral ala, arcuate line, pecten pubis, pubic crest, and the upper border of the pubic symphysis. The pelvic brim is the landmark that separates the greater pelvis from the lesser pelvis.
- The pelvic outlet is rhomboid in shape and bound by pubic symphysis, ischiopubic rami, ischial tuberosities, sacrotuberous ligaments, and coccyx.
- The pelvic cavity is subdivided by the **pelvic diaphragm** (Levator ani and coccygeus muscles) into the true pelvis above and perineum below.[4]

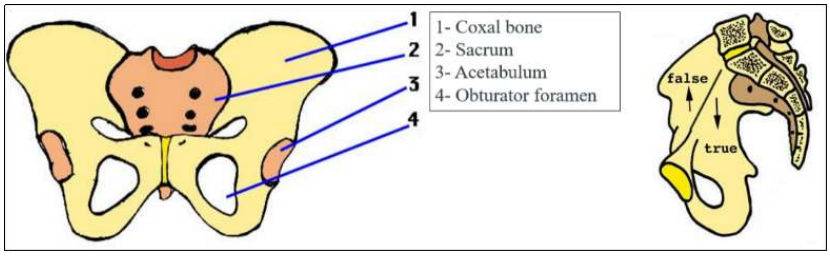


Figure 1.3 Diagram demonstrating the four bones of the pelvis showing how pelvic brim separates between false and true pelvis.
Image Source: Dauzvardis, Michael F., Ph.D. Assistant Professor Emeritus, Loyola University; used with permission.

1.1.2 Dimensions of the Pelvis

1.1.2.1 Inlet

- Antero-posterior diameters: measured between the sacral promontory and the symphysis pubis.
  - Upper border of the pubic symphysis: true (obstetric conjugate).
  - Lower border of the pubic symphysis: diagonal conjugate.
- Transverse diameter: measured between the farthest 2 points on the iliopectineal line.
- Oblique diameter: measured between the sacroiliac joint and opposite ilio-pubic eminence.

1.1.2.2 Outlet

Transverse diameters: bi-tuberous diameter between 2 ischial tuberosities and bi-spinous/Interspinous diameter between 2 ischial spines (smallest pelvic diameter).

- Antero-posterior diameters: From the lower border of the symphysis pubis to the tip of the coccyx (anatomical) and the tip of the sacrum (obstetric).[5]

> Applied Anatomy
>
> **The obstetric (true) conjugate** is the narrowest fixed distance through which a baby's head must pass during vaginal delivery (10 cm). If <10 cm, it is called a contracted pelvic inlet. The obstetric conjugate cannot be measured in pelvic exam clinically but can be estimated by (diagonal conjugate – 2.5 cm)

1.1.3 Comparison of Male and Female Pelvis

The differences between the male and female structure of the pelvis are related to human function and body size. In general, the bones of a male pelvis are thicker and heavier, which is an adaptation to help support the more muscular and physical build of males (Figure 1.4). In comparison, the main differences in the shape of males and females are due to the physiological adaptation of childbirth. The sides of the male's pelvis converge from the inlet to the outlet, whereas the sides of the female pelvis are wider apart. The angle between the inferior pubic rami is acute (roughly 70 degrees) in males and (90-100 degrees) in females. The male's sacrum is longer, narrower, and straighter and has a pronounced sacral promontory. The female's sacrum is shorter, wider, curved more posteriorly, and has a less pronounced sacral promontory. The **acetabula** are wider apart in females compared to males, which is narrower. The acetabulum faces more laterally in males and more anteriorly in females. Consequently, the leg can move forward and backward in a single plane when males walk. In females, the leg must swing forward and inward, from where the pivoting head of the femur moves the leg back in another plane. The change in the angle of the femoral head gives the female gait its characteristic of swinging hips.[6]

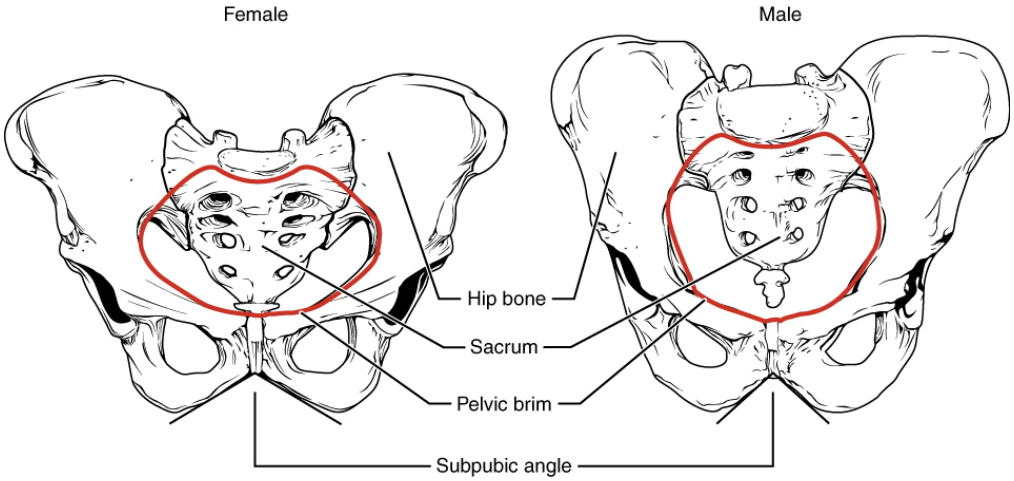


Figure 1.4 Diagram summarizing the differences between the male and female pelvis. The red outlined circle outlines the structural shape of the pubic outlet and inlet in comparison of females to males.
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1.1.4 Joints of the Pelvis

1.1.4.1 Public symphysis (single)

A secondary cartilaginous joint that connects the two pubic bones. Superior and inferior pubic ligaments support it (Figure 1.5).

1.1.4.2 Sacroiliac joints (right & left)

A plane synovial joint that connects the sacral and iliac articular surfaces. It has anterior, interosseous, and posterior sacroiliac ligaments. Both joints help in the transmission of the body weight from the vertebral columns to the hip bones.

1.1.4.3 Sacrococcygeal joint (single)

A secondary cartilaginous joint that connects the apex of the sacrum to the base of the coccygeal bone.

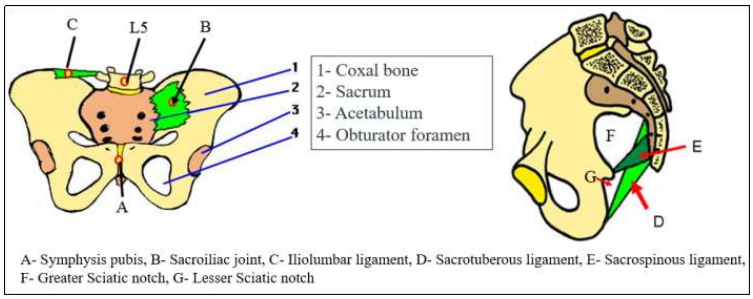


Figure 1.5 The diagram shows the joints and the ligaments the connect and support the pelvis together.
Image Source: Dauzvardis, Michael F., Ph.D. Assistant Professor Emeritus, Loyola University; used with permission.

1.1.5 Ligaments of the Pelvis

1.1.5.1 Iliolumbar

Connects L5 to the iliac crest.

1.1.5.2 Lumbosacral

Connects L5 to the ala of the sacrum, where it blends with the anterior sacroiliac ligament. Both protect the displacement of L5 under the body weight effect.

1.1.5.3 Sacrotuberous and Sacrospinous

Ligaments covert the greater and lesser sciatic notches into foramina (Table 1.1).

Attachment of the sacrotuberous and sacrospinous ligaments

Ligament	Origin	Insertion	Action
Sacrotuberous	Posterior sacroiliac ligament; posterior superior iliac spine; inferolateral sacrum; superolateral coccyx	Ischial tuberosity of ischium; tendon of biceps femoris muscle	Prevention of nutation; stabilization of the sacroiliac joint
Sacrospinous	Ischial spine	Lateral sacrum and coccyx	Prevention of nutation; stabilization of the sacroiliac joint

Table 1.1 Table summarizing the attachment of the sacrotuberous and sacrospinous ligaments.
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1.1.6 Muscles & Fascia of the Pelvis

1.1.6.1 Pelvic Muscles

- Two muscles line the pelvic wall - the **piriformis**, which arises from the middle three sacral vertebrae, and **obturator internus,** which arises from the inner surface of the obturator membrane (Table 1.2. & Figure 1.6.).
- Two muscles form the pelvic diaphragm - the **levator ani** and **coccygeus muscles**.

1.1.6.2 Muscles of the Pelvic wall

Summary of the attachment of the piriform & obturator internus muscles

MUSCLE	ORIGIN	INSERTION	INNERVATION	ACTION
Obturator internus	Inner surface of obturator foramen and surrounding bones	Medial surface of greater trochanter of femur Trochanteric fossa of the femur	Nerve to obturator internus via L5 and S1 Obturator nerve via L3 and L4	Laterally rotates the thigh when extended; abducts the thigh when flexed; stabilization of femoral head in the acetabulum.
Piriformis	The anterior surface of the sacrum; sacrotuberous ligament	The superior border of the greater trochanter of the femur	S1 and S2 spinal nerves	Lateral hip rotation, abduction, and extension; stabilization of femoral head in the acetabulum

Table 1.2 Table summarizing the attachment of the piriform & obturator internus muscles.
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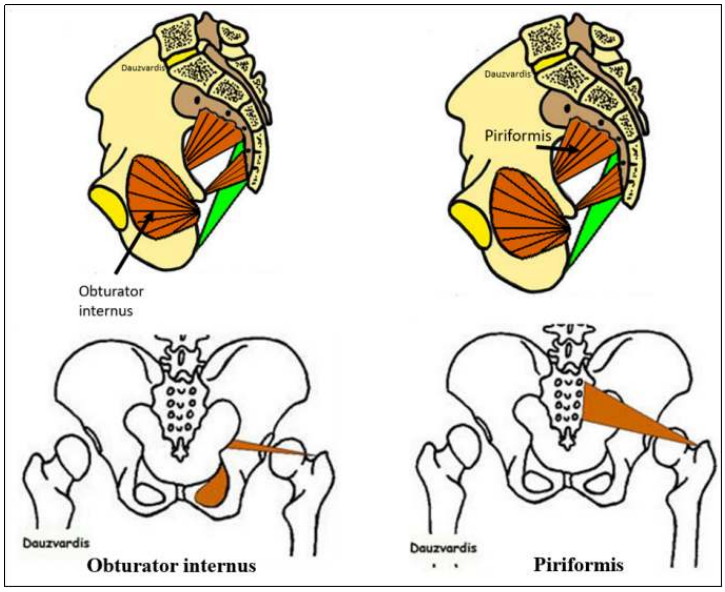


Figure 1.6 The diagram shows the origin and the insertion of the piriform and obturator internus muscles, demonstrating its lateral location at the pelvic wall.
Image Source: Dauzvardis, Michael F., Ph.D. Assistant Professor Emeritus, Loyola University; used with permission.

1.1.6.3 Muscles of the Pelvic Diaphragm

The pelvic diaphragm looks bowl-shaped and forms the floor of the pelvic cavity. It consists of two muscles - the **levator ani** & **coccygeus**.

- Levator ani
  - The levator ani is formed of iliococcygeus, pubococcygeus, and puborectalis (Figure 1.7).
  - The anterior fibers of the pubococcygeus are termed pubovaginalis in females (acts as a sphincter to the vagina) and puboprostaticus in males (acts as a levator to the prostate).
  - The Puborectalis muscle, the intermediate fibers of the pubococcygeus that continue with the opposite side to form a sling behind the anorectal junction.
  - The posterior fibers of the pubococcygeus, together with the iliococcygeus, share in the formation of the anococcygeal raphe.
- Coccygeus muscle

  The coccygeus muscle is a triangular muscle that originates from the ischial spine and sacrospinous ligament to the coccyx. It assists the levator ani in supporting the pelvic fascia. It is supplied by S4 & S5.

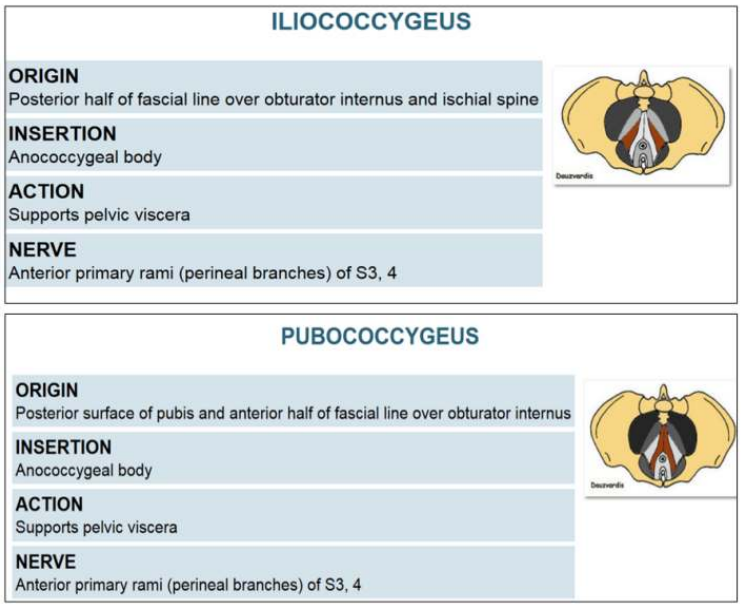


Figure 1.7 The diagram shows the origin, insertion, nerve supply and action of the pubococcygeus and iliococcygeus of levator ani demonstrating how it supports the pelvic floor.
Image Source: Dauzvardis, Michael F., Ph.D. Assistant Professor Emeritus, Loyola University; used with permission.

1.1.6.4 Features of the Pelvic Diaphragm

- Function

  The levator ani muscle group acts as a diaphragm that separates the pelvis from the perineum. It has a vital role in supporting the pelvic organs to maintain urinary and fecal continence.

- Nerve supply

  Is from the pelvic surface; branches S3-S5 from the sacral plexus and from the perineal surface; inferior rectal nerve from the pudendal nerve.

- Pelvic Fascia

  The pelvic fascia is broken into two divisions: the parietal and visceral divisions. The parietal fascia is part of the lining of the abdominal and pelvic walls. It makes up part of the pelvic floor as the superior and inferior fasciae of the pelvic diaphragm. It also lines the lateral pelvic wall as the obturator fascia. The obturator fascia lines the obturator internus and the lateral wall of the ischiorectal fossa. A fascia tunnel in this wall, the pudendal canal, houses the **pudendal nerve** and vessels.

For more information

More information about the female pelvic cavity and its related clinical application can be found at:

Anatomy, Abdomen, and Pelvis: Female Pelvic Cavity - StatPearls - NCBI Bookshelf (nih.gov)

1.1.7 Blood Supply and Venous Drainage of the Pelvis

1.1.7.1 Arteries of the Pelvis

The pelvis is supplied by the common iliac artery that branches from the abdominal aorta. The common iliac artery then branches into:

- External iliac artery supplies the lower limb as it turns to the femoral artery once it crosses the inguinal ligament.

- The internal iliac artery supplies most of the pelvis organs, pelvic walls, and pelvic floor as it divides later into two divisions: anterior and posterior. Each division give the following branches illustrated below in Figure 1.8.

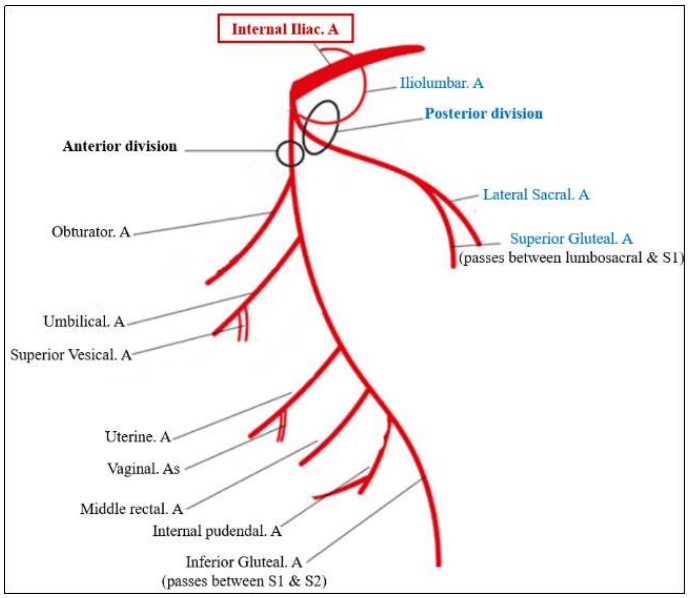


Figure 1.8 Diagram demonstrating an overview of the branches of the internal iliac artery.
Image Source: Modified and adapted from Rand, T., Patel, R., Magerle, W. et al. CIRSE standards of practice on gynaecological and obstetric haemorrhage. CVIR Endovasc 3, 85 (2020). CC BY 4.

- Anterior Division: (3 parietal + 3 visceral branches)
  - Umbilical: runs from the internal iliac to the umbilicus and branches to the urinary bladder as Superior Vesicle A. Its distal part is fibrosed and forms the medial umbilical ligament.
  - Obturator A.
  - Inferior Vesicle A. (in males) and Vaginal & Uterine A. (in females).
  - Middle Rectal A.
  - Inferior Gluteal A. (passes between S1 & S2)
  - Internal Pudendal A.
- Posterior Division: All are parietal branches
  - Iliolumbar; to iliacus, psoas, and quadratus lumborum muscles.
  - lateral sacral; arteries of the sacral canal.
  - superior gluteal (passes between Lumbosacral & S1).

1.1.7.2 Veins of the Pelvis

The pelvic floor is drained by the veins of the pelvic floor, including the **external iliac** vein, the **internal iliac** vein and the **common iliac** vein. These three veins correspond with the three major pelvic arteries. A condition referred to as pelvic congestion syndrome occurs when blood builds within the veins of the pelvic region. Symptoms are chronic pelvic pain, the feeling of needing to urinate and enlarged veins of the pelvic region and thighs. Estrogen and other hormones dilate veins and may play a role in pelvic congestion syndrome.[7]

1.1.8 Innervation of the Pelvis

1.1.8.1 Sacral Plexus (L4 - S5)

The **sacral plexus** rests on the piriformis muscle. (Figure 1.9) There are several branches from the sacral plexus to the pelvis and perineum. It is formed of the ventral rami of S1 - S4; and receives L4 and L5 contributions from the lumbosacral trunk.

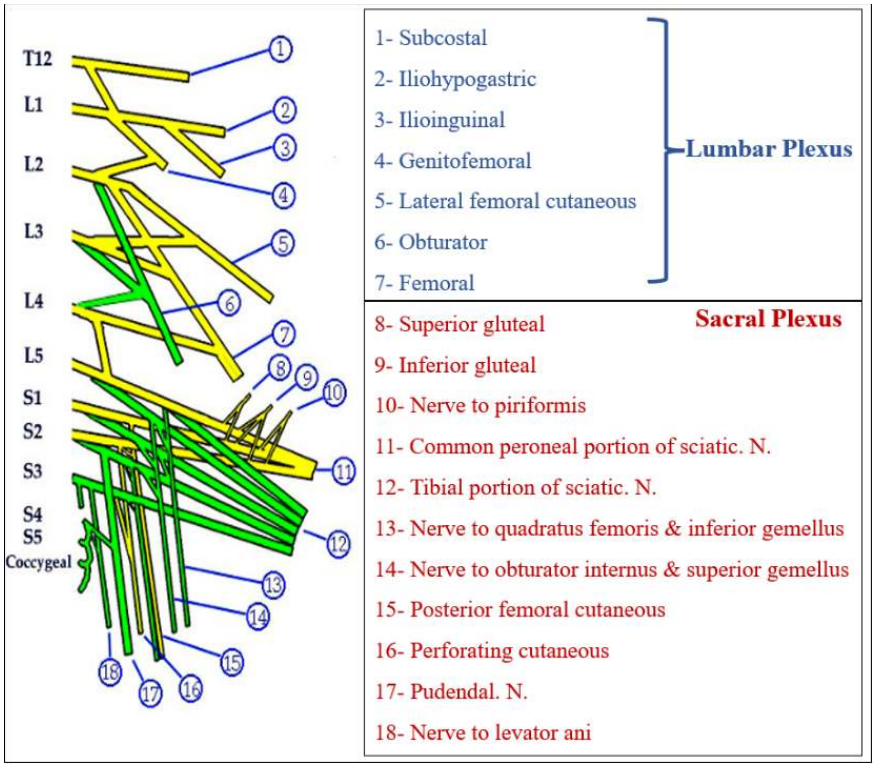


Figure 1.9 Diagram shows the root value and the branches of the lumbar and sacral plexus.
Image Source: Dauzvardis, Michael F., Ph.D. Assistant Professor Emeritus, Loyola University; used with permission

- Branches to pelvis and perineum (before the formation of the plexus)
  - N. to piriformis; S1,2
  - N. to levator ani a& coccygeus; S4
  - Pelvic splanchnic: parasympathetic; S2,3,4
  - Perineal branch of S4
- Four branches to the muscles in the gluteal region
  - Superior gluteal n; L4,5, S1
  - Inferior gluteal n.; L5, S1,2
  - Nerve to quadratus femoris and inferior gemellus; L4,5, S1
  - N. to obturator internus and to superior gemellus; L5, S1,2
- Two Cutaneous branches
  - Posterior femoral cutaneous n.
  - Perforating cutaneous nerves.
- Two Terminal branches
  - Pudendal n; S2,3,4
  - Sciatic n.; L4,5, S1,2,3

1.1.8.2 Pelvic Floor

The pelvic floor muscles are innervated through somatic, visceral, and central pathways. The pudendal nerves pass through the pudendal canal. The main nerve that innervates the pelvic floor is the pudendal nerve that arises from the ventral branches S2-S4 of the sacral plexus. The pudendal canal is located through the lateral wall of the ischiorectal fossa. The nerves and vessels are surrounded by a fascia sheath. The pudendal nerve is derived from the second, third, and fourth sacral spinal nerves. The nerve exits the

pelvis through to the gluteal region between piriformis and coccygeus through the greater sciatic foramen and crossing through the sacrospinous ligament close to the attachment spot to the ischial spine. It then divides into the dorsal and perineal nerve of the penis or clitoris.

1.1.9 Autonomics of the Pelvis

1.1.9.1 Sympathetic = makes you stop going

- Sympathetic trunks descend from abdomen along sacrum and converge to form the ganglion impar. (The last and unpaired sympathetic ganglion)
- Superior Hypogastric Plexus (SHP) represents the inferior projection of the intermesenteric plexus. It receives contributions from the lumbar splanchnic nerves. The branches of the SHP spill over into the pelvis as the right & left Hypogastric nerves. They mix with the pelvic splanchnic to form the Inferior Hypogastric Plexus (HIP). The IHP also receives sacral splanchnic (sympathetic).

1.1.9.2 Parasympathetic = makes you go

Pelvic splanchnic(S2-4) combine with the sympathetic branches to form the inferior hypogastric plexus (IHP)on the walls of the pelvis.

Lumbar splanchnic (sympathetic), sacral splanchnic (sympathetic), and pelvic splanchnic (parasympathetic), all mingle with the aortic, mesenteric, and hypogastric plexus to innervate the pelvic viscera.

Videos

Video 1.1 Let's Build a Pelvis 1

Video 1.2 Let's Build a Pelvis 2

Print your own 3D Model

STL files for printing a 3D model of Normal Female Pelvis can be found in Chapter 9.

Glossary Terms

Acetabulum
: part of the pelvis that comprises the pelvic socket where the head of FEMUR joins to form HIP JOINT (acetabulofemoral joint)

Coccyx (tailbone)
: small bone at the lower tip of the spine

Coccygeus (muscles)
: see Ischiococcygeus

Common iliac vein
: one of a pair of veins that flows into the inferior vena cava at the level of L5; the left common iliac vein drains the sacral region; divides into external and internal iliac veins near the inferior portion of the sacroiliac joint

External iliac vein
: formed when the femoral vein passes into the body cavity; drains the legs and leads to the common iliac vein

Iliolumbar (ligament)
: TBD

Ilium
: superior portion of the hip bone

Ischiococcygeus (muscle)
: muscle that assists the levator ani and pulls the coccyx anteriorly

Ischium
: one of three bones that make up the coxal bone of the pelvic girdle. In tetrapods, it is the part of the pelvis that projects backward on the ventral side, and in primates, it bears the weight of the sitting animal

Internal iliac vein
: vein on either side of the body which is formed by the union of the external and internal iliac veins and passes upward to join with its fellow of the opposite side to form the inferior vena cava

Levator ani (muscle)

muscle that makes up the levator ani along with the iliococcygeus

Lumbosacral (ligament)

region of the back including the LUMBAR VERTEBRAE, SACRUM, and nearby structures

Obstetric conjugate

narrowest fixed distance through which a baby's head must pass during vaginal delivery (10 com)

Obturator internus (muscle)

muscle deep to the gluteus maximus on the lateral surface of the thigh that laterally rotates the femur at the hip

Parietal branches

group of arterial branches of the thoracic aorta; includes those that supply blood to the thoracic cavity, vertebral column, and the superior surface of the diaphragm

Pelvic diaphragm

pelvic floor is soft tissue formed mainly by the pelvic diaphragm, which is composed of the two levator ani and two coccygeus muscles; the pelvic diaphragm lies just below the pelvic aperture (outlet) and separates the pelvic cavity from the PERINEUM. It extends between the PUBIC BONE anteriorly and the COCCYX posteriorly

Pelvic Girdle

hip girdle; consists of a single hip bone, which attaches a lower limb to the sacrum of the axial skeleton

Piriformis (muscle)

muscle deep to the gluteus maximus on the lateral surface of the thigh that laterally rotates the femur at the hip

Pubic symphysis (joint)

joint formed by the articulation between the pubic bodies of the right and left hip bones

Pubis

anterior portion of the hip bone

Pudendal nerve

nerve which originates in the sacral spinal cord (S2 to S4) and innervates the PERINEUM, the external GENITALIA, the external ANAL SPHINCTER and the external urethral sphincter.

Sacral plexus

nerve plexus associated with the lower lumbar and sacral spinal nerves

Sacrum

shield-shaped bony structure that is located at the base of the lumbar vertebrae and that is connected to the pelvis. The sacrum forms the posterior pelvic wall and strengthens and stabilizes the pelvis. Joined at the very end of the sacrum are two to four tiny, partially fused vertebrae known as the coccyx or "tail bone". The coccyx provides slight support for the pelvic organs but actually is a bone of little use

Sacrococcygeal (joint)

body region between (and flanking) the SACRUM and COCCYX

Sacroiliac (joint)

term used to describe the place where the sacrum and the iliac bones join

Sacrospinous (ligament)

ligament that spans the sacrum to the ischial spine of the hip bone

Sacrotuberous (ligament)

ligament that spans the sacrum to the ischial tuberosity of the hip bone

Symphysis pubis (joint)

joint formed by the articulation between the pubic bodies of the right and left hip bones

Visceral branches

branches of the descending aorta that supply blood to the viscera

Footnotes

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2. PHED 301 Students, 2018

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- Rand, Thomas, Rafiuddin Patel, Wolfgang Magerle, and Raman Uberoi. "CIRSE standards of practice on gynaecological and obstetric haemorrhage." *CVIR Endovasc* 3, No. 85 (2020). This work is made available under a CC BY 4.0 license. doi.org/10.1186/s42155-020-00174-7

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1.2: Female Reproductive Organs

The female reproductive system functions to produce gametes and reproductive hormones, just like the male reproductive system; however, it also has the additional task of supporting the developing fetus and delivering it to the outside world. Unlike its male counterpart, the female reproductive system is primarily inside the pelvic cavity (Figure 1.10).

This section will cover the peritoneum of the female pelvis, urinary bladder, female urethra, female external genitalia (Vulva), and female internal genitalia (Ovary, Uterine tube, Uterus, and Vagina).

1.2.1 Peritoneum of the Female Pelvis

Following the reflection of the female peritoneum; Vertically, the peritoneum is reflected on the upper part of the posterior vaginal wall, covers the upper surface of the uterus, the inferior surface of the uterus down to the internal os, then reflected onto the upper surface of the urinary bladder then the anterior abdominal wall. This reflection will form two pouches: rectovaginal (pouch of Douglas) and uterovaginal pouches. Horizontally, the peritoneum in female covers the uterus and forms the broad ligaments, which extends from the uterus to the side walls of the pelvis, where they become parietal and line the pelvic walls. The uterine tube runs in the free border of the broad ligament and pierces the upper layer to open into the peritoneal cavity (Figure. 1.10).

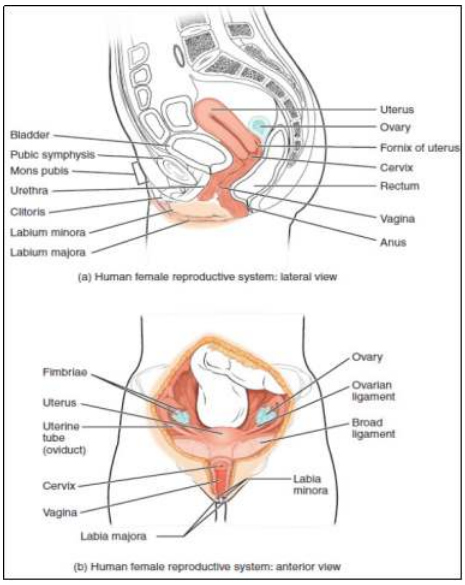


Figure 1.10 Diagram shows the female reproductive organs demonstrating the horizontal and the vertical reflection of the peritoneum.

Image Source: Betts, J. Gordon, Kelly A. Young, James A. Wise, Eddie Johnson, Brandon Poe, Dean H. Kruse, Oksana Korol, Jody E. Johnson, Mark Womble, Peter DeSaix. Anatomy and Physiology. (2013). Open Stax, 2013 This work is distributed under a CC BY 4.0 license. Available from Open Stax

1.2.2 Urinary Bladder and Female Urethra

Like the Digestive System with the digestive tract, the Urinary System also has a urinary tract, which includes the **ureters**, **urinary bladder**, and **urethra**. This section will start with urine excretion, tracing urine flow from the renal pelvis to the ureter, urinary bladder, and urethra.[8]

The kidneys and ureters are completely retroperitoneal, and the bladder has a peritoneal covering only over the dome. As urine is formed, it drains into the calyces of the kidney, which merge to form the funnel-shaped renal pelvis in the hilum of each kidney. The hilum narrows to become the ureter of each kidney. As urine passes through the ureter, it does not passively drain into the bladder but rather is propelled by waves of peristalsis. As the ureters enter the pelvis, they sweep laterally, hugging the pelvic walls. As they approach the bladder, they turn medially and pierce the bladder wall obliquely. This is important because it creates a one-way valve (a **physiological sphincter** rather than an **anatomical sphincter**) that allows urine into the bladder but prevents reflux of urine from the bladder back into the ureter. Children born lacking this oblique course of the ureter through the bladder wall are susceptible to "vesicoureteral reflux," dramatically increasing their risk of serious UTI. Pregnancy also increases the likelihood of reflux and UTI.[9]

The course of the ureter can be divided into three parts: from the pelvic brim to the level of the ischial spine, from the ischial spine to the urinary bladder, and the intravesical part of the ureter.

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>
> In females, the ureter runs below the root of the broad ligament. Here, the uterine artery crosses the ureter on its way to the broad ligament (from lateral to medial).

> Definition: *Water Under the Bridge*
>
> refers to urine/ureter (water) under the uterine artery (bridge). This mnemonic has an important clinical application. During hysterectomy, the ureter may accidentally be ligated with the uterine artery, which results in obstruction of the urine flow.

1.2.2.1 Urinary Bladder

The urinary bladder collects urine from both ureters (Figure 1.11). The bladder lies anterior to the uterus in females, posterior to the pubic bone, and anterior to the rectum. During late pregnancy, its capacity is reduced due to compression by the enlarging uterus, resulting in an increased frequency of urination. In males, the anatomy is similar, minus the uterus and with the addition of the prostate inferior to the bladder. The bladder is partially retroperitoneal (outside the peritoneal cavity), with its peritoneal-covered "dome" projecting into the abdomen when the bladder is distended with urine.[10]

The bladder is a highly distensible organ because the middle layer comprises irregular crisscrossing bands of smooth muscle collectively called the **detrusor muscle**. The interior

surface is made of transitional cellular epithelium structurally suited for the large volume fluctuations of the bladder. When empty, it resembles columnar epithelia, but when stretched, it “transitions” (hence the name) to a squamous appearance (see Figure 1.11). Volumes in adults can range from nearly zero to 500–600 mL—the detrusor muscle contracts with significant force in the young. The bladder’s strength diminishes with age, but voluntary contractions of abdominal skeletal muscles can increase intra-abdominal pressure to promote more forceful bladder emptying. Such voluntary contraction is also used in forceful defecation and childbirth.[11]

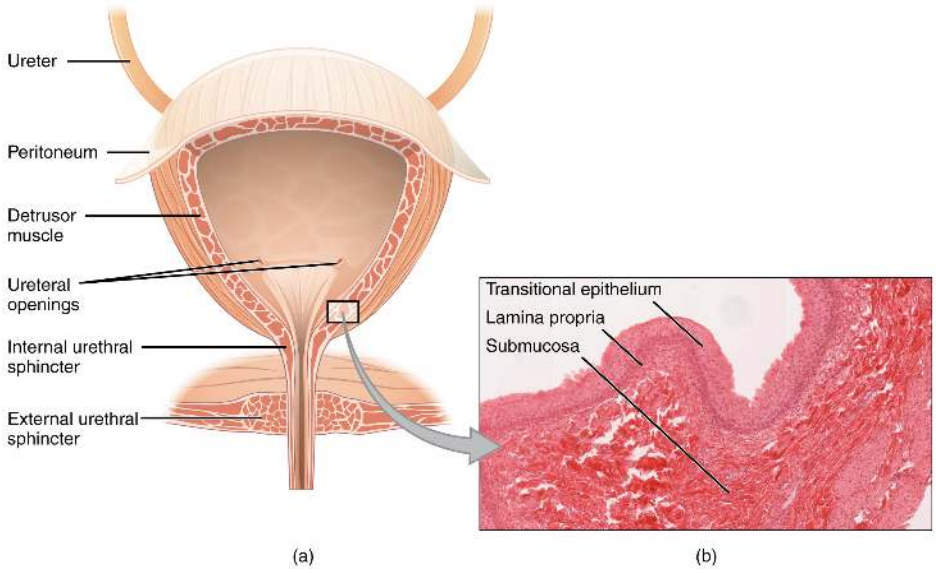


Figure 1.11 Bladder. (a) Anterior cross-section of the bladder. (b) The detrusor muscle of the bladder (source: monkey tissue) LM × 448; Micrograph provided by the Regents of the University of Michigan Medical School © 2012.

Image Source: Menefee, Whitney, Julie Jenks, Chiara Mazzasette and Im-Lelloni Nguyen. 2021. "22.4 Urinary System: Urinary Tract" in *Human Anatomy (OERI)*. This work is made available under a CC BY 4.0. Access from Libretexts

The small triangular area lies between the orifices of the ureters and the internal urethra sphincter, called the **trigone** of the bladder. Its mucous membrane is smooth, adherent to the underlying muscle, and it is sensitive and vascular so that in cystoscope, it appears red-violet in color (it is mesodermal in origin).

1.2.2.2 Functional Features of the Bladder

- Blood supply

  In females, by the superior vesical and vaginal arteries. In males, by the superior and inferior vesical arteries.

- Venous drainage

  Is by vesical venous plexus, which communicates with vaginal venous plexus in females and prostatic venous plexus in males.

- Innervation

Is by vesical nerve plexus, which is derived from the inferior hypogastric plexus and contains parasympathetic (pelvic splanchnic, motor to detrusor muscle) and sympathetic efferent.

Micturition Reflex

Micturition is a less-often used, but proper term for urination or voiding. It results from an interplay of involuntary and voluntary actions by the internal and external urethral sphincters. When bladder volume reaches about 150 mL, an urge to void is sensed but is easily overridden. Voluntary control of urination relies on consciously preventing relaxation of the external urethral sphincter to maintain urinary continence. As the bladder fills, subsequent urges become harder to ignore. Ultimately, voluntary constraint fails with resulting **incontinence**, which will occur as bladder volume approaches 300 to 400 mL.

Nerves involved in the control of urination include the hypogastric, pelvic, and pudendal. Normal micturition is a result of stretch receptors in the bladder wall that transmit nerve impulses to the sacral region of the spinal cord to generate a spinal reflex. The resulting parasympathetic neural outflow causes contraction of the detrusor muscle and relaxation of the involuntary internal urethral sphincter. At the same time, the spinal cord inhibits somatic motor neurons, resulting in the relaxation of the skeletal muscle of the external urethral sphincter. The micturition reflex is active in infants, but with maturity, children learn to override the reflex by asserting external sphincter control, thereby delaying voiding (potty training). This reflex may be preserved even in the face of spinal cord injury that results in paraplegia or quadriplegia. However, relaxation of the external sphincter may not be possible in all cases, and therefore, periodic catheterization may be necessary for bladder emptying.[12]

For more information

For more information regarding Development, Blood supply, and clinical & surgical application to the urinary bladder, please visit Anatomy, Abdomen, and Pelvis: Bladder - StatPearls - NCBI Bookshelf (nih.gov)

1.2.3 Urethra

The urethra transports urine from the bladder to the outside of the body for disposal. The urethra is the only urologic organ that shows any significant anatomic difference between males and females; all other urine transport structures are identical (Figure 1.12). The urethra in both males and females begins inferior and central to the two ureteral openings, forming the

three points of a triangular-shaped area at the base of the bladder called the trigone (Greek tri- = “triangle” and the root of the word “trigonometry”). The urethra tracks posterior and inferior to the pubic symphysis (see Figure 1.12). In both males and females, the proximal urethra is lined by transitional epithelium, whereas the terminal portion is nonkeratinized, stratified squamous epithelium. In the male, pseudostratified columnar epithelium lines the urethra between these two cell types. Voiding is regulated by an involuntary autonomic nervous system-controlled internal urinary sphincter, consisting of smooth muscle and voluntary skeletal muscle external urinary sphincter below it.[13]

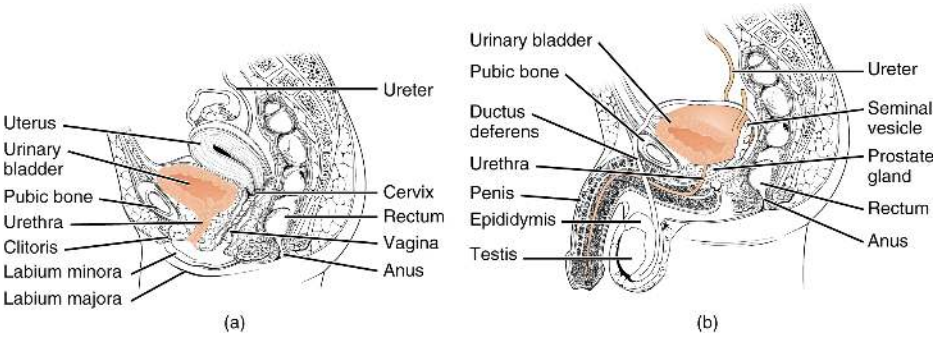


Figure 1.12 Female and Male Urethras. Urethra transports urine from the bladder to the outside of the body. This image shows (a) a female urethra and (b) a male urethra.

Image Source: Betts, J. Gordon, Kelly A. Young, James A. Wise, Eddie Johnson, Brandon Poe, Dean H. Kruse, Oksana Korol, Jody E. Johnson, Mark Womble, Peter DeSaix. Anatomy and Physiology. (2013). Open Stax, 2013 This work is distributed under a CC BY 4.0 license. Available from Open Stax

1.2.3.1 Female Urethra

The external urethral orifice is embedded in the anterior vaginal wall inferior to the clitoris, Superior to the vaginal opening (introitus), and medial to the labia minora. Its short length, about 4 cm, is less of a barrier to fecal bacteria than the longer male urethra and the best explanation for the greater incidence of UTI in women. Voluntary control of the external urethral sphincter is a function of the pudendal nerve. It arises in the sacral region of the spinal cord, traveling via the S2–S4 nerves of the sacral plexus.

Comparing the male urethra to female urethra, the male urethra passes through the prostate gland immediately inferior to the bladder before passing below the pubic symphysis (see Figure 1.12). The length of the male urethra varies between men but averages 20 cm in length. It is divided into four regions: the preprostatic urethra, the prostatic urethra, the membranous urethra, and the spongy or penile urethra. The preprostatic urethra is very short and incorporated into the bladder wall. The prostatic urethra passes through the prostate gland. During sexual intercourse, it receives sperm via the ejaculatory ducts and secretions from the seminal vesicles. Paired Cowper’s glands (bulbourethral glands) produce and secrete mucus into the urethra to buffer urethral pH during sexual stimulation. The mucus neutralizes the usually acidic environment and lubricates the urethra, decreasing the resistance to ejaculation. The membranous urethra passes through the deep muscles of the perineum, where it is

invested by the overlying urethral sphincters. The spongy urethra exits at the tip (external urethral orifice) of the penis after passing through the corpus spongiosum. Mucous glands are found along much of the length of the urethra and protect the urethra from extremes of urine pH. Innervation is the same in both males and females.[14]

1.2.4 Vagina

The vagina is a muscular canal (approximately 10 cm long) that serves as the entrance to the reproductive tract. It also serves as the exit from the uterus during menses and childbirth. The outer walls of the anterior and posterior vagina are formed into longitudinal columns, or ridges, and the superior portion of the vagina—called the **fornix**—meets the protruding uterine cervix. The walls of the vagina are lined with an outer, fibrous adventitia; a middle layer of smooth muscle; and an inner mucous membrane with transverse folds called **rugae** (Figure 1.15). Together, the middle and inner layers allow the expansion of the vagina to accommodate intercourse and childbirth. The thin, perforated hymen can partially surround the opening to the vaginal orifice. The hymen can be ruptured with strenuous physical exercise, penile–vaginal intercourse, and childbirth. The Bartholin's glands and the lesser vestibular glands (located near the clitoris) secrete mucus, which keeps the vestibular area moist.

The vagina is home to a normal population of microorganisms that help to protect against infection by pathogenic bacteria, yeast, or other organisms that can enter the vagina. In a healthy woman, the most predominant type of vaginal bacteria is from the genus *Lactobacillus*. This family of beneficial bacterial flora secretes lactic acid, and thus protects the vagina by maintaining an acidic pH (Figure 1.15). Potential pathogens are less likely to survive in these acidic conditions. Lactic acid, in combination with other vaginal secretions, makes the vagina a self-cleansing organ. However, douching—or washing out the vagina with fluid—can disrupt the normal balance of healthy microorganisms and increase a woman's risk for infections and irritation. Indeed, the American College of Obstetricians and Gynecologists recommend that women do not douche, and that they allow the vagina to maintain its normal healthy population of protective microbial flora.[15]

For more information

For more information regarding development, physiological variants, surgical and clinical applications of the vagina please visit Physiology, Vaginal - StatPearls - NCBI Bookshelf (nih.gov). (Gold and Shrimanker 2023)

1.2.5 Ovaries

The **ovaries** are the female gonads. Paired ovals, they are each about 2 to 3 cm in length, about the size of an almond (Figure. 1.13 & 1.14). The ovaries are located within the pelvic cavity, and are supported by the **mesovarium**, an extension of the peritoneum that connects the ovaries to the **broad ligament.** Extending from the mesovarium itself is the **suspensory ligament** that contains the ovarian blood and lymph vessels. Finally, the ovary itself is attached

to the uterus via the **ovarian ligament**. The ovary comprises an outer covering of cuboidal epithelium called the ovarian surface epithelium that is superficial to a dense connective tissue covering called the tunica albuginea. Beneath the tunica albuginea is the cortex, or outer portion, of the organ. The cortex is composed of a tissue framework called the ovarian stroma that forms the bulk of the adult ovary. Oocytes develop within the outer layer of this stroma, each surrounded by supporting cells. This grouping of an oocyte and its supporting cells is called a **follicle.**[16]

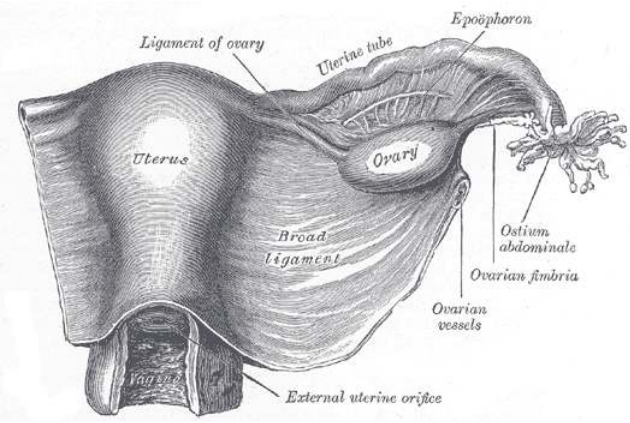


Figure 1.13 Uterus and right broad ligament, seen from behind. The broad ligament has been spread out, and the ovary drawn downward. The ligament of the ovary is labeled at the center top. The suspensory ligament of the ovary (not labeled), which may be confused with ligament of ovary, is shown incompletely and in section; it surrounds the ovarian vessels (labeled).
Image Source: "Uterus and Ligaments" by Henry Gray is in the Public Domain CC0

> **Note**
>
> There are several names for the ovarian ligament such as Proper ovarian ligament, ligament of the ovary, or round ligament the of ovary) which all the same, and it attaches the ovary to the side of the uterus

1.2.5.1 Functional Features of the Ovary

- Blood supply

  Ovarian arteries (both right and left) are direct branches of the abdominal aorta.

- Venous drainage

  The right ovarian vein drains to IVC while the left ovarian vein drains into the left renal vein.

- Innervation

  Is by vesical nerve plexus, which is derived from the inferior hypogastric plexus and contains parasympathetic (pelvic splanchnic, motor to detrusor muscle) and sympathetic efferent.

1.2.6 Uterine tube (fallopian tube)

The **uterine tubes** (also called fallopian tubes or oviducts) serve as the conduit of the oocyte from the ovary to the uterus (Figure. 1.14). Each of the two uterine tubes is close to, but not directly connected to, the ovary. It is divided into sections. The **isthmus** is the narrow medial end of each uterine tube that is connected to the uterus. The wide distal **infundibulum** flares out with slender, finger-like projections called **fimbriae**. The middle region of the tube, called the **ampulla,** is where fertilization often occurs. The uterine tubes also have three layers: an outer serosa, a middle smooth muscle layer, and an inner mucosal layer. In addition to its mucus-secreting cells, the inner mucosa contains ciliated cells that beat in the direction of the uterus, producing a current that will be critical to move the oocyte.[17]

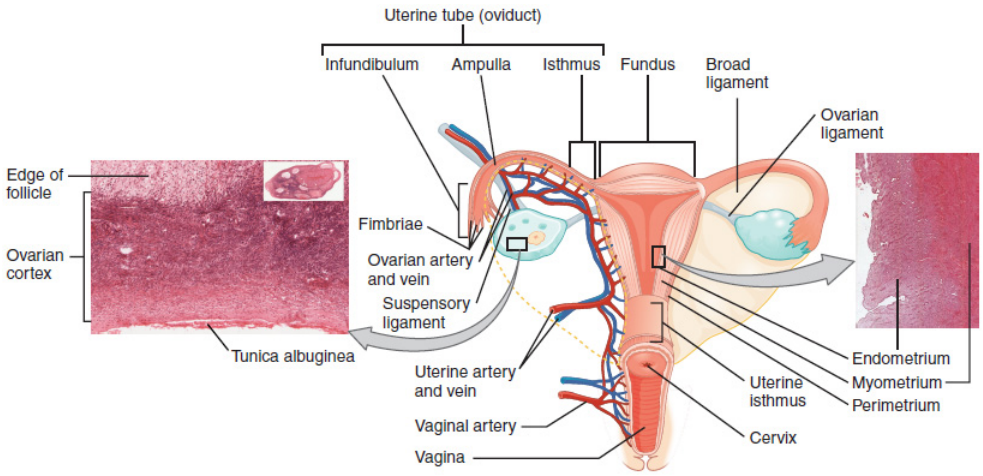


Figure 1.14 Ovaries, Uterine Tubes, and Uterus. This anterior view shows the relationship of the ovaries, uterine tubes (oviducts), and uterus. Sperm enters through the vagina, and fertilization of an ovulated oocyte usually occurs in the distal uterine tube. From left to right, LM × 400, LM × 20; Micrographs provided by the Regents of University of Michigan Medical School © 2012.

Image Source: Menefee, Whitney, Julie Jenks, Chiara Mazzasette and Im-Lelloni Nguyen. 2021. "22.4 Urinary System: Urinary Tract" in *Human Anatomy (OERI)*. This work is made available under a CC BY 4.0. Access from Libretexts Medicine

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- The uterine tube is the most common site for **ectopic pregnancy (abnormal implantation)** presented with abdominal pain and missed period.
- Infection of the uterine tube led to blockage of the tube, which is a common cause of infertility in females.
- The uterine tube forms a direct connection between the peritoneal cavity and the uterine cavity. So, infection in the uterus and/or uterine tube may result in **peritonitis**.

For more infomration

For more information regarding Development, physiological variants, surgical consideration, and clinical applications to the uterine tube, please visit.

Anatomy, Abdomen and Pelvis: Fallopian Tube - StatPearls - NCBI Bookshelf (nih.gov) (Han and Sadiq, 2023)

Anatomy, Abdomen and Pelvis: Female Internal Genitals - StatPearls - NCBI Bookshelf (nih.gov) (Hoare and Khan, 2023)

1.2.7 Uterus and Cervix

The **uterus** is the muscular organ that nourishes and supports the growing embryo (Figure 1.14). Its average size is approximately 5 cm wide by 7 cm long (approximately 2 in by 3 in) when a female is not pregnant. It has three sections. The portion of the uterus superior to the opening of the uterine tubes is called the **fundus**. The middle section of the uterus is called the body of uterus (or corpus). The **cervix** is the narrow inferior portion of the uterus that projects into the vagina. The cervix produces mucus secretions that become thin and stringy under the influence of high systemic plasma estrogen concentrations, and these secretions can facilitate sperm movement through the reproductive tract.[18]

1.2.7.1 Anatomical Features of the Uterus

- Shape

  Is hollow, thick wall, pear-shaped (piriform in shape).

- Dimensions in nullipara

  Length, width, thickness around 3x2x1 inches.

- Position

  Is anteverted (angle between uterus and vagina about 90), Anteflexed (angle between the body of the uterus and the cervix about 170 degrees).

- Parts

  Include fundus (rounded part of body superior to the entrance of uterine tubes), body (upper 2/3), and cervix (lower 1/3).

1.2.7.2 Functional Features of the Uterus

- Blood Supply

  uterine arteries are direct branches of the internal iliac arteries

- Venous Drainage

  uterine veins drain to the internal iliac veins

- Innervation

  Sympathetic: T12 – L1 via hypogastric plexus
  Parasympathetic: pelvic nerve from S1-4

1.2.7.3 Uterine Ligaments

- Broad Ligament

  Is a double-layered fold of peritoneum that extends from the sides of the uterus to the lateral wall of the pelvis. It surrounds the uterine tube (Fig 1.15).

  a. Mesovarium: between the broad ligament and the ovary.
  b. Mesosalpinx: between the uterine tube and the ovarian ligament.
  c. Myometrium: between the ovarian ligament and body of uterus.
  d. Ovarian ligament: lies anteroinferior within the broad ligament.

- Cardinal ligament

  Also known as the lateral, transverse cervical, or Mackenrodt's ligament, it forms the inferior border of the broad ligament and attaches to the lateral cervix on either side; contains the uterine artery and veins.

- Suspensory ligament of ovary

  Is a peritoneal fold that extends from the ovary to the lateral pelvic wall (bilateral); contains the ovarian artery and vein, ovarian nerve plexus, and lymphatic vessels.

- Uterosacral ligament

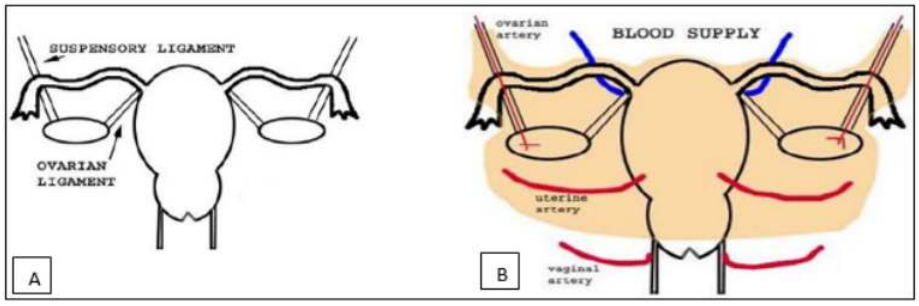
  Extends from each side of the rectum to the sacrum; suspends the cervix and vaginal tube, ensuring the craniodorsal orientation of their long axes.

- Pubocervical ligament

  Extends from the pubis to the cervix.

- Round ligament of the uterus

  Extends from the superior and lateral aspect of the uterus, crosses the pelvis through the deep inguinal ring, traverses the inguinal canal, and then enters the labia majora, where it terminates with its fibers blending into the mons pubis.



Men

Figure 1.15 Cartoon drawing shows A: the attachment of ovarian ligament and suspensory ligament of the ovary, B: shows how the vessels approach the broad ligament of the uterus.
Image Source: Dauzvardis, Michael F., Ph.D. Assistant Professor Emeritus, Loyola University; used with permission. [19]

For more inforamtion

For more information regarding Development, physiological variants, surgical consideration, and clinical applications to the ligaments of uterus and the round ligament of the uterus, please visit.

- Anatomy, Abdomen and Pelvis: Uterus Round Ligament - StatPearls - NCBI Bookshelf (nih.gov)
- Anatomy and histology of apical support: a literature review concerning cardinal and uterosacral ligaments - Ramanah, Rajeev, Mitchell B. Berger, Bernard M. Parratte, and John O.L. DeLancey. "Anatomy and histology of apical support: a literature review concerning cardinal and uterosacral ligaments." *Int Urogynecol J* 23 (2012):1483–1494. doi.org/10.1007/s00192-012-1819-7

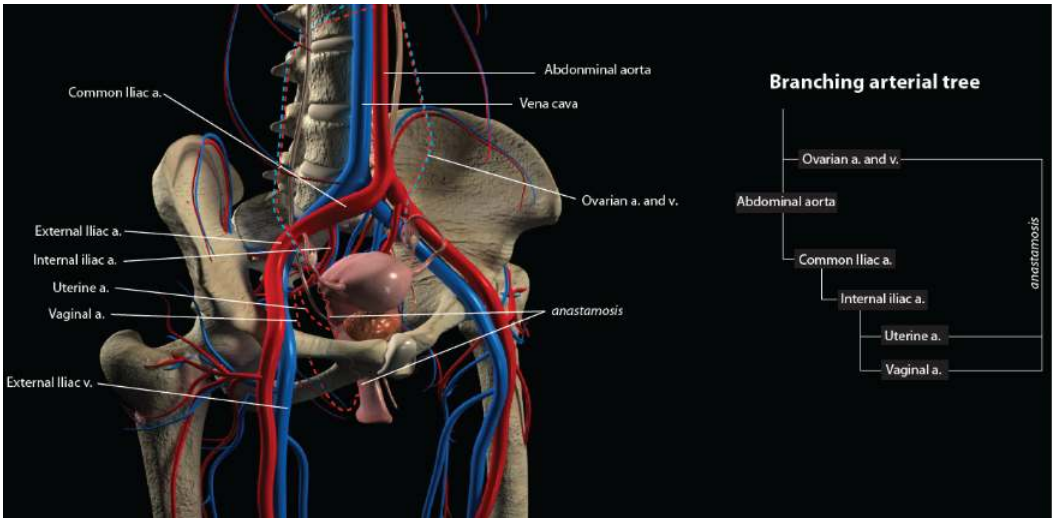


Figure 1.16 The diagram shows the arterial tree of the female reproductive organs and multiple anastomoses between branches.
Image Source: Sinn-Hanlon, Janet, iLearning@VetMed, University of Illinois at Urbana; used with permission.

Summary of the blood supply of the female reproductive organs

Arterial supply

- ovarian artery (from aorta)
- uterine artery (from internal iliac a)
- multiple anastomoses between branches
- vaginal artery (from internal iliac a) also supplies the inferior cervix and superior vaginal.

Venous drainage

- ovarian veins to inferior vena cava (Rt.) or left renal v (Lt.)
- uterine vein, vaginal veins to internal iliac vein

1.2.8 Female External Genitals

The external female reproductive structures are referred to collectively as the vulva (Figure 1.17). The **mons pubis** is a pad of fat located at the anterior, over the pubic bone. After puberty, it becomes covered in pubic hair. The **labia majora** (labia = “lips”; majora = “larger”) are folds of hair-covered skin that begin just posterior to the mons pubis. The thinner and more pigmented **labia minora** (labia = “lips”; minora = “smaller”) extends medial to the labia majora. Although they naturally vary in shape and size from woman to woman, the labia minora serve to protect the female urethra and the entrance to the female reproductive tract.[20]

The superior, anterior portions of the labia minora come together to encircle the **clitoris** (or glans clitoris), which originates from the same cells as the glans penis and has abundant nerves that make it important in sexual sensation and orgasm. The **hymen** is a thin membrane that sometimes partially covers the entrance to the vagina. An intact hymen cannot be used as an indication of “virginity”; even at birth, this is only a partial membrane, as menstrual fluid and other secretions must be able to exit the body, regardless of penile–vaginal intercourse. The vaginal opening is located between the opening of the urethra and the anus. It is flanked by outlets to the **Bartholin’s glands** (or greater vestibular glands) which secrete mucoid secretions to aid in vaginal and vulvar lubrication; they are the equivalent of Cowper's glands in men. Skene's glands (or lesser vestibular glands) flank the urethral opening and lubricate the opening to the urethra; their secretions have an antimicrobial quality. Similar to male anatomy, women also have corpus cavernosum.[21]

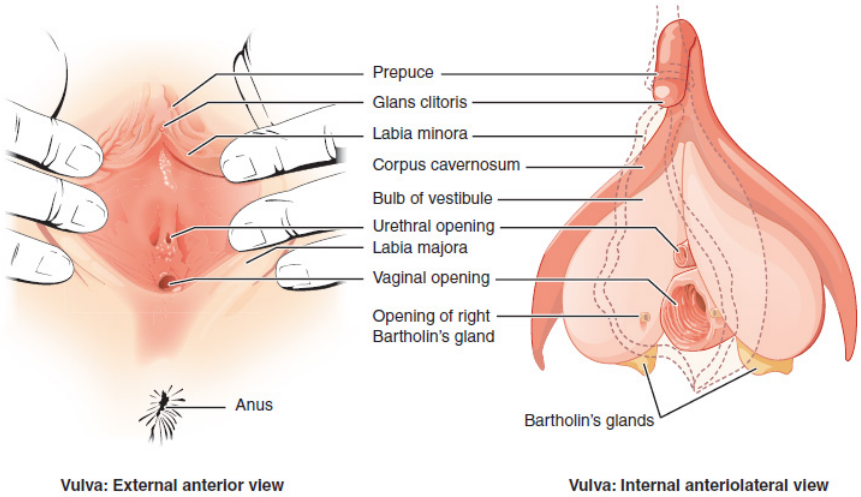


Figure 1.17 The Vulva. The external female genitalia are referred to collectively as the vulva. Just deep to the skin are glands and structures similar to those found in male anatomy.
Image Source: Menefee, Whitney, Julie Jenks, Chiara Mazzasette and Im-Lelloni Nguyen. 2021. "22.4

Urinary System: Urinary Tract" in *Human Anatomy (OERI)*. This work is made available under a CC BY 4.0. Access from Libretexts Medicine

Glossary Terms

Ampulla

(of the uterine tube) middle portion of the uterine tube in which fertilization often occurs

Bartholin's glands

(also, greater vestibular glands) glands that produce a thick mucus that maintains moisture in the vulva area; also referred to as the greater vestibular glands

Cervix

narrow inferior portion of the uterus that projects into the vagina

Clitoris

(or glans clitoris), an organ that originates from the same cells as the glans penis and has abundant nerves that make it important in sexual sensation and orgasm

Detrusor (muscle)

smooth muscle in the bladder wall; fibers run in all directions to reduce the size of the organ when emptying it of urine

Fimbriae

fingerlike projections on the distal uterine tube

Follicle (ovarian)

ovarian structure of one oocyte and surrounding granulosa (and later theca) cells

Fornix

superior portion of the vagina

Fundus

dome-shaped region of the stomach above and to the left of the cardia

Hymen

thin membrane that sometimes partially covers the entrance to the vagina

Infundibulum

(of the uterine tube) wide, distal portion of the uterine tube terminating in fimbriae

Incontinence

loss of ability to control micturition

Isthmus

narrow, medial portion of the uterine tube that joins the uterus

Labia majora

(labia = “lips”; majora = “larger”), folds of hair-covered skin that begin just posterior to the mons pubis

Labia minora

(labia = “lips”; minora = “smaller”), which is thinner and more pigmented and extends medially to the labia majora

Mesovarium

an extension of the peritoneum that connects the ovaries to the broad ligament

Mons pubis

a pad of fat that is located at the anterior, over the pubic bone. After puberty, it becomes covered in pubic hair

Ovarian ligament

ligament that attaches the ovary to the uterus

Ovaries

female gonads that produce oocytes and sex steroid hormones (notably estrogen and progesterone)

Rugae

(of the vagina) folds of skin in the vagina that allow it to stretch during intercourse and childbirth

Sphincter

A ring-shaped muscle that relaxes or tightens to open or close a passage or opening in the body. Examples are the anal sphincter (around the opening of the anus) and the pyloric sphincter (at the lower opening of the stomach)

Trigone

area at the base of the bladder marked by the two ureters in the posterior–lateral aspect and the urethral orifice in the anterior aspect oriented like points on a triangle

Ureters

A pair of thick-walled tubes that transports urine from the KIDNEY PELVIS to the URINARY BLADDER

Urethra

transports urine from the bladder to the outside environmen

Urinary bladder

A musculomembranous sac along the URINARY TRACT. URINE flows from the KIDNEYS into the bladder via the ureters (URETER), and is held there until URINATION

Uterine tubes

(also, fallopian tubes or oviducts) ducts that facilitate transport of an ovulated oocyte to the uterus

Uterus

(also, fallopian tubes or oviducts) ducts that facilitate transport of an ovulated oocyte to the uterus

Footnotes

8. Menefee, Whitney, Julie Jenks, Chiara Mazzasette and Im-Lelloni Nguyen. 2021. "22.4 Urinary System: Urinary Tract" in *Human Anatomy (OERI)*. This work is made available under a CC BY 4.0. Access from Libretexts Medicine
9. Menefee et al, 2021
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21. Menefee et al, 2021

Image Acknowledgements

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- Sinn-Hanlon, Janet iLearning@VetMed, University of Illinois at Urbana for her generous permission to use proprietary images.

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1.3: Female Mammary Glands

1.3.1 Whereas the breasts are located far from the other female reproductive organs, they are considered accessory organs of the female reproductive system. The function of the breasts is to supply milk to an infant in a process called lactation. The external features of the breast include a nipple surrounded by a pigmented **areola** (Figure. 1.18) whose coloration may deepen during pregnancy. The areola is typically circular and can vary in size from 25 to 100 mm in diameter. The areolar region is characterized by small, raised areolar glands that secrete lubricating fluid during lactation to protect the nipple from chafing. When a baby nurses, or draws milk from the breast, the entire areolar region is taken into the mouth.[22]

Breast milk is produced by the **mammary glands**, which are modified sweat glands. The milk itself exits the breast through the nipple via 15 to 20 **lactiferous ducts** that open on the surface of the nipple. These lactiferous ducts each extend to a **lactiferous sinus** that connects to a glandular lobe within the breast itself that contains groups of milk-secreting cells in clusters called **alveoli** (Figure. 1). The clusters can change in size depending on the amount of milk in the alveolar lumen. Once milk is made in the alveoli, stimulated myoepithelial cells that surround the alveoli contract to push the milk to the lactiferous sinuses. From here, the baby can draw milk through the lactiferous ducts by suckling. The lobes themselves are surrounded by fat tissue, which determines the size of the breast; breast size differs between individuals and does not affect the amount of milk produced. Supporting the breasts are multiple bands of connective tissue called **suspensory ligaments** that connect the breast tissue to the dermis of the overlying skin.[23]

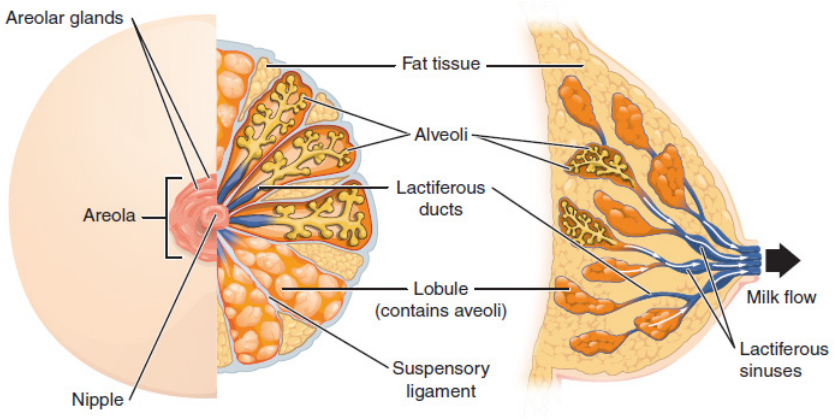


Figure 1.18 The diagram shows the anatomy of the breast shows the arrangement of the lactiferous ducts and the suspensory ligament.

Image Source: Menefee, Whitney, Julie Jenks, Chiara Mazzasette and Im-Lelloni Nguyen. 2021. "23.3 Anatomy of the Female Reproductive System" in *Human Anatomy (OERI)*. This work is made available under a CC BY 4.0. Access from Libretexts Medicine

For more information

For more information regarding Development, physiological variants, surgical consideration, lymphatic drainage, and clinical applications to the uterine tube, please visit.

- Anatomy, Thorax, Mammary Gland - StatPearls - NCBI Bookshelf (nih.gov)(Khan and Sajjad 2023)
- Anatomy, Thorax, Breast - StatPearls - NCBI Bookshelf (nih.gov) (Rivard, Galarza-Paez, and Peterson 2023)

Glossary Terms

Alveoli
(of the breast) milk-secreting cells in the mammary gland

Areola
highly pigmented, circular area surrounding the raised nipple and containing areolar glands that secrete fluid important for lubrication during suckling

Lactiferous ducts
ducts that connect the mammary glands to the nipple and allow for the transport of milk

Lactiferous sinus
area of milk collection between alveoli and lactiferous duct

Mammary glands
glands inside the breast that secrete milk

Suspensory ligaments
bands of connective tissue that suspend the breast onto the chest wall by attachment to the overlying dermis

Footnotes

22. Menefee, Whitney, Julie Jenks, Chiara Mazzasette and Im-Lelloni Nguyen. 2021. "23.3 Anatomy of the Female Reproductive System" in Human Anatomy (OERI). This work is made available under a CC BY 4.0. Access from Libretexts Medicine
23. Menefee et al, 2021, 23.

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1.4: The Perineum

1.4.1 Boundaries of the Perineum

The **perineum** is a diamond-shaped area on the inferior surface of the trunk between the **symphysis pubis** and the **coccyx**. It has the following boundaries:

- Anterior: symphysis pubis & pubic arch
- Lateral: pubic and ischial rami, ischial tuberosity, **sacrotuberous ligament**
- Posterior: **sacrum** and coccyx, and Roof: the **pelvic diaphragm**

The perineum is divided into two triangles by drawing an imaginary line between the two ischial tuberosities, the anterior urogenital (UG) triangle and the posterior anal triangle. (Figure 1.19)

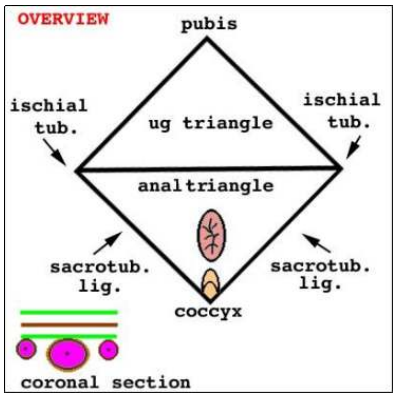


Figure 1.19 Cartoon drawing shows the layout and the general attachments of the urogenital and anal triangles.
Image Source: Michael F. Dauzvardis, Ph.D. Assistant Professor Emeritus, Loyola University; use of image with permission.

1.4.2 Urogenital Triangle

The Urogenital Triangle is anterior to a line connecting the ischial tuberosities and includes:

- Perineal Membrane
- Superficial Perineal Pouch (Female)
- Deep Perineal Pouch (Female)

> Before going over the urogenital triangle, consider the fascial planes:
>
> Through the three fascial layers, the urogenital triangle contains two pouches: superficial and deep perineal pouches. From superficial to deep, here is the arrangement of fascia and pouches of the female perineum:
>
> - Skin
> - Membranous layer of superficial fascia.
> - Superficial perineal pouch.
> - Perineal Membrane (inferior fascia of urogenital Diaphragm (UG diaphragm).
> - Deep perineal pouch (the space between the superior and inferior fascia of the UG diaphragm).
> - Superior fascia of UG Diaphragm.
> - Deep fascia of Pelvic Diaphragm.

1.4.3 Perineal Membrane

The perineal membrane forms the base for clitoral musculature and clitoris in females (penile in males). The space deep to the perineal membrane is the deep pouch, and the space superficial to the perineal membrane

is the superficial pouch.

1.4.4 Superficial Perineal Pouch

Urogenital structures: Root of Clitoris (formed of two crura), splitting of the bulb of the vestibule around the urethral and vaginal openings, and the greater vestibular glands.

1.4.4.1 Functional Features of the Superficial Perineal Pouch

- Muscles
  - Ischiocavernosus muscles attach to ischiopubic rami and cover the crura of clitoris
  - Bulbospongiosus muscles split to cover the bulb of the vestibule
  - Superficial transverse perinei muscles
- Vessels

  Perineal artery (a branch of the internal pudendal), which feeds dorsal and deep arteries of the clitoris, in addition to labial branches and muscular branches.
- Nerves

  Perineal n. (a branch of pudendal n), dorsal nerve of clitoris and labial branches.

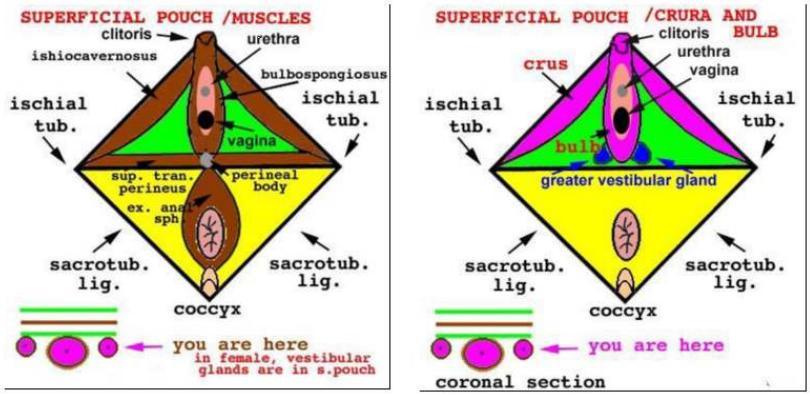


Figure 1.20 Cartoon drawing shows the contents and the muscles of the superficial perineal pouch.
Image Source: Michael F. Dauzvardis, Ph.D. Assistant Professor Emeritus, Loyola University; use of image with permission.

1.4.5 Deep Perineal Pouch

1.4.5.1 Functional Features of the Deep Perineal Pouch

- Muscles

  Sphincter urethrae and deep transverse perinei muscles. Note that the UG diaphragm comprises these two muscles (deep transverse perinei and sphincter urethrae). (Figure 1.21)
- Vessels

  The internal pudendal artery, which gives the following branches:
  - Artery of the bulb of the vestibule pierces the perineal membrane to enter the bulb of the clitoris
  - Dorsal & deep arteries of the clitoris pierces the perineal membrane to reach the dorsum of the penis or clitoris
  - Muscular branches
- Nerves

  Dorsal nerve of the clitoris.

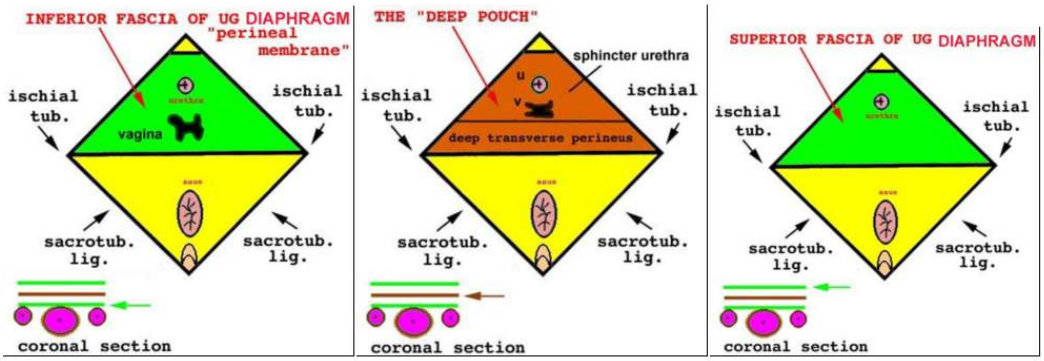


Figure 1.21 Cartoon drawing shows the content and the muscles of the deep perineal pouch.
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For more information

For more information about the superficial perineal pouch and related clinical applications, please visit:

Anatomy, Abdomen, and Pelvis: Superficial Perineal Space - StatPearls - NCBI Bookshelf (nih.gov) (Fahmy, Sanganeria, and Munakomi 2022)

Anatomy, Abdomen, and Pelvis: Deep Perineal Space - StatPearls - NCBI Bookshelf (nih.gov) (Bolla, Hoare, and Varacallo 2023)

1.4.6 Anal Triangle

The I-Anal Triangle is posterior to a line connecting the ischial tuberosities and includes:

- Anal Canal
- Anal Sphincters
- Ischiorectal Fossa
- Pudendal Canal

1.4.6.1 Anal Canal

The anal canal is ia continuation of rectum beyond the puborectalis m.

1.4.6.2 Functional Features of the Anal Canal

- Arterial supply

  Superior rectal artery above the pectinate line and inferior rectal artery below the pectinate line

- Venous drainage

  Superior rectal vein above the pectinate line and inferior rectal vein below the pectinate line

- Innervation

  Autonomic, by the inferior hypogastric plexus, somatic by the inferior rectal nerve

1.4.6.3 Anal Sphincters

- Internal Anal **Sphincter** (smooth muscle) innervated by the inferior hypogastric nerve plexus. It is the thickened lower end of the inner circular muscle of the rectum.
- External Anal Sphincter (skeletal muscle) innervated by the inferior rectal branch of the pudendal nerve. It has three parts:
  - Deep: encircles the anal canal and is fused with puborectalis m.
  - Subcutaneous: complete circle just deep to the skin
  - Superficial: attached posteriorly to the coccyx, anteriorly to the perineal body.

1.4.6.4 Ischiorectal Fossa

The ischiorectal fossa is the fat-filled space lateral to the anal triangle, used as dead space for the anus to expand. It has the following boundaries:

- Lateral wall = fascia of **obturator internus** muscle, sacrotuberous ligament, and ischial tuberosity.
- Medial wall = anal canal and **levator ani** muscle.
- Posterior = gluteus maximus and sacrotuberous ligament.
- Anterior = transverse perineal muscles.

The pudendal canal is formed by the fascia of the obturator internus, which splits to enclose the pudendal neurovascular bundle and connects the lesser sciatic foramen to the posterior perineal membrane. Perineal Body: lies at the front of the anal canal; it is composed of interdigitating fibers of pubovaginalis (puboprostaticus in males), superficial external anal sphincter, and transverse perineal muscles.

1.4.6.5 Functional Features of the Pudendal Canal

- Blood supply

  The internal pudendal artery and vein feed the following branches, including the inferior rectal artery and the perineal artery, that supply the superficial pouch and continue into the deep pouch.

- Innervation

  The pudendal nerve, which branches into the inferior rectal nerve (posterior) and the dorsal nerve of the penis (clitoris), and the perineal nerve (anterior) near the anterior end of the pudendal canal.

For more information

For more information about the pudendal nerve, its branches, and the clinical application of pudendal nerve block please visit Anatomy, Abdomen and Pelvis, Pudendal Nerve - StatPearls - NCBI Bookshelf (nih.gov) (Kinter and Newton 2023)

For more information about the anal triangle and the clinical application of ischiorectal fossa, please visit Anatomy, Abdomen and Pelvis: Anal Triangle - StatPearls - NCBI Bookshelf (nih.gov) (Nauman and Samra 2023)

Videos

Video 1.3 Let's build a perineum

Glossary Terms

Coccyx
(tailbone) - The tailbone (coccyx) is the small bone at the lower tip of the spine. The most common cause of injury to the tailbone is a backward fall onto a hard surface, such as a slippery floor or ice

Levator ani
(muscle) - muscle that makes up the levator ani along with the iliococcygeus

Obturator internus
muscle deep to the gluteus maximus on the lateral surface of the thigh that laterally rotates the femur at the hip

Pelvic diaphragm
muscular sheet that comprises the levator ani and the ischiococcygeus

Sacrotuberous ligament
ligament that spans the sacrum to the ischial tuberosity of the hip bone

Sacrum
single bone located near the inferior end of the adult vertebral column that is formed by the fusion of five sacral vertebrae; forms the posterior portion of the pelvis

Sphincter
A ring-shaped muscle that relaxes or tightens to open or close a passage or opening in the body. Examples are the anal sphincter (around the opening of the anus) and the pyloric sphincter (at the lower opening of the stomach)

Symphysis pubis
joint formed by the articulation between the pubic bodies of the right and left hip bones

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1.5: Glossary

To review common anatomical and directional terms, please see Chapter 1. Anatomy of the Female Reproductive System.

Acetabulum - The part of the pelvis that comprises the pelvic socket where the head of FEMUR joins to form HIP JOINT (acetabulofemoral joint). [4]

Alveoli - (of the breast) milk-secreting cells in the mammary gland. [3]

Areola - highly pigmented, circular area surrounding the raised nipple and containing areolar glands that secrete fluid important for lubrication during suckling. [3]

Ampulla - (of the uterine tube) middle portion of the uterine tube in which fertilization often occurs [3]

Bartholin's glands - (also, greater vestibular glands) glands that produce a thick mucus that maintains moisture in the vulva area; also referred to as the greater vestibular glands. [3]

Broad Ligament - wide ligament that supports the uterus by attaching laterally to both sides of the uterus and pelvic wall. [3]

Cardinal ligament - cardinal ligament, otherwise known as the transverse cervical ligament, is attached from the lateral aspect of the cervix to the respective pelvic wall. It forms the inferior border of the broad ligament and houses the uterine artery and uterine veins. [6]

Cervix - narrow inferior portion of the uterus that projects into the vagina. [1]

Clitoris - (or glans clitoris), an organ that originates from the same cells as the glans penis and has abundant nerves that make it important in sexual sensation and orgasm. [1]

Coccyx (tailbone) - The tailbone (coccyx) is the small bone at the lower tip of the spine. The most common cause of injury to the tailbone is a backward fall onto a hard surface, such as a slippery floor or ice. [2]

Coccygeus (muscle) - see Ischiococcygeus

Common iliac vein - one of a pair of veins that flows into the inferior vena cava at the level of L5; the left common iliac vein drains the sacral region; divides into external and internal iliac veins near the inferior portion of the sacroiliac joint. [3]

Coxal bones (Pelvic bones)- hip bones [3]

Detrusor (muscle) - smooth muscle in the bladder wall; fibers run in all directions to reduce the size of the organ when emptying it of urine [3]

Ectopic pregnancy - A potentially life-threatening condition in which EMBRYO IMPLANTATION occurs outside the cavity of the UTERUS. Most ectopic pregnancies (>96%) occur in the FALLOPIAN TUBES, known as TUBAL PREGNANCY. They can be in other locations, such as UTERINE CERVIX; OVARY; and abdominal cavity (PREGNANCY, ABDOMINAL). [4]

External iliac vein - formed when the femoral vein passes into the body cavity; drains the legs and leads to the common iliac vein. [3]

Fallopian tubes - (also, uterine tubes or oviducts) ducts that facilitate transport of an ovulated oocyte to the uterus. [3]

Fimbriae - fingerlike projections on the distal uterine tube. [3]

Follicle (ovarian) - ovarian structure of one oocyte and surrounding granulosa (and later theca) cells [3]

Fornix - superior portion of the vagina [3]

Fundus - dome-shaped region of the stomach above and to the left of the cardia . [3]

Hymen - thin membrane that sometimes partially covers the entrance to the vagina. [1]

Iliococcygeus - muscle that makes up the levator ani along with the pubococcygeus. [3]

Iliolumbar

Ilium - superior portion of the hip bone. [3]

Incontinence (urinary) - loss of ability to control micturition [3]

Infundibulum - (of the uterine tube) wide, distal portion of the uterine tube terminating in fimbriae [3]

Internal iliac vein - vein on either side of the body which is formed by the union of the external and internal iliac veins and passes upward to join with its fellow of the opposite side to form the inferior vena cava. [4]

Ischiococcygeus (muscle) - muscle that assists the levator ani and pulls the coccyx anteriorly [3]

Ischium - one of three bones that make up the coxal bone of the pelvic girdle. In tetrapods, it is the part of the pelvis that projects backward on the ventral side, and in primates, it bears the weight of the sitting animal. [4]

Isthmus - narrow, medial portion of the uterine tube that joins the uterus. [3]

Labia majora - (labia = “lips”; majora = “larger”), folds of hair-covered skin that begin just posterior to the mons pubis. [1]

Labia minora - (labia = “lips”; minora = “smaller”), which is thinner and more pigmented and extends medially to the labia majora. [1]

Lactiferous ducts - ducts that connect the mammary glands to the nipple and allow for the transport of milk. [3]

Lactiferous sinus - area of milk collection between alveoli and lactiferous duct. [3]

Levator ani (muscle) - muscle that makes up the levator ani along with the iliococcygeus. [3]

Lumbosacral - Region of the back including the LUMBAR VERTEBRAE, SACRUM, and nearby structures. [4]

Mammary glands - glands inside the breast that secrete milk. [3]

Mesovarium - an extension of the peritoneum that connects the ovaries to the broad ligament. [3]

Mons pubis - a pad of fat that is located at the anterior, over the pubic bone. After puberty, it becomes covered in pubic hair. [1]

Obstetric conjugate - narrowest fixed distance through which a baby's head must pass during vaginal delivery (10 com). [in text definition, Chapter 1.1)

Obturator internus - muscle deep to the gluteus maximus on the lateral surface of the thigh that laterally rotates the femur at the hip. [3]

Ovaries - female gonads that produce oocytes and sex steroid hormones (notably estrogen and progesterone). [3]

Ovarian ligament - ligament that attaches the ovary to the uterus. [chapter 1.2]

Ovum - haploid female gamete resulting from completion of meiosis II at fertilization. [3]

Parietal (branches) - (also, somatic branches) group of arterial branches of the thoracic aorta; includes those that supply blood to the thoracic cavity, vertebral column, and the superior surface of the diaphragm [3]

Pelvic girdle - hip girdle; consists of a single hip bone, which attaches a lower limb to the sacrum of the axial skeleton [3]

Pelvic diaphragm - muscular sheet that comprises the levator ani and the ischiococcygeus [3]

Perineum - diamond-shaped region between the pubic symphysis, coccyx, and ischial tuberosities [3]

Peritoneum - serous membrane that lines the abdominopelvic cavity and covers the organs found there [3]

Peritonitis - INFLAMMATION of the PERITONEUM lining the ABDOMINAL CAVITY as the result of infectious, autoimmune, or chemical processes. Primary **peritonitis** is due to infection of the PERITONEAL CAVITY via hematogenous or lymphatic spread and without intra-abdominal source. Secondary **peritonitis** arises from the ABDOMINAL CAVITY itself through RUPTURE or ABSCESS of intra-abdominal organs. [4]

Piriformis (muscle) - muscle deep to the gluteus maximus on the lateral surface of the thigh that laterally rotates the femur at the hip. [3]

Pubic symphysis - joint formed by the articulation between the pubic bodies of the right and left hip bones. [3]

Pubis - anterior portion of the hip bone. [3]

Pubocervial ligament - pubocervical ligament is attached to the cervix and extends to the posterior surface of the pubic symphysis. [6]

Pubococcygeus - muscle that makes up the levator ani along with the iliococcygeus. [3]

Puboprostaticum

Puborectalis

Pubovaginalis

Pudendal nerve - A nerve which originates in the sacral spinal cord (S2 to S4) and innervates the PERINEUM, the external GENITALIA, the external ANAL SPHINCTER and the external urethral sphincter. It has three major branches: the perineal nerve, inferior anal nerves, and the dorsal nerve of penis or clitoris. [4]

Round ligament - round ligament and medial ovarian ligaments develop from the embryonic gubernaculum. [6]

Rugae - (of the vagina) folds of skin in the vagina that allow it to stretch during intercourse and childbirth. [3]

Sacral plexus - nerve plexus associated with the lower lumbar and sacral spinal nerves. [3]

Sacrococcygeal (joint) - The body region between (and flanking) the SACRUM and COCCYX. [4]

Sacroiliac (joint) - a term used to describe the place where the sacrum and the iliac bones join. [2]

Sacrospinous ligament - ligament that spans the sacrum to the ischial spine of the hip bone. [3]

Sacrotuberous ligament - ligament that spans the sacrum to the ischial tuberosity of the hip bone. [3]

Sacrum - single bone located near the inferior end of the adult vertebral column that is formed by the fusion of five sacral vertebrae; forms the posterior portion of the pelvis [3]

Sphincter - A ring-shaped muscle that relaxes or tightens to open or close a passage or opening in the body. Examples are the anal sphincter (around the opening of the anus) and the pyloric sphincter (at the lower opening of the stomach). [5]

Suspensory ligament - bands of connective tissue that suspend the breast onto the chest wall by attachment to the overlying dermis. [3]

Symphysis pubis - see *pubic symphysis*

Trigone - area at the base of the bladder marked by the two ureters in the posterior–lateral aspect and the urethral orifice in the anterior aspect oriented like points on a triangle. [3]

Ureters - A pair of thick-walled tubes that transports urine from the KIDNEY PELVIS to the URINARY BLADDER. [4]

Urethra - transports urine from the bladder to the outside environment. [3]

Urinary bladder - A musculomembranous sac along the URINARY TRACT. URINE flows from the KIDNEYS into the bladder via the ureters (URETER), and is held there until URINATION. [5]

Urinary tract - bundle of axons in the central nervous system having the same function and point of origin. [3]

Uterosacral ligament - The uterosacral ligaments provide, along with the cardinal ligaments, the key support for the uterus within the pelvis and attach from the cervix below the peritoneum backward to the anterior aspect of the sacrum. [6]

Uterine tubes -(also, fallopian tubes or oviducts) ducts that facilitate transport of an ovulated oocyte to the uterus. [3]

Uterus - muscular organ that nourishes and supports the growing embryo. Its average size is approximately 5 cm wide by 7 cm long, and it has three sections. [1]

Vagina - muscular canal (approximately 10 cm long) that is the entrance to the reproductive tract. It also serves as the exit from the uterus during menses and childbirth. The outer walls of the anterior and posterior vagina are columns with ridges. The superior fornix meets the uterine cervix. The cervix is the opening to the uterus. [1]

Visceral (branches) - branches of the descending aorta that supply blood to the viscera [3]

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CHAPTER OVERVIEW

2: Physiology and Histology of the Female Reproductive System

2.1: Ovaries and Ovarian Cycle
2.2: Hormonal Control of the Ovarian Cycle
2.3: Functional Histology of the Uterine Tubes and Oocyte Journey into the Uterine Tube
2.4: The Uterus and Cervix
2.5: The Menstrual Cycle
2.6: Glossary

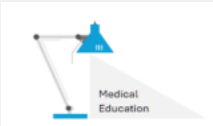
Chapter Author: Samar Hegazy, MD, Ph.D., MEHP

About this Chapter

This chapter starts with providing the physiologic principles of the hormonal control of the ovarian and menstrual cycle. The normal histologic structures and functional histology of relevant parts of the female reproductive system are integrated with physiological principles. The rest of the chapter covers abnormalities of the menstrual cycle, dysfunctional uterine bleeding, and common pathological conditions affecting different parts of the female reproductive system and the breast.

The main physiologic function of the female reproductive system is to produce hormones and gametes, support the development of the fetus, and carry out the delivery process. For details about the macro anatomy of different parts of the female reproductive system, please refer to Chapter 1.

The content of this chapter is appropriate for, or easily adapted for the following audiences:





Learning Objectives

By the end of this chapter, you should be able to

- Explain the timing and hormonal processes that regulate ovulation
- Evaluate normal histology of the uterus, fallopian tube, and ovary

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2.1: Ovaries and Ovarian Cycle

2.1.1 Ovaries

The **ovaries** are the female gonads responsible for the production of the female gametes (i.e., **oocytes**).

Normally, each female has two ovaries; each is about 2-3 cm long (i.e., almond-size). For details on the anatomy of the ovaries, please refer to Chapter 1.

Each ovary is both an **exocrine** (production of oocytes) and an **endocrine** (production of **estrogen** and **progesterone**) organ. The ovary is divided into an outer cortex and inner medulla (Figure 2.1.1, A and B, respectively). The ovarian medulla is composed of loose connective tissue with blood vessels, lymphatic vessels, and nerves (Figure 2.1.1, C). The ovary is suspended from the broad ligament of the uterus by the **mesovarium** (Figure 2.1.1, D), through which blood vessels enter and leave the ovary.

The exterior of the ovary is covered by a serous membrane, or serosa (Figure 2.1.1, E and F), composed of a simple cuboidal **epithelium** (mesothelium) overlying a band of dense connective tissue, the **tunica albuginea** (Figure 2.1.1, G and H). Usually, the serosa epithelium elsewhere is simple squamous epithelium. The serosal epithelium of the ovary was originally given the misnomer “germinal epithelium” because it was thought to be the site of germ cell formation.[1]

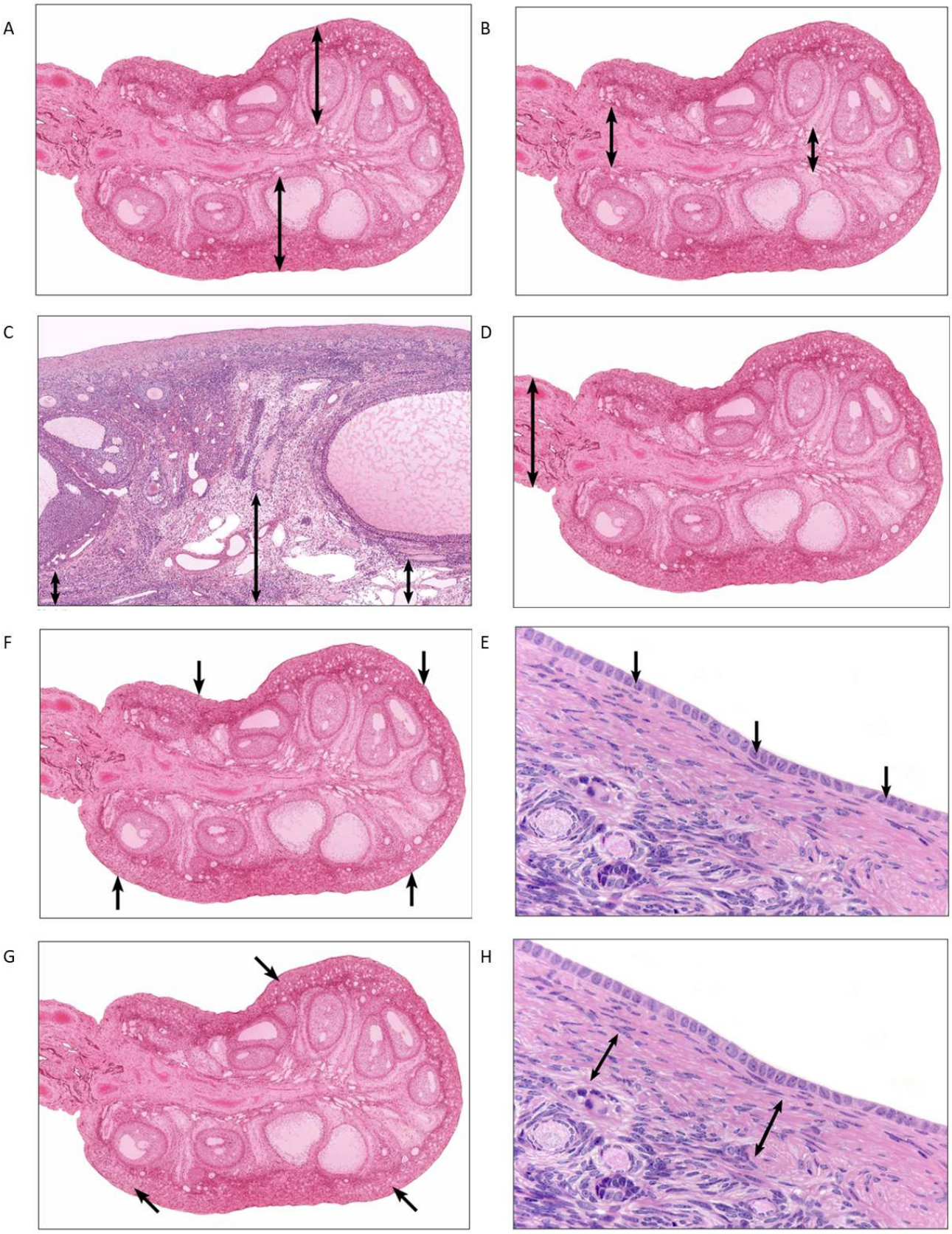

A
B
C
D
F
E
G
H

Figure 2.1.1 (A) Ovarian cortex, magnified 10x: the cortex forms the outer zone of the ovary. It contains follicles, the corpus luteum, and their degenerating elements. These elements are follicles undergoing atresia and corpora albicantia (singular. corpus albicans). (B). Ovarian medulla, magnified 10x: the medulla occupies the center of the ovary and is composed of connective tissue containing blood vessels, lymphatic vessels, and nerves that supply the ovary. (C) Ovarian medulla at higher magnification (40x). (D) Mesovarium, magnified 10x: The ovary is suspended from the broad ligament of the uterus by the mesovarium, through which blood vessels enter and leave the ovary. (E). Ovarian serosa (magnified 10x): The serosa (serous membrane or visceral peritoneum) covering the ovary possesses a simple cuboidal, rather than a simple squamous, epithelium. This epithelium is referred to as the germinal epithelium. (F). Simple cuboidal epithelium of the ovarian serosa at higher magnification (400x). (G) Tunica albuginea, magnified 10x: A tunica albuginea of dense connective tissue forms an outer shell beneath the serosa. (H) Tunica Albuginea at higher magnification (400x).

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The ovarian cortex is located underneath the tunica albuginea and is composed of the ovarian **stroma**, which forms the bulk of the adult ovary. The cortex hosts the ovarian **follicles** at different stages of development, as well as **atretic follicles**, **corpus luteum**, and **corpora albicans** (Figure 2.1.2, A, B).

Oocytes develop within the outer layer of the ovarian stroma. Each oocyte is surrounded by supporting cells. The ovarian follicle is composed of an oocyte and its supporting cells.

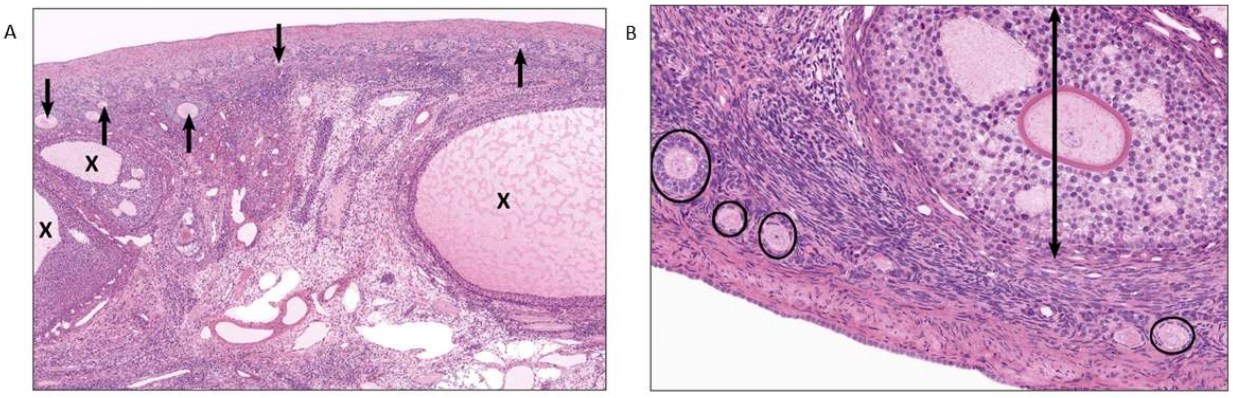


Figure 2.1.2 (A) Small follicles (arrows) are clustered beneath the tunica albuginea, while larger follicles (X) are located deeper in the cortex. 40x. (B) The surface of the ovary shows the position and size of the smallest follicles, the primordial and primary unilaminar follicles, located just beneath the tunica albuginea. Larger follicles (primary multilaminar and secondary follicles) are located deeper in the cortex. Follicles are epithelial structures that house developing oocytes, the germ cells. 100x.

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2.1.2 Ovarian Cycle

The ovarian cycle is the set of predictable changes in a female's oocytes and ovarian follicles. The ovarian cycle is approximately 28 days during a woman's reproductive years and is correlated with the menstrual cycle. It is important to note that the ovarian cycle is different from the menstrual cycle. The ovarian cycle includes two interrelated processes: **oogenesis** (the production of female gametes) and **folliculogenesis** (the growth and development of ovarian follicles).

2.1.2.1 Oogenesis

Also known as gametogenesis, oogenesis starts during fetal life. The process begins with the ovarian stem cells, or **oogonia** (Figure 2.1.3). Oogonia are formed during fetal development and divide via mitosis (like spermatogonia in the testis). Unlike spermatogonia, oogonia form primary oocytes in the fetal ovary before birth. The primary oocytes are arrested in this stage of **meiosis** I until puberty. At the beginning of puberty, the primary oocyte resumes meiosis and continues until the woman is near menopause. The number of primary oocytes in the ovaries declines from one to two million in an infant to approximately 400,000 at puberty, to zero by the end of menopause.[2]

The release of an oocyte from the ovary is called **ovulation**. This process marks the transition from puberty into reproductive maturity for women. From this time and throughout the female reproductive years, ovulation occurs approximately every 28 days. A surge of **luteinizing hormone** before ovulation triggers the primary oocytes to resume meiosis. This results in the transition of a primary oocyte to a secondary oocyte. This meiotic cell division does not result in two identical cells. Because the cytoplasm is divided unequally, one daughter cell is much larger than the other. This larger cell is the secondary oocyte that eventually leaves the ovary during ovulation. The smaller cell is called the first polar body. If the first polar body completes meiosis, it will produce a second polar body. It will remain a first polar body if it does not complete meiosis. In either case, polar bodies undergo disintegration. Therefore, although oogenesis produces up to four cells, only one survives, which is the secondary oocyte.[3]

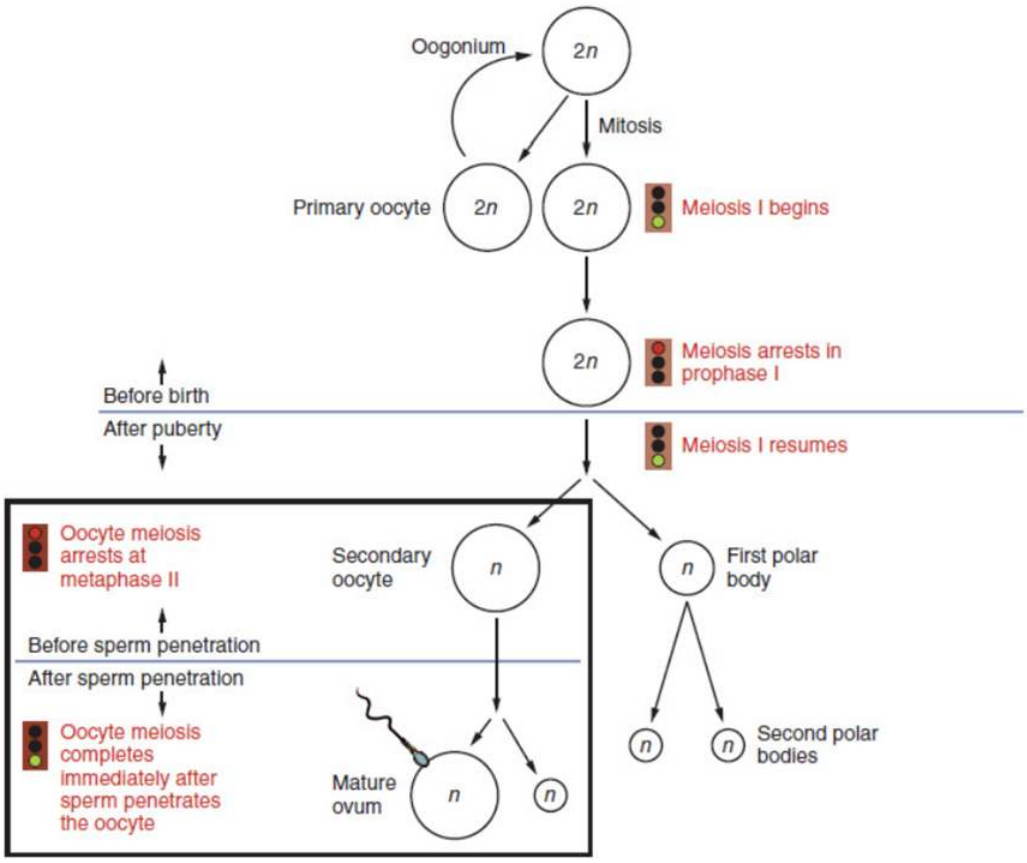


Figure 2.1.3 Oogenesis. The unequal cell division of oogenesis produces one to three polar bodies that later degrade, as well as a single haploid ovum, which is produced only if a sperm cell penetrates the secondary oocyte.

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- How does the diploid secondary oocyte become an ovum—the haploid female gamete?

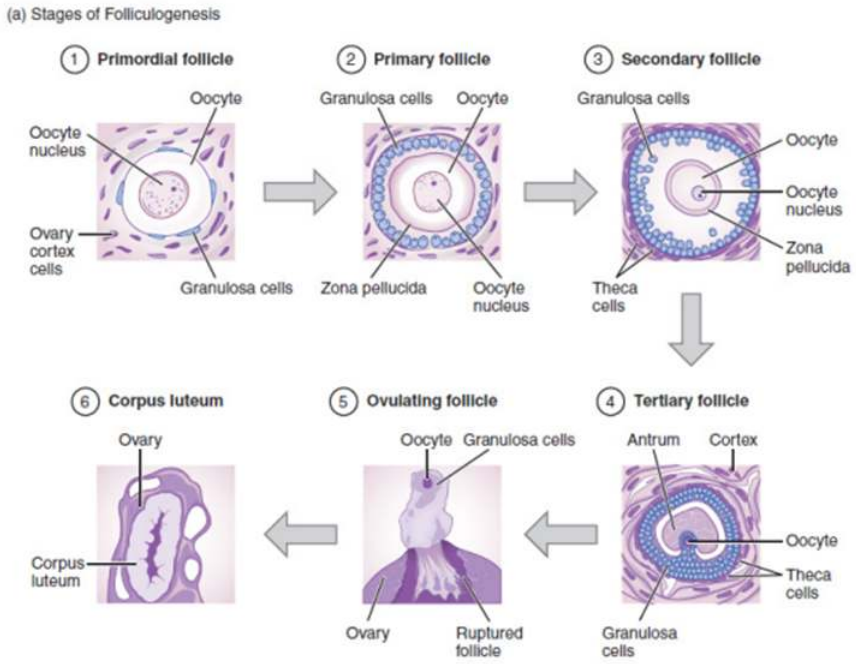
Meiosis of a secondary oocyte is completed only if a sperm succeeds in penetrating its barriers. Meiosis II then resumes, producing one **haploid ovum** that, at the instant of **fertilization** by a (haploid) sperm, becomes the first diploid cell of the new offspring (a **zygote**). Thus, the ovum can be thought of as a brief, transitional, haploid stage between the diploid oocyte and diploid zygote.

The larger amount of **cytoplasm** contained in the female gamete is used to supply the developing zygote with nutrients between fertilization and implantation into the uterus. Interestingly, sperm contributes only DNA at fertilization—not cytoplasm. Therefore, the cytoplasm and all of the cytoplasmic organelles in the developing embryo are of maternal origin. This includes mitochondria, which contain their own DNA. Scientific research in the 1980s determined that mitochondrial DNA was maternally inherited, meaning that you can trace

your mitochondrial DNA directly to your mother, her mother, and so on back through your female ancestors.[4]

2.1.2.2 Folliculogenesis

Ovarian follicles are oocytes and their supporting cells. Folliculogenesis is the process of the development of ovarian follicles to prepare for ovulation (Figure 2.1.4). Approximately every 28 days, typically, one ovarian follicle undergoes ovulation. Follicular atresia is the death of ovarian follicles that can happen at any point during follicular development. A female infant will have one to two million oocytes within her ovarian follicles at birth. Because of follicular atresia, this number declines throughout life until it reaches zero around menopause. Based on the maturation stages of the follicles, there are different types of ovarian follicles: primordial, primary, secondary, and tertiary. The oocytes inside the follicles remain as primary oocytes until before ovulation.[5]



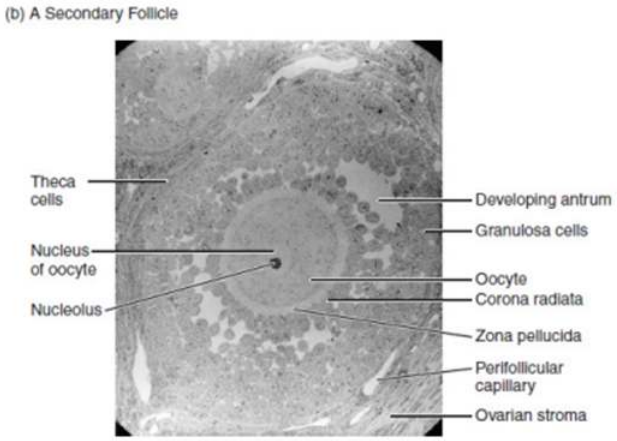


Figure 2.1.4 Folliculogenesis. (A) The maturation of a follicle is shown in a clockwise direction proceeding from the primordial follicles. FSH stimulates the growth of a tertiary follicle, and LH stimulates estrogen production by granulosa and theca cells. Once the follicle is mature, it ruptures and releases the oocyte. Cells remaining in the follicle then develop into the corpus luteum. (B) In this electron micrograph of a secondary follicle, the oocyte, theca cells (thecae folliculi), and developing antrum are visible. EM × 1100.
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- Primordial Follicles

Folliculogenesis begins with follicles in a resting state. Follicles in the resting state are called **primordial follicles**. They are present in newborn females and are the dominant follicle type in the adult ovary (Figure 2.1.5, A). In primordial follicles, the oocyte is surrounded by a single flat layer of support cells called granulosa cells (Figure 2.1.5, B and C). Primordial follicles can remain in the resting state for years, even until just before menopause. After puberty, a few primordial follicles become primary follicles in response to recruitment signals.[6]

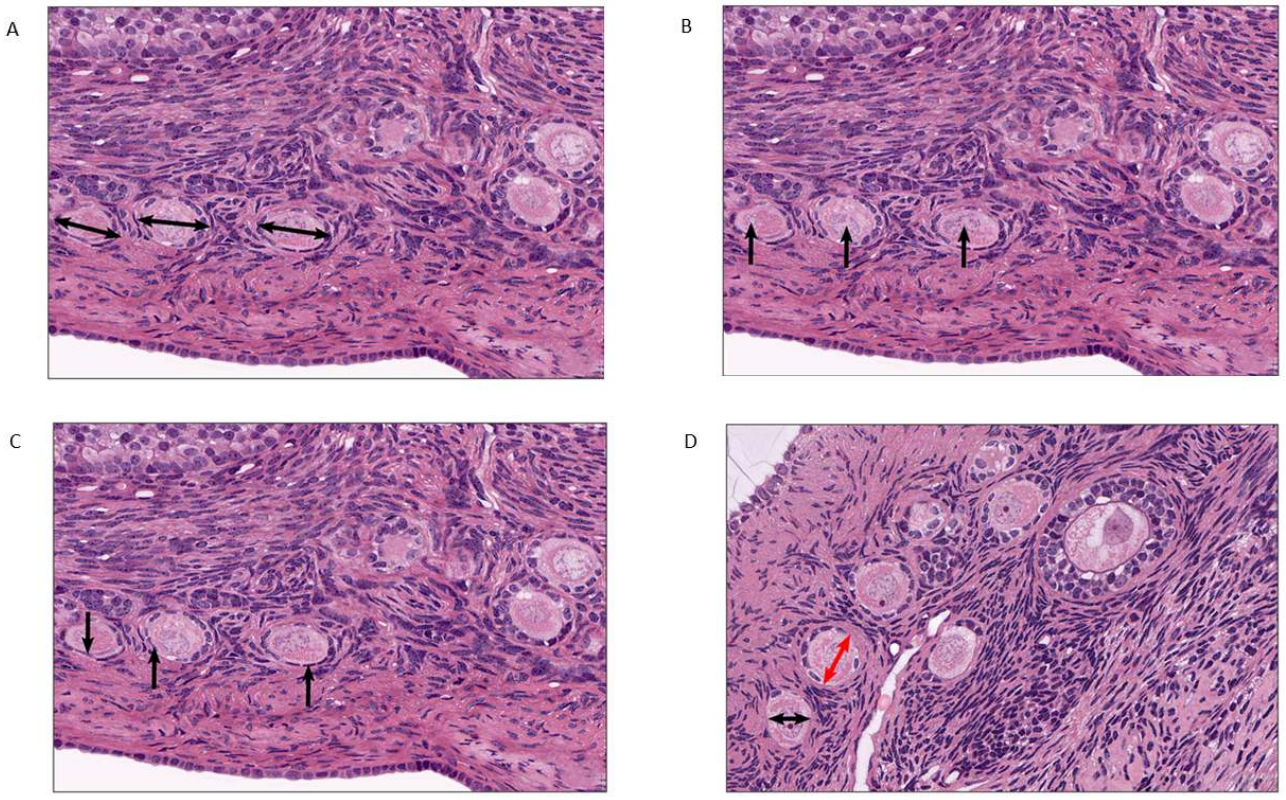


Figure 2.1.5 (A) Primordial follicles frequently appear in clusters near the surface of the ovarian cortex. These follicles develop in fetal ovaries during gestation and are seen in this position throughout the reproductive life of the female. Primordial follicles consist of a primary oocyte (B) surrounded by follicular cells, composed of a simple squamous epithelium and its underlying basement membrane (C). 400x. (B) Primary oocytes correspond to the same developmental stage as primary spermatocytes. However, diploid primary oocytes are formed before birth and arrest in the prophase of the first meiotic division at that time. A

primary oocyte has a large nucleus, displaying dispersed chromatin, and a prominent nucleolus. (D) One follicle (red arrow) is in transition, lined with simple squamous follicular cells to the right of the arrow (primordial follicle) and by simple cuboidal follicular cells (primary unilaminar follicle) to the left of the arrow. 400x.

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- Primary Follicles

These primary follicles are immature growing follicles. In the primary follicles, the primary oocyte is surrounded by a single layer of granulosa cells. These granulosa cells become active and increase in size and number as they proliferate, transitioning from a flat or squamous shape to a rounded, cuboidal shape. The primary unilaminar follicles are larger than primordial follicles; their follicular cells have increased in height to form a simple cuboidal or columnar epithelium (Figure 2.1.6, A). The primary oocyte has also increased in size from that present in the primordial follicle (Figure 2.1.6, B). Follicular cells continue to increase in volume and number, becoming a stratified epithelial layer and forming a primary multilaminar follicle (Figure 2.1.6, C). In the primary multilaminar follicle, the follicular cells are now termed granulosa cells (Figure 2.1.6, E), and the stromal cells surrounding the follicles differentiate into **thecal cells** (theca folliculi) (Figure 2.1.6, F). A thick glycoprotein layer develops between the oocyte and the zona granulosa, called the Zona Pellucida (Figure 2.1.6, G), and plays a critical role in

fertilization.

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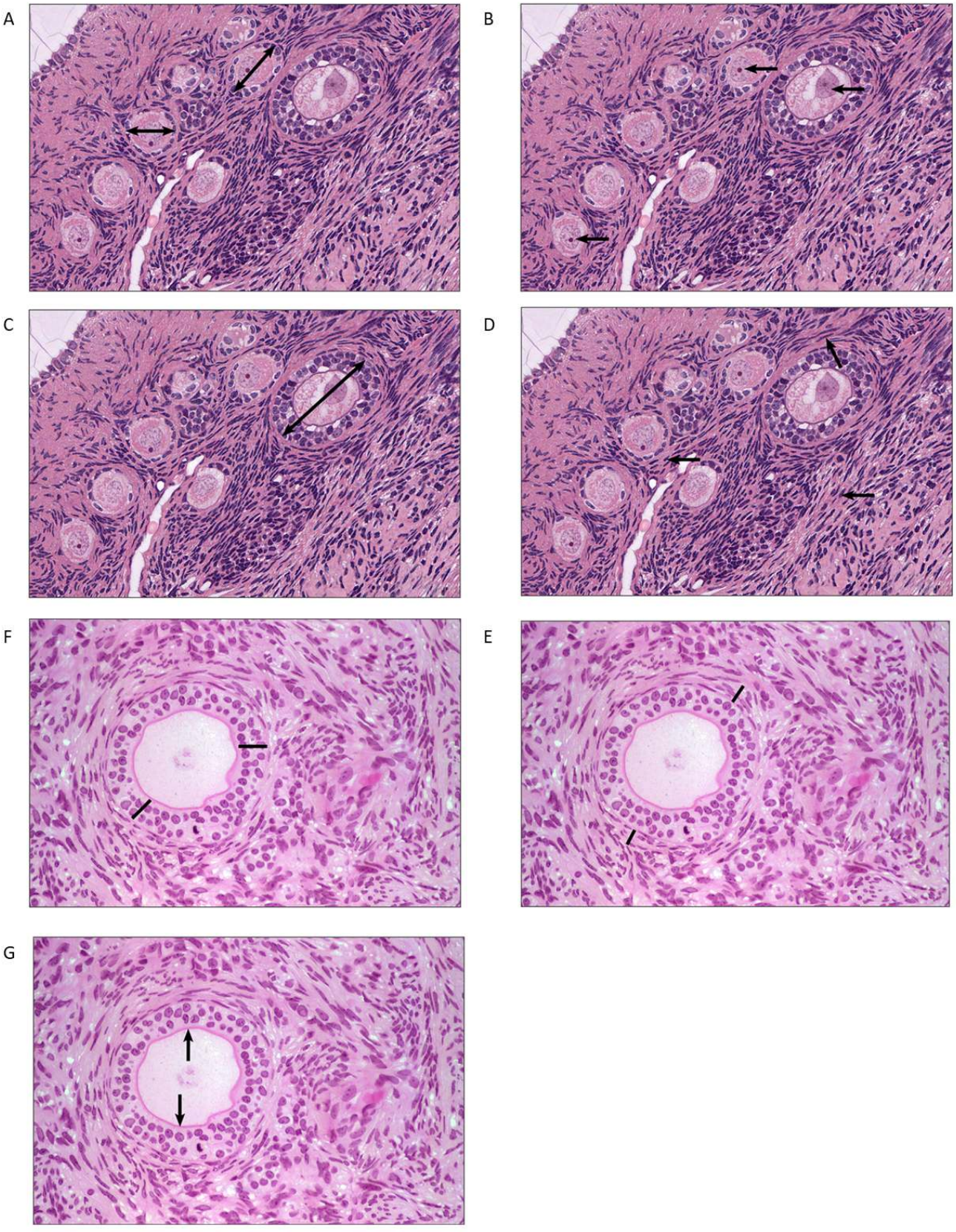

A
B
C
D
F
E
G

Figure 2.1.6 (A) Primary unilaminar follicles. (B) Primary oocytes. Each primordial and primary follicle contains a primary oocyte. Each oocyte increases in diameter as the follicular cells increase in size and number. (C) A primary multilaminar follicle. (D) Stromal cells are located in the connective tissue surrounding the follicles. These connective tissue cells are multipotential and produce not only the connective tissue stroma of the ovary but also differentiate into the thecal layers surrounding advanced follicles. (E) Granulosa cells in a primary multilaminar follicle. (F) Stromal cells surrounding the follicle differentiate into the theca (theca folliculi). (G) Zona pellucida, a highly refractile, glycoproteinaceous layer, is prominent around the oocyte at this stage. 400x

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- Secondary Follicles

The primary follicle develops into a secondary follicle (Figure 2.1.7). The secondary follicles look very similar to primary follicles, except that they are larger, they have more follicular cells, and there are small accumulations of fluid in the spaces between granulosa cells called follicular fluid (which provides oocytes with nutrients). These spaces gradually coalesce to form an **antrum**. The primary oocyte remains arrested in the prophase of the first meiotic division. Granulosa cells surrounding the antrum are now called the stratum granulosum. The granulosa cells surrounding the primary oocyte are called the cumulus oophorus (Greek for "egg-bearing heap"). The surrounding theca differentiates into two layers: the outer, more fibrous (spindle-shaped like cells) theca externa cells and the inner (rounded) theca internal cells that secrete follicular fluid, androgens, and progesterone in response to the luteinizing hormone (LH). The granulosa cells convert the androgens estrogen. Granulosa cells produce estrogen in response to follicular stimulating hormone (FSH); granulosa cells in pre-ovulatory follicles also respond to LH and produce progesterone (as will be explained in the section on hormonal control of the ovarian cycle).[7]

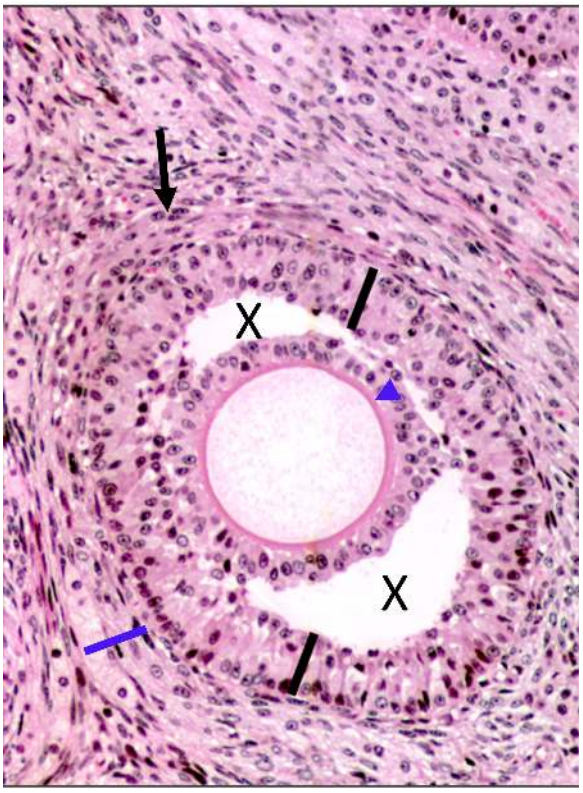


Figure 2.1.7 A secondary follicle; antral spaces (x), stratum granulosum (black rods), theca interna (blue rod), and theca externa (black arrow). Zona pellucida (blue arrowhead) is surrounding a primary oocyte. Granulosa cells around the primary oocyte and zona pellucida are called cumulus oophorus (200x.)
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- Tertiary (Graffian) Follicles

Tertiary (Graffian) follicles are follicles in which the antrum becomes large and fully formed (Figure 2.1.8, A and B). Therefore, tertiary follicles are also called antral follicles. The first meiotic division is now completed, and the oocyte is now a secondary oocyte. The oocyte, zona pellucida, and follicular cells surrounding the oocyte (known as the corona radiata) are all expelled at ovulation and enter the fallopian tube. Once released, the oocyte begins its second meiotic division, as far as metaphase II. Several follicles can be at the same maturation stage at the same time. Most of the tertiary follicles undergo follicular atresia (Figure 2.1.8, C). The one that does not die will continue to grow and develop until ovulation. Around 99% of the ovarian follicles undergo atresia.[8]

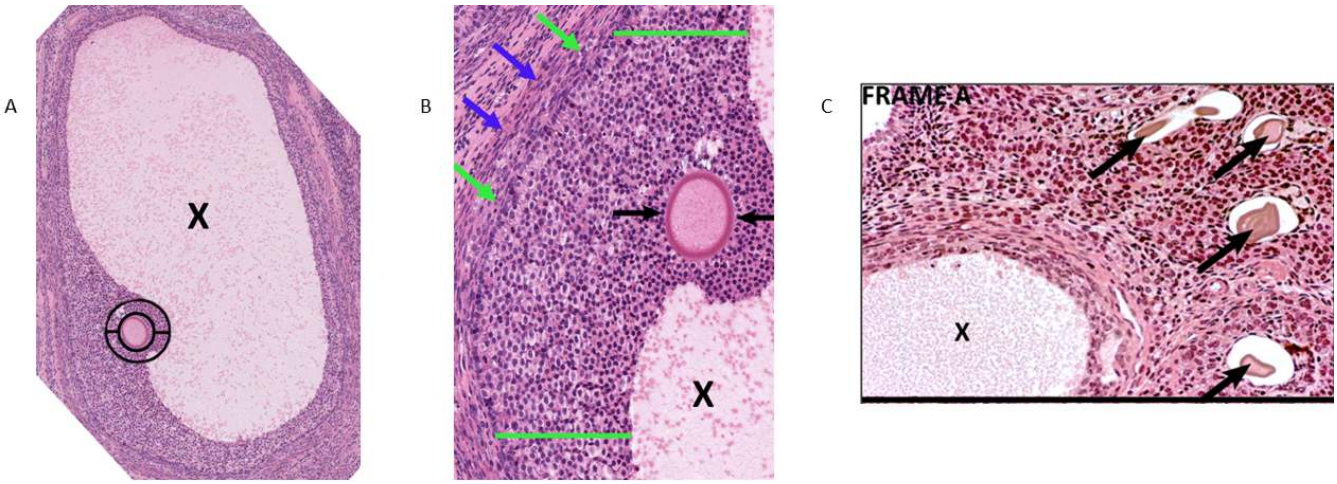


Figure 2.1.8 (A) A tertiary or Graffian follicle; antrum (x); Stratum granulosal cells form a hillock surrounding the oocyte, termed the cumulus oophorus (black circles). 100x (B) The first row of cumulus cells outside the zona pellucida is the corona radiata (black arrows), stratum granulosum (green rods), theca interna (green arrows), and theca externa (blue arrow). 1000x. (C) Two different types of atretic follicles are seen. The antrum of an atretic secondary follicle (X) is visible; note the granulosal cells sloughed into the antrum. Each atretic follicle labeled with an arrow is composed only of its zona pellucida; the remainder of each follicle has degenerated. 100x.

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Glossary Terms

Antrum

Fluid-filled chamber that characterizes a mature tertiary (antral) follicle

Corpora albicans

Nonfunctional structure remaining in the ovarian stroma following structural and functional regression of the corpus luteum

Corpus luteum

Transformed follicle after ovulation that secrets progesterone

Cytoplasm

Internal material between the cell membrane and nucleus of a cell, mainly consisting of a water-based fluid called cytosol, within which are all the other organelles and cellular solute and suspended materials

Endocrine

Groups of cells that release chemical signals into the intercellular fluid to be picked up and transported to their target organs by blood

Epithelium

Refers to layers of cells that line hollow organs and glands. It is also those cells that make up the outer surface of the body

Estrogen

Class of predominantly female sex hormones important for the development and growth of the female reproductive tract, secondary sex characteristics, the female reproductive cycle, and the maintenance of pregnancy

Exocrine

Group of epithelial cells that secrete substances through ducts that open to the skin or to internal body surfaces that lead to the exterior of the body

Fertilization

Occurs when sperm and an oocyte combine. Because each of these reproductive cells is a haploid cell containing half of the genetic material needed to form a human being, their combination forms a diploid cell. This new single cell is called a zygote

Follicle

Ovarian structure of one oocyte and surrounding granulosa (and later theca) cells

Folliculogenesis

Development of ovarian follicles from primordial to tertiary under the stimulation of gonadotropins

Haploid ovum

Contains a single copy of each chromosome with the sex chromosome always an X chromosome

Luteinizing hormone

Anterior pituitary hormone that triggers ovulation and the production of ovarian hormones in females, and the production of testosterone in males

Meiosis

Type of CELL NUCLEUS division, occurring during maturation of the GERM CELLS. Two successive cell nucleus divisions following a single chromosome duplication (S PHASE) result in daughter cells with half the number of CHROMOSOMES as the parent cells

Mesovarium

Extension of the peritoneum that connects the ovaries to the broad ligament

Oocytes

Cells that result from the division of the oogonium and undergoes meiosis I at the LH surge and meiosis II at fertilization to become a haploid ovum

Oogensis

process by which oogonia divide by mitosis to primary oocytes, which undergo meiosis to produce the secondary oocyte and, upon fertilization, the ovum

Ovaries

Female gonads that produces oocytes and sex steroid hormones (notably estrogen and progesterone)

Ovulation

Release of a secondary oocyte and associated granulosa cells from an ovary

Primordial follicles

Least developed ovarian follicles that consist of a single oocyte and a single layer of flat (squamous) granulosa cells

Progesterone

Sex hormone important in regulating the reproductive cycle in those with ovaries and the maintenance of pregnancy

Stroma

Connective tissue cells of an organ found in the loose connective tissue. These are most often associated with the uterine mucosa and the ovary as well as the hematopoietic system and elsewhere

Thecal cells

Estrogen-producing cells in a maturing ovarian follicle

Tunica albuginea

Fibrous-elastic sheath of connective tissue that surrounds the shaft and glans of the clitoris

Zygote

Fertilized OVUM resulting from the fusion of a male and a female gamete

Footnotes

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4. Lang, Damaris-Lois. "Anatomy and Physiology of the Female Reproductive System." Chapter 43, Bio 140 Human Biology I, (2022). Hostas Library. CC BY NC 4.0
5. Karve, Simantini, 2022
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7. Paxton, Steve, Michelle Peckham, Adele Knibbs, Steve Paxton, Adele Knibbs, and Michelle Peckham. "Female Reproductive system." The Leeds Histology Guide, (2003). University of Leeds.
8. Paxton et al., 2003.

Image Acknowledgements

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2.2: Hormonal Control of the Ovarian Cycle

> Before learning the details of the hormonal control of the ovarian cycle, let's have a brief overview of the hypothalamic-pituitary axis.

2.2.1 The Hypothalamic–Pituitary Axis

The **hypothalamus** is made up of a series of nuclei located at the base of the brain. The hypothalamic neurons contract synapses throughout the central nervous system. The hypothalamus is linked with the anterior **pituitary gland** by the portal system of blood supply. The posterior pituitary gland or neurohypophysis is like a "repository" for the hypothalamic hormones **ADH** and **oxytocin**. In fact, it contains the axonal terminals of neurons arising in the **supraoptic (SO) nucleus** that produces ADH and the **paraventricular nucleus (PVN)** that produces oxytocin in the hypothalamus. The hypothalamus produces **gonadotropin-releasing hormone (GnRH),** a decapeptide that stimulates gonadotropins biosynthesis and secretion: **follicle-stimulating hormone (FSH)** and **luteinizing hormone (LH)**. Pulsatile GnRh input is required for the activation and maintenance of GnRh receptors; changes in GnRH pulse frequency affect the absolute levels and the ratio of LH and FSH release.

The anterior pituitary gland contains five hormone-producing cell types: gonadotrophs (LH and FSH), lactotrophs (PRL), somatotrophs (GH), thyrotrophs (TSH), and adrenocorticotrophs (ACTH). All the pituitary hormones are stimulated by hypothalamic neuroendocrine secretion, while PRL is under **tonic inhibition**, and its expression is primarily under inhibitory regulation by **dopamine**. In fact, the gonadotropins (LH and FSH) are regulated by GnRH. The biosynthesis of ACTH is stimulated by the corticotropin-releasing hormone. The secretion of TSH is induced by the thyrotropin-releasing hormone.[9]

2.2.2 Follicular Phase

In humans, follicular development from the **primordial** to the early **tertiary follicle** occurs in approximately two months. The stage of development from a tertiary follicle to ovulation of a secondary **oocyte** spans approximately 28 days. The hormonal regulation of follicular development involves GnRH, LH, and FSH.

2.2.2.1 Early Follicular Phase

In the early follicular phase, the ovary is least hormonally active, resulting in low serum **estradiol** and **progesterone** concentrations. Influenced by the negative feedback effects of estradiol, progesterone, and probably **inhibin**, there is an increase in the hypothalamus's GnRH production (in a pulsatile manner). GnRH subsequently stimulates the anterior pituitary gland to produce the gonadotropins FSH and LH (Figure 2.2.9), increasing serum follicle-stimulating hormone (FSH) concentrations by approximately 30%. At this time, LH pulse frequency increases rapidly from one pulse every four hours in the late luteal phase to one pulse every 90 min in the early follicular phase. The FSH and LH leave the pituitary through the

bloodstream to the ovaries. In the ovaries, they bind to receptors on the granulosa and theca cells of the follicles.

This small increase in FSH secretion is required to recruit the next cohort of developing follicles, one of which will become the dominant and then ovulatory follicle during that cycle (hence its name of follicle-stimulating hormone).

The LH stimulates the granulosa and theca cells of the follicles to produce the sex steroid hormone **estradiol**, a type of estrogen. This ovarian cycle phase, when the tertiary follicles are growing and secreting estrogen, is known as the follicular phase. The more **granulosa** and **theca** cells a follicle has (the larger and more developed it is), the more estrogen it will produce in response to LH stimulation. As a result of these large follicles producing large amounts of estrogen, systemic plasma estrogen concentrations increase.

Serum anti-Müllerian hormone (AMH) has been used as a potential marker of ovarian health and aging. It is secreted by small antral follicles and correlates with the total number of ovarian antral follicles. The variability of serum AMH across the menstrual cycle appears to be minimal.

Ultrasonographically, the ovary is quiescent in the early follicular phase, except for the occasionally visible resolving corpus luteum from the previous cycle. It is possible to see small follicles of 3 to 8 mm in diameter at this time. The **endometrium** is relatively indistinct during **menses**, becoming a thin line once menses are completed. In this phase, the endometrium appears as a brightly echogenic stripe comprising the basal layer; minimal fluid can be appreciated endovaginally within the endometrium in the menstrual phase.[10]

2.2.2.2 Mid Follicular Phase

In the mid-follicular phase, the moderate rise in FSH secretion progressively stimulates **folliculogenesis** and estradiol production, leading to the progressive growth of the cohort of follicles selected. When several follicles initially grow to the antral stage (several antral follicles of 9–10 mm are visible on ovarian ultrasonography), their granulosa cells increase in size and divide, producing increasing serum concentrations of estradiol via FSH stimulation of **aromatase** and then inhibin A from the granulosa cells in the ovaries. The increase in estradiol production negatively affects the hypothalamus–pituitary axis, suppressing the FSH and LH concentrations as well as the LH pulse amplitude. At the same time, the GnRH pulse generator accelerates slightly to a mean LH pulse frequency of approximately one per hour (versus one per 90 min in the early follicular phase). This GnRH stimulation is probably due to the negative feedback effects of progesterone from the previous luteal phase.

Several antral follicles of 9–10 mm are visible on ovarian ultrasonography. There is a proliferation of the uterine endometrium, which thickens with an increase in the number of glands and the typical aspect of a “triple stripe” caused by increased estradiol concentrations. The endometrium's triple stripe or trilaminar appearance comprises an outer echogenic basal layer, a middle hypoechoic functional layer, and an inner echogenic stripe at the central interface.

2.2.2.3 Late Follicular Phase

In the late follicular phase, the week before ovulation, the growing follicle induces the increase of estradiol and inhibin A. This increase in estradiol is responsible for reducing the concentrations of FSH and LH because of negative feedback effects. Once the dominant follicle has been selected, FSH induces LH receptors in the ovary and increases ovarian secretion of intrauterine growth factors.

After a single dominant follicle has been selected, it increases by 2 mm per day until it reaches a mature size of 20 to 26 mm. The rest of the growing cohort of follicles gradually stop developing and undergo **atresia**. The uterine endometrium gradually thickens because of the rising estradiol concentrations and changes in the cervical mucus; in particular, there is an increase in the amount and “stringiness.” Stringiness refers to the stretchy quality of the cervical mucous around the time of ovulation.

2.2.3 Ovulation

Following a classic negative feedback loop, the high estrogen concentrations will stimulate the hypothalamus and pituitary to reduce the production of GnRH, LH, and FSH. Because the large tertiary follicles require FSH to grow and survive at this point, this decline in FSH caused by negative feedback leads most of them to die (atresia). Typically, only one follicle, now called the dominant follicle, will survive this reduction in FSH, and this follicle will be the one that releases an oocyte.

Scientists have studied many factors that lead to a particular follicle becoming dominant: size, the number of granulosa cells, and the number of FSH receptors on those granulosa cells all contribute to a follicle becoming the one surviving dominant follicle. When only one dominant follicle remains in the ovary, it again begins to secrete estrogen. It produces more estrogen than all developing follicles did before negative feedback. It produces so much estrogen that normal negative feedback doesn’t occur. Instead, these extremely high concentrations of systemic plasma estrogen trigger a regulatory switch in the anterior pituitary that responds by secreting large amounts of LH and FSH into the bloodstream (Figure 2.2.9).

The positive feedback loop by which more estrogen triggers the release of more LH and FSH only occurs at this point in the cycle. This large burst of LH (called the LH surge) leads to the ovulation of the dominant follicle. The LH surge induces many changes in the dominant follicle; the primary oocyte in the dominant follicle completes its first **meiotic division** and becomes a secondary oocyte. As noted earlier, the polar body that results from unequal cell division simply degrades. The LH surge also triggers proteases (enzymes that cleave proteins) to break down structural proteins in the ovary wall on the surface of the bulging dominant follicle. This degradation of the wall, combined with pressure from the large, fluid-filled antrum, results in the expulsion of the oocyte surrounded by granulosa cells into the peritoneal cavity. This release is ovulation and occurs approximately 36 hours after the LH surge.

At the same time, there is an increase in the secretion of **plasminogen activator** and other cytokines required for the ovulation process. Before the oocyte is released, the granulosa cells begin to luteinize and produce progesterone. Progesterone is responsible for reducing LH pulse that becomes less frequent by the termination of the surge. Follicular rupture and oocyte release are closely related to the LH surge; as a result, serum or urine LH measurements can be used to estimate the time of ovulation in women.

As the endometrium becomes more uniformly bright, the “triple stripe” image is lost. This is due to the impact of progesterone increase responsible for cessation of mitoses and “organization” of the glands.[11]

2.2.4 Luteal Phase

The surge of LH also stimulates a change in the granulosa and theca cells that remain in the follicle after ovulation. This change is called **luteinization** (recall that the full name of LH is luteinizing hormone), and it transforms the collapsed follicle into a new endocrine structure called the corpus luteum, a term meaning “yellowish body” (Figure 2.2.9).

Instead of estrogen, the luteinized granulosa and theca cells of the corpus luteum begin to produce large amounts of the sex steroid hormone progesterone. The post-ovulatory phase of progesterone secretion is known as the luteal phase of the ovarian cycle. Progesterone triggers negative feedback at the hypothalamus and pituitary, which keeps GnRH, LH, and FSH secretions low, so no new dominant follicles develop at this time. A decrease in LH secretions results in a gradual fall in progesterone and estradiol production by the corpus luteum in the absence of a fertilized oocyte.

If the oocyte is fertilized after ovulation, it is implanted in the endometrium. The early embryo begins to produce human chorionic gonadotropin (HCG), which maintains the corpus luteum and progesterone production until the placenta can take over progesterone production. Inhibin A is also produced by the corpus luteum, and serum concentrations of inhibin A peak in the mid-luteal phase. Inhibin B secretion is virtually absent during the luteal phase. Progesterone is critical for the establishment and maintenance of pregnancy; therefore, it is a “pro-gestational hormone.” If pregnancy does not occur within 10 to 12 days, the corpus luteum will stop secreting progesterone and degrade into the corpus albicans, a nonfunctional “whitish body” that will disintegrate in the ovary over several months. In response to estradiol and progesterone decline due to the resolution of the corpus luteum, the endometrium loses the blood supply and starts to break and slough. This is called menstruation, which marks the low point for estrogen activity and is the starting point of a new cycle. Menstruation is the cyclic, orderly sloughing of the uterine lining approximately 14 days after the LH surge. Simultaneously, secondary to reduced progesterone levels, the hypothalamic–pituitary axis induces the FSH and LH secretion, and a new cycle starts with the follicular phase involving a

new cohort of early tertiary follicles starting to grow and secrete estrogen.[12]

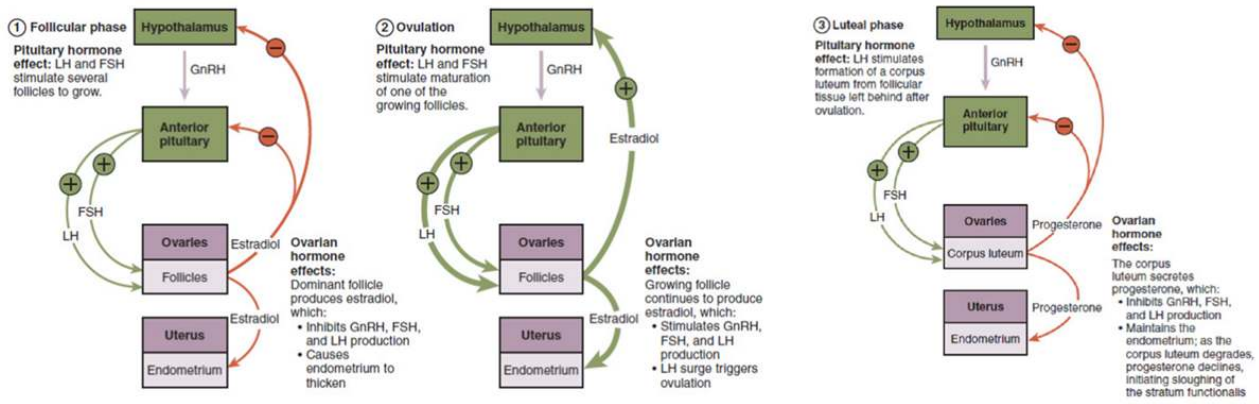


Figure 2.2.9 Hormonal regulation of ovulation. The hypothalamus and pituitary gland regulate the ovarian cycle and ovulation. GnRH activates the anterior pituitary to produce LH and FSH, which stimulate the ovaries' production of estrogen and progesterone.

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Glossary Terms

Antidiuretic hormone (ADH)
Hypothalamic hormone that is stored by the posterior pituitary and that signals the kidneys to reabsorb water

Aromatase
Enzyme that catalyzes the desaturation (aromatization) of the ring A of C19 androgens and converts them to C18 estrogens. In this process, the 19-methyl is removed. This enzyme is membrane-bound, located in the endoplasmic reticulum of estrogen-producing cells of ovaries, placenta, testes, adipose, and brain tissues

Atresia
Absence or abnormal narrowing of an opening or passage in the body

Dopamine
One of the catecholamine NEUROTRANSMITTERS in the brain. It is derived from TYROSINE and is the precursor to NOREPINEPHRINE and EPINEPHRINE. Dopamine is a major transmitter in the extrapyramidal system of the brain, and important in regulating movement

Endometrium
Inner lining of the uterus, part of which builds up during the secretory phase of the menstrual cycle and then sheds with menses

Estradiol
17-beta-isomer of estradiol, an aromatized C18 steroid with hydroxyl group at 3-beta- and 17-beta-position. Estradiol-17-beta is the most potent form of mammalian estrogenic steroids

Follicle stimulating hormone (FSH)
Interior pituitary hormone that stimulates the production and maturation of sex cells

Folliculogenesis
Development of ovarian follicles from primordial to tertiary under the stimulation of gonadotropins

Granulosa

Supportive cells in the ovarian follicle that produce estrogen

Hypothalamus

Major region of the diencephalon that is responsible for coordinating autonomic and endocrine control of homeostasis

Inhibin

Hormone secreted by the gonads that inhibits FSH production by the anterior pituitary ischemia

Luteinization

Formation of CORPUS LUTEUM. This process includes capillary invasion of the ruptured OVARIAN FOLLICLE, hypertrophy of the GRANULOSA CELLS and the THECA CELLS, and the production of PROGESTERONE

Luteinizing hormone (LH)

Anterior pituitary hormone that triggers ovulation and the production of ovarian hormones in females, and the production of testosterone in males

Meiotic division

Type of CELL NUCLEUS division, occurring during maturation of the GERM CELLS. Two successive cell nucleus divisions following a single chromosome duplication (S PHASE) result in daughter cells with half the number of CHROMOSOMES as the parent cells

Menses

Shedding of the inner portion of the endometrium out though the vagina; also referred to as menstruation

Oxytocin

Oxytocin injection is used to begin or improve contractions during labor. Oxytocin also is used to reduce bleeding after childbirth. It also may be used along with other medications or procedures to end a pregnancy. Oxytocin is in a class of medications called oxytocic hormones

Paraventricular nucleus (PVN)

Nucleus in the anterior part of the HYPOTHALAMUS

Pituitary Gland

Bean-sized organ suspended from the hypothalamus that produces, stores, and secretes hormones in response to hypothalamic stimulation (also called hypophysis)

Plasminogen activator

Heterogeneous group of proteolytic enzymes that convert PLASMINOGEN to FIBRINOLYSIN. They are concentrated in the lysosomes of most cells and in the vascular endothelium, particularly in the vessels of the microcirculation

Primordial follicles

Least developed ovarian follicles that consist of a single oocyte and a single layer of flat (squamous) granulosa cells

Progesterone

Sex hormone important in regulating the reproductive cycle in those with ovaries and the maintenance of pregnancy

Supraoptic nucleus

Hypothalamic nucleus overlying the beginning of the OPTIC TRACT

Tertiary follicle

(also, antral follicles) Ovarian follicles with a primary or secondary oocyte, multiple layers of granulosa cells, and a fully formed antrum

Theca

Estrogen-producing cells in a maturing ovarian follicle

Tonic inhibition

form of neurotransmission usually thought to reduce the excitability of all neurons

Footnotes

9. Section adapted from Nappi, Luigi, Felice Sorrentino, Sorrentino, Francesca Greco, Laura Vona, Francesco Maria Zullo and Stefano Bettocchi F. "Pathophysiology of Female Reproduction and Clinical Management." This work is openly licensed via CC BY 4.0 DEED Creative Commons license. Bettocchi, C., Busetto, G.M., Carrieri, G., Cormio, L. (eds) Practical Clinical Andrology. Springer, Cham. (2023). doi.org/10.1007/978-3-031-11701-5_16.
10. Section adapted from Nappi, L. et al, 2023.
11. Section adapted from Nappi, L. et al, 2023.
12. Karve, Simantini. "Anatomy and Physiology of the Female Reproductive System." *Human Physiology for Allied Health Professionals*, (2022). This work is openly licensed via CC BY NC SA 4.0 Creative Commons License. Available from LibreText, Skyline College

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2.3: Functional Histology of the Uterine Tubes and Oocyte Journey into the Uterine Tube

2.3.1 Uterine Tubes

The **uterine tubes** (also called fallopian tubes or oviducts) serve as the conduit of the **oocyte** from the **ovary** to the **uterus**. Each of the two uterine tubes is close but not directly connected to the ovary and divided into sections. The **isthmus** is the narrow medial end of each uterine tube connected to the uterus. The wide distal **infundibulum** flares out with slender, finger-like projections called **fimbriae**. The middle region of the tube, called the **ampulla**, is where fertilization often occurs.

The uterine tubes have three layers: an outer serosa, a middle smooth muscle layer, and an inner mucosal layer (Figure 2.3.10, A). In addition to its mucus-secreting cells, the inner mucosa contains ciliated cells that beat in the direction of the uterus, producing a current that will be critical to move the oocyte (Figure 2.3.10, B). Following ovulation, the secondary oocyte, surrounded by a few granulosa cells, is released into the **peritoneal cavity**. The nearby uterine tube, either left or right, receives the oocyte.

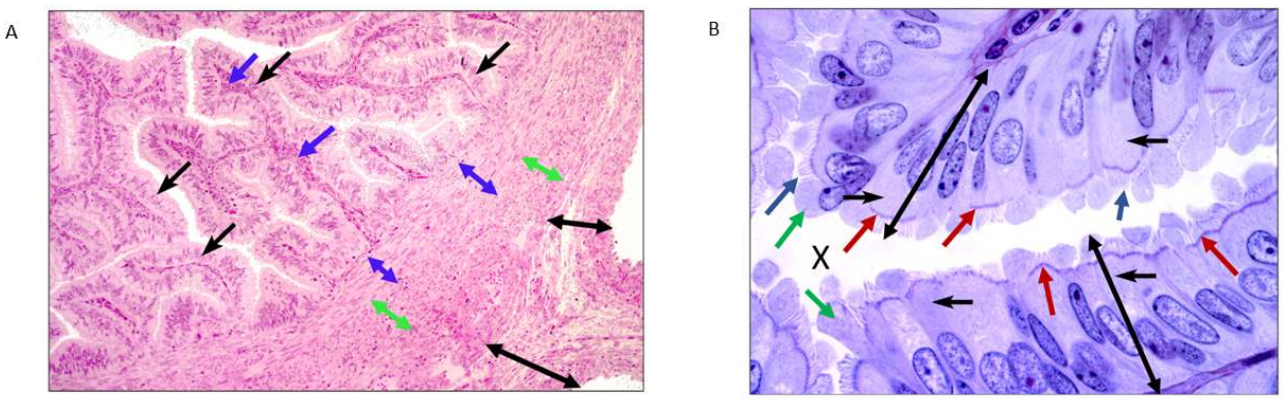


Figure 2.3.10 (A) A cross-section in the ampulla of the fallopian tube. The wall has a highly enfolded mucosa (columnar epithelium, black arrows; and lamina propria, blue arrows). Muscularis externa consists of inner circular (blue double-headed arrows) and outer longitudinal layers (green double-headed arrows) that intermingle. The fallopian tube is surrounded by a serosa (black double-headed arrows) and suspended by a mesosalpinx (red double-headed arrow) from the broad ligament. 400x. (B) Two folds of the fallopian tube mucosa of the ampulla are shown. The simple columnar epithelium lining the oviduct (black double-headed arrows) possesses both ciliated (black arrow) and secretory cells (green arrows), whose activity is regulated by ovarian hormones. Cilia (blue arrows), basal bodies (red arrows), and lumen (X). 1000x.

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Unlike sperm, oocytes lack **flagella** and, therefore, cannot move on their own. So, how do they travel into the uterine tube and toward the uterus? High concentrations of estrogen that occur around the time of ovulation induce contractions of the smooth muscle along the length of the

uterine tube. These contractions occur every 4 to 8 seconds, resulting in a coordinated movement that sweeps the surface of the ovary and the pelvic cavity. Current flowing toward the uterus is generated by coordinated beating of the **cilia** that line the outside and **lumen** of the length of the uterine tube. These cilia beat more strongly in response to the high estrogen concentrations that occur around the time of ovulation. As a result of these mechanisms, the oocyte–granulosa cell complex is pulled into the interior of the tube.

Once inside, the muscular contractions and beating cilia move the oocyte slowly toward the uterus. When fertilization does occur, sperm typically meets the egg while it is still moving through the ampulla. If the oocyte is successfully fertilized, the resulting **zygote** will begin to divide into two cells, then four, and so on, as it makes its way through the uterine tube and into the uterus. There, it will implant and continue to grow.

If the egg is not fertilized, it will simply degrade—either in the uterine tube or in the uterus, where it may be shed with the next menstrual period.

Glossary Terms

Ampulla
(of the uterine tube) Middle portion of the uterine tube in which fertilization often occurs

Cilia
Small appendage on certain cells formed by microtubules and modified for movement of materials across the cellular surface

Fimbriae
Fingerlike projections on the distal uterine tubes

Flagellum
Appendage on certain cells formed by microtubules and modified for movement

Infundibulum
(of the uterine tube) Wide, distal portion of the uterine tube terminating in fimbriae

Isthmus
Narrow, medial portion of the uterine tube that joins the uterus portion of the uterine tube terminating infimbriae

Lumen
Interior of a tubular structure such as a blood vessel or a portion of the alimentary canal through which blood, chyme, or other substances travel luteinization meiosis

Oocyte
Cell that results from the division of the oogonium and undergoes meiosis I at the LH surge and meiosis II at fertilization to become a haploid ovum

Ovary
Female gonad that produces oocytes and sex steroid hormones (notably estrogen and progesterone)

Peritoneal cavity
Space enclosed by the peritoneum. It is divided into two portions, the greater sac and the lesser sac or omental bursa, which lies behind the STOMACH. The two sacs are connected by the foramen of Winslow, or epiploic foramen

Uterine tubes
(also, fallopian tubes or oviducts) Ducts that facilitate transport of an ovulated oocyte to the uterus

Uterus

Muscular hollow organ in which a fertilized egg develops into a fetus

Zygote

Fertilized OVUM resulting from the fusion of a male and a female gamete

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2.4: The Uterus and Cervix

2.4.1 The Uterus

The **uterus** is the muscular organ that nourishes and supports the growing **embryo** (Figure 2.4.11). Its average size is approximately 5 cm wide by 7 cm long (approximately 2 in by 3 in) when a female is not pregnant. It has three sections. The portion of the uterus superior to the opening of the uterine tubes is called the **fundus**. The middle section of the uterus is called the body of the uterus (or **corpus**). The **cervix** is the narrow inferior portion of the uterus that projects into the vagina. The cervix produces mucus secretions that become thin and stringy under the influence of high systemic plasma estrogen concentrations, and these secretions can facilitate sperm movement through the reproductive tract.

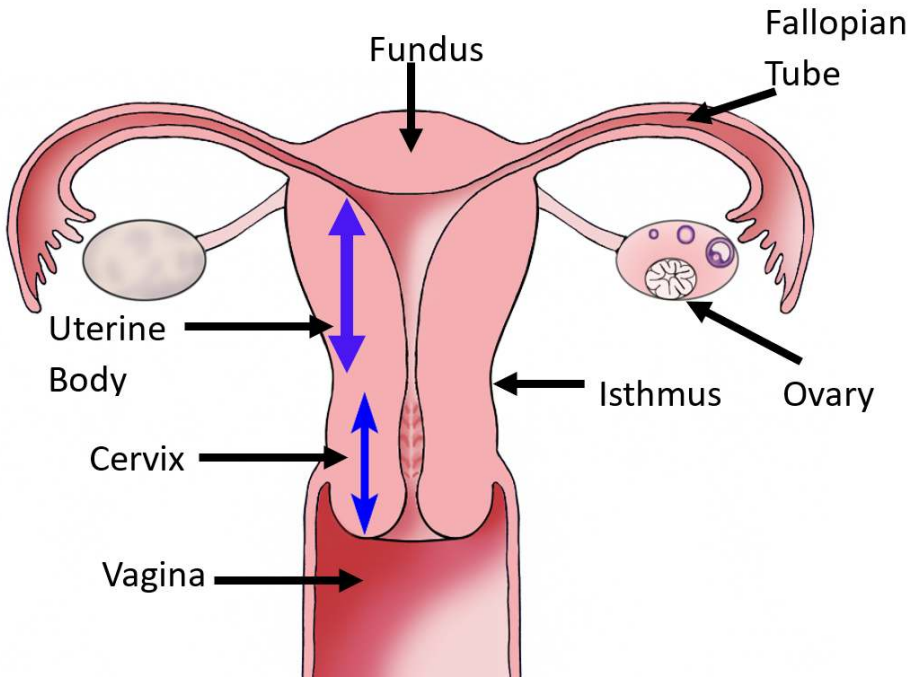


Figure 2.4.11 The drawing illustrates the internal organs of the female reproductive system: paired ovaries, paired oviducts (Fallopian tubes), uterus, and vagina.
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2.4.1.1 Uterine Wall

The wall of the uterus is made up of three layers (Figure 2.4.12).

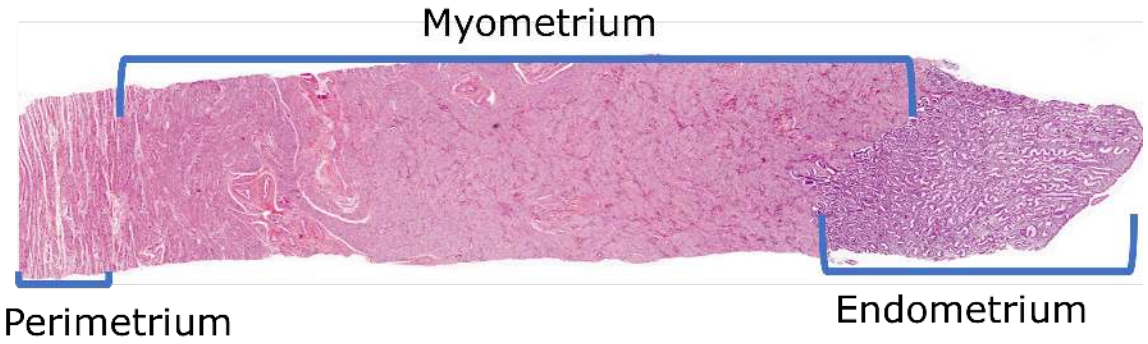


Figure 2.4.12 The uterus comprises an endometrium, similar to a mucosa; a myometrium, analogous to muscularis externa; and a perimetrium, which is either a serosa or an adventitia, depending on its location. The endometrium, influenced by ovarian hormones, changes during the menstrual cycle, preparing for implantation of the blastocyst. 10x

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- Perimetrium

The most superficial layer is the serous membrane, or perimetrium, which consists of **epithelial tissue** that covers the exterior portion of the uterus.

- Myometrium

The middle layer, or myometrium, is a thick, highly vascularized, smooth muscle layer responsible for uterine contractions. The smooth muscles of the myometrium enlarge in size due to cell growth (hypertrophy) and increase in number due to cell division (hyperplasia) during pregnancy. Most of the uterus is myometrial tissue, and the muscle fibers run horizontally, vertically, and diagonally, allowing the powerful contractions that occur during labor and the less powerful contractions (or cramps) that help to expel menstrual blood during a woman's period. Anteriorly directed myometrial contractions also occur near the time of ovulation and are thought to possibly facilitate the transport of sperm through the female reproductive tract.

- Endometrium

The innermost layer of the uterus is called the endometrium. The endometrium contains a connective tissue lining, the **lamina propria**, which is covered by simple columnar epithelial tissue that lines the lumen. Structurally, the endometrium consists of two layers: the stratum basalis and the stratum functionalis (the basal and functional layers) (Figure 2.4.13). The **stratum basalis** layer is part of the lamina propria and is adjacent to the myometrium; this layer is not shed during menses. In contrast, the thicker **stratum functionalis** layer contains the glandular portion of the lamina propria and the endothelial tissue that lines the uterine lumen. The stratum functionalis grows and thickens in response to increased levels of estrogen and progesterone. In the **luteal phase** of the menstrual cycle, special branches of the uterine

artery called spiral arteries supply the thickened stratum functionalis. This inner functional layer provides the proper site of implantation for the fertilized egg, and—should fertilization not occur—it is only the stratum functionalis layer of the endometrium that sheds during menstruation.

Recall that during the follicular phase of the ovarian cycle, the tertiary follicles grow and secrete estrogen. At the same time, the stratum functionalis of the endometrium is thickening to prepare for a potential implantation. The post-ovulatory increase in progesterone, which characterizes the luteal phase, is critical for maintaining a thick stratum functionalis. As long as a functional corpus luteum is present in the ovary, the endometrial lining is prepared for implantation. Indeed, if an embryo implants, signals are sent to the corpus luteum to continue secreting progesterone to maintain the endometrium and thus maintain the pregnancy. If an embryo does not implant, no signal is sent to the corpus luteum, and it degrades, ceasing progesterone production and ending the luteal phase. Without progesterone, the endometrium thins, and under the influence of prostaglandins, the spiral arteries of the endometrium constrict and rupture, preventing oxygenated blood from reaching the endometrial tissue. As a result, endometrial tissue dies, and blood, pieces of the endometrial tissue, and white blood cells are shed through the vagina during menstruation or **menses**. The first menses after puberty, called **menarche**, can occur either before or after the first ovulation.

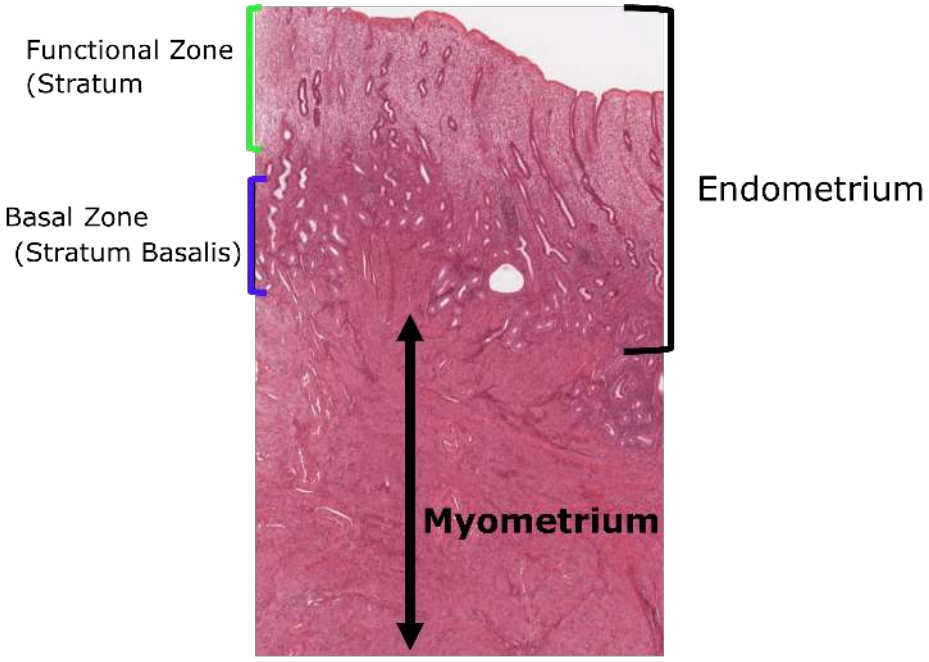


Figure 2.4.13 The endometrium, facing the uterine lumen, is composed of a simple columnar epithelium and its underlying lamina propria, called uterine stroma. The basal zone of the endometrium lies adjacent to the myometrium and is retained during menstruation. Following menstruation, cellular proliferation in the basal zone restores the glands, the surface epithelium, and the stroma (connective tissue lamina propria). In response to ovarian hormones, the functional zone of the endometrium is entirely sloughed during menstruation. The appearance of the glands in the functional zone helps to identify each menstrual stage. In this photomicrograph, some glands are wavy. 10x.

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Glossary Terms

Cervix

Elongate inferior end of the uterus where it connects to the vagina

Embryo

Group of cells of blastocyst that will become an embryo - the embryo is what will develop into a baby

Epithelial tissue

(cuboidal, serosa, squamos) - The term "epithelium" refers to layers of cells that line hollow organs and glands. It is also those cells that make up the outer surface of the body

Fundus

Dome-shaped region of the stomach above and to the left of the cardia

Lamina propria

Areolar connective tissue underlying a mucous membrane

Luteal phase

Period in the **menstrual cycle** that follows **ovulation**, characterized by the development of the **corpus luteum**, increase in **progesterone** production by the **ovary**, and secretion by the glandular epithelium of the **endometrium**. The luteal phase begins with ovulation and ends with the onset of **menstruation.**

Menarche

First menstruation in a pubertal female

Menses

Shedding of the inner portion of the endometrium out though the vagina; also referred to as menstruation

Stratum basale

Deepest layer of the epidermis, made of epidermal stem cells

Stratum functionalis

A highly vascularized mucosal layer that undergoes monthly cyclical changes and is lost during menstruation

Uterus

Muscular hollow organ in which a fertilized egg develops into a fetus

Image Acknolwedgements

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2.5: The Menstrual Cycle

2.5.1 Menses

Let's put together what we learned about **ovulation**, the buildup and then shedding of the **endometrial lining** in the **uterus**, and the function of the uterine tubes and vagina, to explore the three phases of the menstrual cycle.

The menstrual cycle is the series of changes in which the uterine lining is shed, rebuilt, and prepared for implantation under the effect of ovarian hormones. The timing of the menstrual cycle starts with the first day of **menses**, referred to as day one of a woman's period. Cycle length is determined by counting the days between the onset of bleeding in two subsequent cycles. Because the average length of a woman's menstrual cycle is 28 days, this is the period used to identify the timing of events in the cycle. This period is also known as the intermenstrual interval. The menstrual cycle length varies among women, and even in the same woman, from one cycle to the next, typically from 21 to 35 days. Changes in the intermenstrual interval are primarily due to changes in the **follicular phase**; in comparison, the **luteal phase** remains relatively constant.

Just as the hormones produced by the **granulosa** and **theca** cells of the ovary "drive" the follicular (14-21 days) and luteal phases (14 days) of the ovarian cycle, they also control the three distinct phases of the menstrual cycle. These are the menses phase, the proliferative phase, and the secretory phase.[13]

2.5.1.1 Menses Phase (Days 1-5)

The menses phase of the menstrual cycle is the phase during which the lining is shed; that is, the days that the woman menstruates (Figure 2.5.14). Although it averages approximately five days, the menses phase lasts 2 to 7 days, or longer. As shown in Figure 2.5.15, the menses phase occurs during the early days of the follicular phase of the ovarian cycle, when **progesterone**, **FSH**, and **LH** levels are low. Recall that progesterone concentrations decline due to the degradation of the **corpus luteum**, marking the end of the luteal phase. This decline in progesterone triggers the shedding of the stratum functionalis of the endometrium (Figure 2.5.14). The **ischemia** produced by the contraction of spiral arteries leads to degeneration and sloughing of the functional zone, leaving only the basal zone remaining at the end of

menstruation. The menstrual flow contains blood, tissue fragments, and uterine fluids.[14]

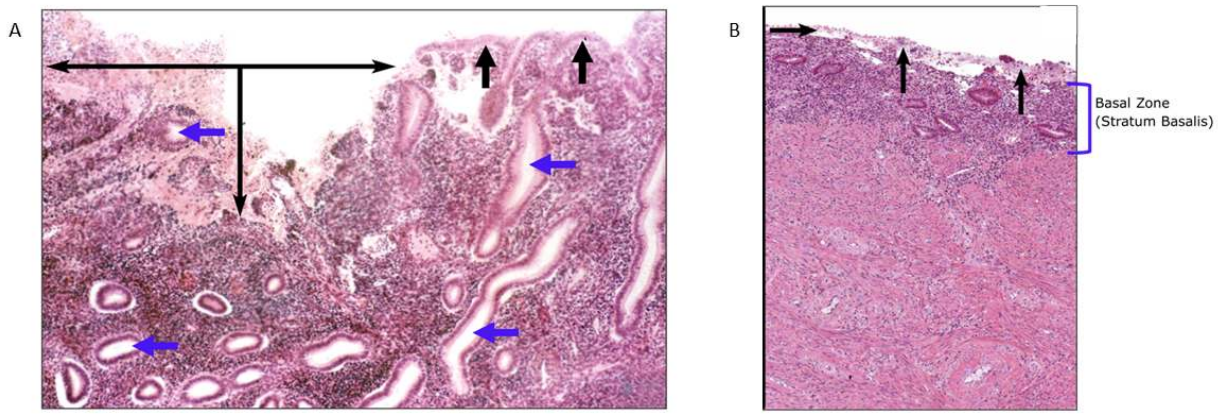


Figure 2.5.14: Menstrual phase (days 1-5). When the ischemic tissue in the functional zone loses its integrity, it is sloughed as menstruation. (A) This image, taken from early in the menstrual phase, shows an intact surface epithelium on the right half of the image (black arrows), while tissue has already begun to slough in other areas (left half; T-shaped arrows). Sloughing of the functional zone is indicated by the lack of surface epithelium, the presence of glands at the luminal surface, and missing portions of the functional zone. The thickness of the remaining functional zone indicates that this tissue was taken during the early days of the menstrual phase. 100x. (B) This image is taken close to the end of the menstrual phase; all of the functional zone has been lost, and only the bases of glands remain, from which new glands will originate. Extravasated blood (arrows) can be seen throughout the endometrium.10x.

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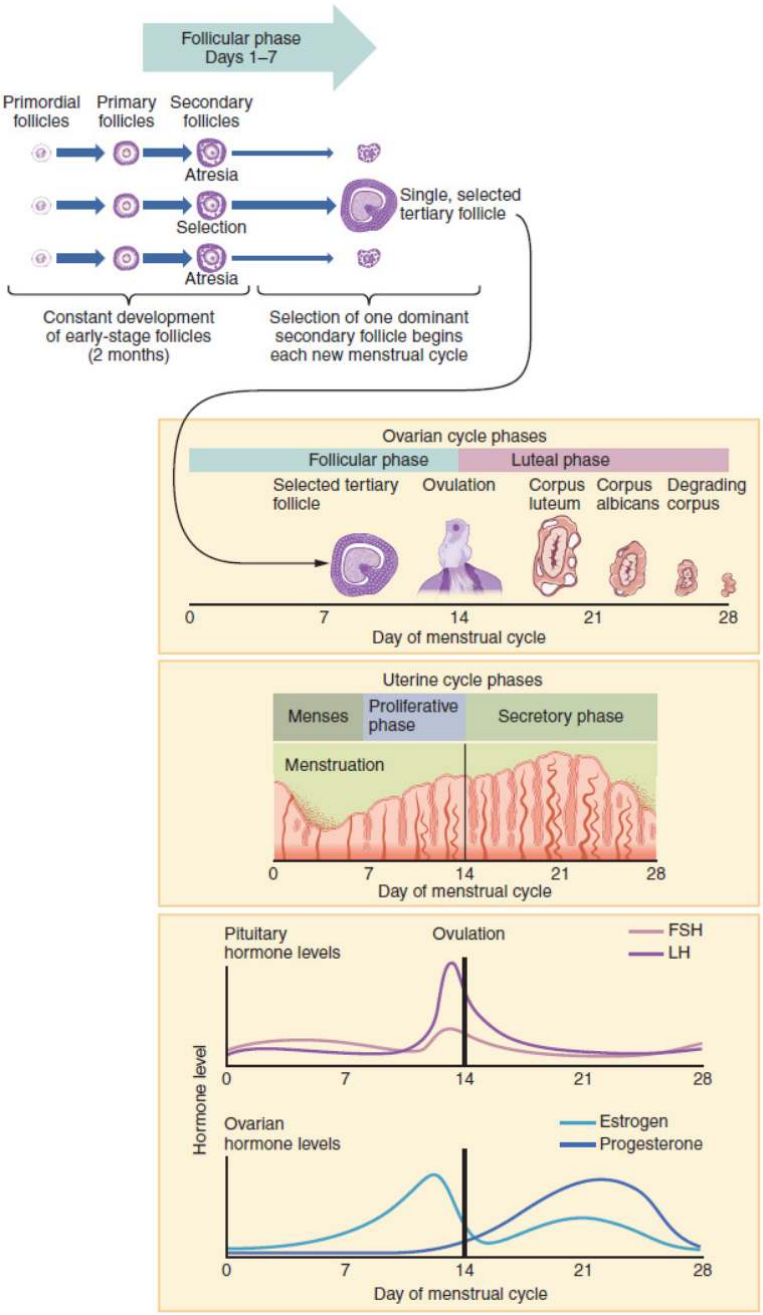


Figure 2.5.15 Hormone levels in ovarian and menstrual cycles. The correlation between hormone levels and their effects on the female reproductive system is shown in this timeline of the ovarian and menstrual cycles. The menstrual cycle begins at day one with the start of menses. Ovulation occurs around day 14 of a 28-day cycle, triggered by the LH surge.

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2.5.1.2 Proliferative Phase (Days 6-14)

Once menstrual flow ceases, the endometrium begins to proliferate again, marking the beginning of the proliferative phase of the menstrual cycle. It occurs when the granulosa and

theca cells of the tertiary follicles begin to produce increased amounts of estrogen. These rising estrogen concentrations stimulate the endometrial lining to rebuild. Recall that the high estrogen concentrations will eventually lead to a decrease in FSH because of negative feedback, resulting in atresia of all but one of the developing tertiary follicles. The switch to positive feedback—which occurs with the elevated estrogen production from the dominant follicle—then stimulates the LH surge that will trigger ovulation. In a typical 28-day menstrual cycle, ovulation occurs on day 14. Ovulation marks the end of the proliferative phase as well as the end of the follicular phase.

The endometrium in the proliferative phase is not very thick, the glands are straight, and the spiral arteries are not readily visible (Figure 2.5.16). The stroma in the basal zone is characterized by relatively smaller and closely packed cells resulting in darker staining (distinguishing features of the basal zone). The bases of the glands, located in this layer, are the source of cells that regenerate the glands and also the surface epithelium of the functional zone following menstruation. Estrogen produced by ovarian follicles induces the rapid growth of the functional zone of the endometrium during the proliferative phase. The simple branched tubular uterine glands are straight; they are non-secretory at this stage. Spiral arteries are present to support the rapidly growing and proliferating functional zone; however, they are not coiled and not prominent histologically.[15]

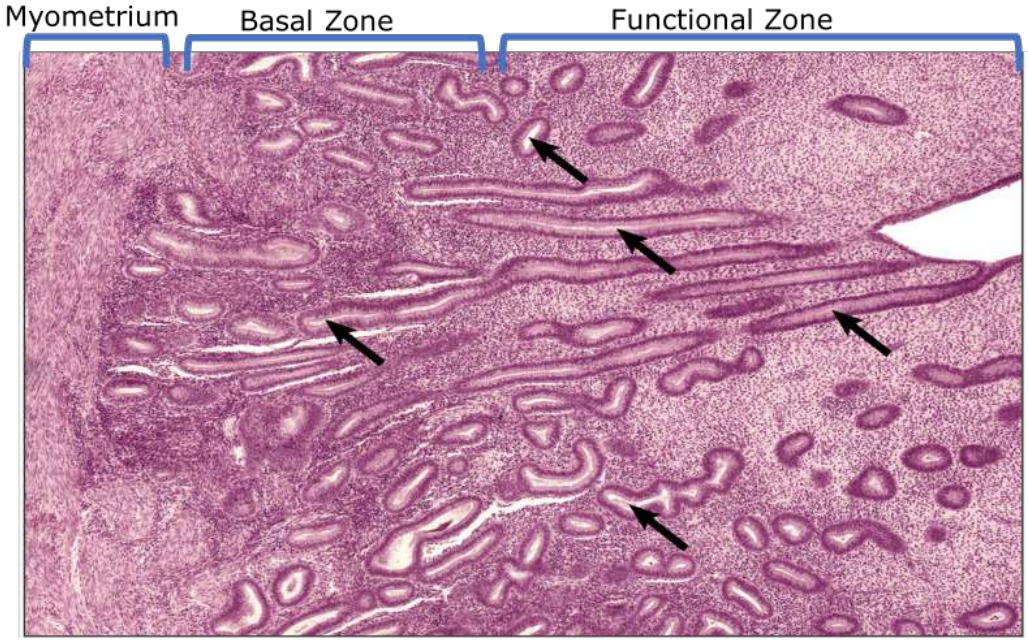


Figure 2,5.16 Proliferative endometrium. Straight, non-secretory endometrial glands (arrows). 100x..
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2.5.1.3 Secretory Phase (Days 14-28)

In addition to prompting the LH surge, high **estrogen** levels increase the uterine tube contractions that facilitate the pickup and transfer of the ovulated **oocyte**. High estrogen levels also slightly decrease the acidity of the vagina, making it more hospitable to sperm. In the ovary, the luteinization of the granulosa cells of the collapsed follicle forms the progesterone-producing corpus luteum, marking the beginning of the luteal phase of the ovarian cycle. In the uterus, progesterone from the corpus luteum begins the secretory phase of the menstrual cycle, in which the endometrial lining prepares for implantation (Figure 2A.17). The endometrial glands secrete a glycogen-rich fluid over the next 10 to 12 days. If fertilization has occurred, this fluid will nourish the ball of cells now developing from the **zygote**. At the same time, the spiral arteries develop to provide blood to the thickened stratum functionalis. If no pregnancy occurs within 10 to 12 days, the corpus luteum will degrade into the corpus albicans. Levels of both estrogen and progesterone will fall, and the endometrium will grow thinner. Prostaglandins will be secreted, which causes constriction of the spiral arteries and reduces oxygen supply. The endometrial tissue will die, resulting in menses—or the first day of the next cycle.

The histological features of the endometrium during the secretory phase (days 14-26) are demonstrated in Figure 2.5.17. The uterine glands become secretory under the effect of estrogen and progesterone. During the early portion of the secretory phase (Figure 2.5.17, A), the endometrium is thicker in comparison to the endometrium of the proliferative phase, the glands are **saccular**, and the spiral arteries are present, but are not highly coiled. Late in the secretory phase, the glands in the functional zone are greatly sacculated and have characteristic saw-tooth features. These glands are distended with secretory product in their lumens. The spiral arteries are coiled and can readily be seen zigzagging through the endometrium at the junction of the basal and functional zones (Figure 2.5.17, B). Around day 24, multipotential **stromal cells** differentiate into cells called **pre-decidual cells** (if there is no pregnancy) or **decidual cells** if implantation occurs. These cells appear first around the spiral arteries and beneath the surface epithelium, as shown in (Figure 2.5.18, C). If fertilization and implantation occur, the decidual cells provide nutrition for the implanting **blastocyst** and form the maternal placenta (decidua).[16]

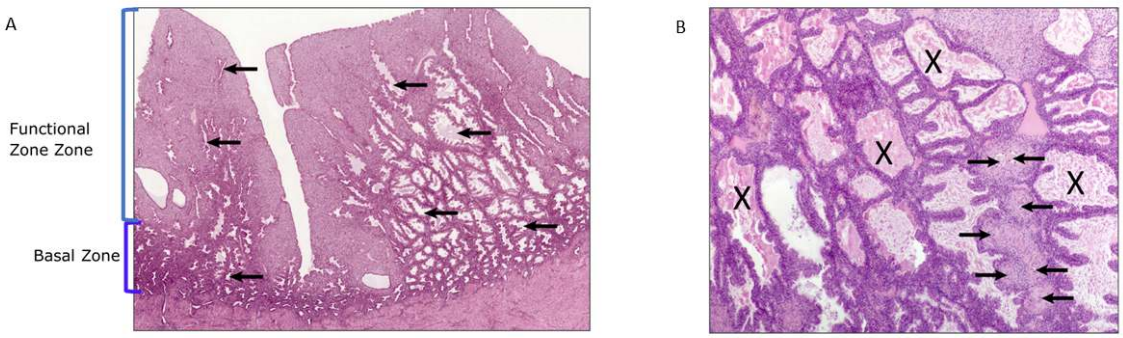


Figure 2.5.17 Secretory Endometrium. (A) Early secretory phase endometrium with secretory products starting to accumulate in some glands (arrows). Glands are increasing in size and become sacculated. 100x. (B) Late secretory phase endometrium; glands are widely sacculated, with characteristic saw-tooth appearance, and lumens distended with secretions (X). The spiral arteries are coiled (arrows). 200x.

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Very late in the secretory phase (days 26-28), also known as the pre-menstrual phase (Figure 2A.18), the endometrium demonstrates certain morphological features secondary to the decreased hormone production by the degrading corpus luteum. The endometrium shrinks and becomes less edematous. The spiral arteries undergo alternate contraction and relaxation resulting in ischemia and degeneration of the endometrial tissue supplied by these arteries; this phase is also known as the ischemic portion of the secretory phase. The degenerating endometrium shows sacculated glands with precipitated secretory products in their lumens, areas of degeneration, and extravasation of blood in the stroma (Figure 2A.18, A, B). Pre-decidual cells can be seen beneath the surface of the epithelium (Figure 2A.18, C).[17]

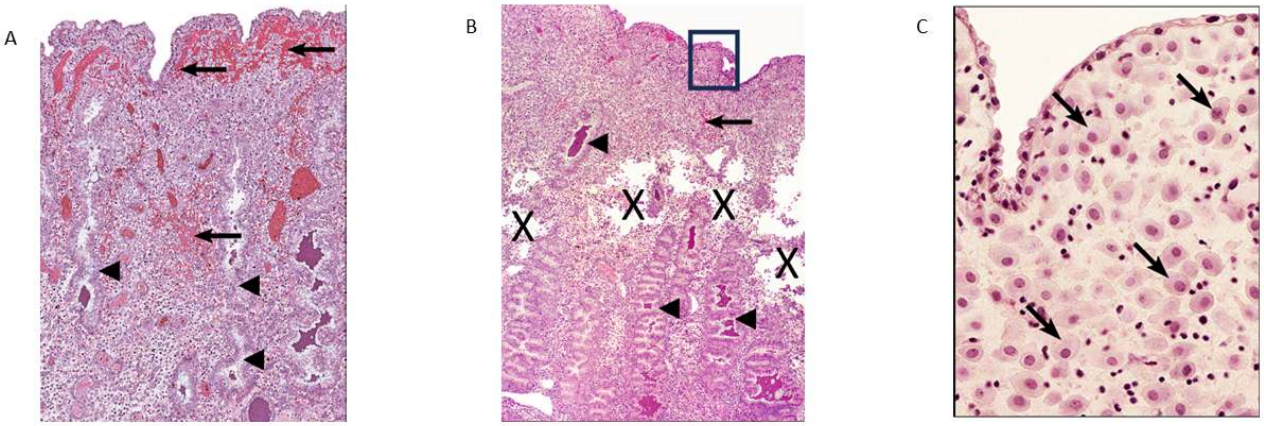


Figure 2.5.18 Pre-menstrual Phase (Days 26-28). (A, B) The functional zone is declining. The sacculated glands (arrowheads) show precipitated secretory product; areas of degeneration are obvious (X); extravasated blood (arrows) is present in the stroma. 40x. (C) The image is from an area similar to that enclosed by the rectangle in (B); pre-decidual cells (arrows) can be seen beneath the surface epithelium. 400x.

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For more information

Kai J, Dutton B, Vinogradova Y, et al. **Rates of medical or surgical treatment for women with heavy menstrual bleeding: the ECLIPSE trial 10-year observational follow-up study.** Southampton (UK): National Institute for Health and Care Research; 2023 Oct.

(Health Technology Assessment, No. 27.17.) Available from: https://www.ncbi.nlm.nih.gov/books/NBK596976/ doi: 10.3310/JHSW0174

Glossary Terms

Blastocyst

Post-**morula** preimplantation mammalian embryo that develops from a 32-cell stage into a fluid-filled hollow ball of over a hundred cells. A blastocyst has two distinctive tissues

Corpus luteum

Transformed follicle after ovulation that secrets progesterone

Decidual cells

Hyperplastic endometrial stromal cells

Estrogen

Class of predominantly female sex hormones important for the development and growth of the female reproductive tract, secondary sex characteristics, the female reproductive cycle, and the maintenance of pregnancy

Follicle-stimulating Hormone (FSH)

Anterior pituitary hormone that stimulates the production and maturation of sex cells

Follicular phase

Period of the **menstrual cycle** representing follicular growth, increase in ovarian estrogen (**estrogens**) production, and epithelial proliferation of the ENDOMETRIUM. Follicular phase begins with the onset of **menstruation** and ends with **ovulation**

Granulosa

Supportive cells in the ovarian follicle that produce estrogen

Ischemia

Insufficient blood flow to the tissues

Luteal phase

Period in the **menstrual cycle** that follows **ovulation**, characterized by the development of **corpus luteum**, increase in **progesterone** production by the **ovary** and secretion by the glandular epithelium of the **endometrium**. The luteal phase begins with ovulation and ends with the onset of **menstruation**

Luteinizing hormone (LH)

Anterior pituitary hormone that triggers ovulation and the production of ovarian hormones in females, and the production of testosterone in males

Menses

Shedding of the inner portion of the endometrium out through the vagina; also referred to as menstruation

Oocyte

Shedding of the inner portion of the endometrium out though the vagina; also referred to as menstruation

Ovulation

Release of a secondary oocyte and associated granulosa cells from an ovary

Progesterone

Sex hormone important in regulating the reproductive cycle in those with ovaries and the maintenance of pregnancy

Saccular

Having the form of a sac

Stromal cells

Connective tissue cells of an organ found in the loose connective tissue. These are most often associated with the uterine mucosa and the ovary as well as the hematopoietic system and elsewhere

Theca

Estrogen-producing cells in a maturing ovarian follicle

Uterus

Muscular hollow organ in which a fertilized egg develops into a fetus

Zygote

Fertilized OVUM resulting from the fusion of a male and a female gamete

Footnotes

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2.6: Glossary

> *To review common anatomical and directional terms, please see* Chapter 1. Anatomy of the Female Reproductive System

Ampulla (of the uterine tube) - The middle portion of the uterine tube in which fertilization often occurs [2]

Anti-Müllerian hormone (AMH) - A glycoprotein that causes regression of **Müllerian ducts**. It is produced by **Sertoli cells** of the **testes**. In the absence of this hormone, the M**ü**llerian ducts develop into structures of the female reproductive tract. In males, defects of this hormone result in persistent M**ü**llerian duct, a form of **male pseudohermaphroditism**. [3]

Antidiuretic hormone (ADH) - Hypothalamic hormone stored by the posterior pituitary that signals the kidneys to reabsorb water

Antrum - Fluid-filled chamber that characterizes a mature tertiary (antral) follicle [2]

Aromatase - An enzyme that catalyzes the desaturation (aromatization) of the ring A of C19 androgens and converts them to C18 estrogens. In this process, the 19-methyl is removed. This enzyme is membrane-bound, located in the endoplasmic reticulum of estrogen-producing cells of ovaries, placenta, testes, adipose, and brain tissues. [3]

Atresia - absence or abnormal narrowing of an opening or passage in the body

Atretic follicles

Blastocyst - A post-**morula** preimplantation mammalian embryo that develops from a 32-cell stage into a fluid-filled hollow ball of over a hundred cells. A blastocyst has two distinctive tissues. The outer layer of trophoblasts gives rise to extra-embryonic tissues. The inner cell mass gives rise to the embryonic disc and eventual embryo proper. [3]

Cervix - The elongate inferior end of the uterus, connected to the vagina. [2]

Cilia - Small appendages on certain cells formed by microtubules and modified for movement of materials across the cellular surface. [2]

Corpus albicans - Nonfunctional structure remaining in the ovarian stroma following structural and functional regression of the corpus luteum. [2]

Corpus luteum - Transformed follicle after ovulation that secrets progesterone. [2]

Cytokines - Non-antibody proteins, secreted by inflammatory leukocytes and some non-leukocytic cells, that act as intercellular mediators. They differ from classical hormones in that they are produced by a number of tissue or cell types rather than by specialized glands. They generally act locally in a paracrine or autocrine rather than endocrine manner. [3]

Cytoplasm - Internal material between the cell membrane and nucleus of a cell, mainly consisting of a water-based fluid called cytosol, within which are all the other organelles and cellular solute and suspended materials [2]

Decidual cells - Hyperplastic endometrial stromal cells

Dopamine - One of the catecholamine **neurotransmitters** in the brain. It is derived from **tyrosine** and is the precursor to **norepinephrine** and **epinephrine**. Dopamine is a major transmitter in the extrapyramidal system of the brain, and important in regulating movement. [3]

Embyro - A group of blastocyst cells that will become an embryo and thus develop into a baby. [6]

Endocrine (gland) - Groups of cells that release chemical signals into the intercellular fluid to be picked up and transported to their target organs by blood. [6]

Endometrium - The inner lining of the uterus, part of which builds up during the secretory phase of the menstrual cycle and then sheds with menses. [2]

Epithelium (cuboidal, serosa, squamos) - Refers to layers of cells that line hollow organs and glands. It is also those cells that make up the outer surface of the body. [4]

Estradiol - The 17-beta-isomer of estradiol, an aromatized C18 steroid with hydroxyl group at 3-beta- and 17-beta-position. Estradiol-17-beta is the most potent form of mammalian estrogenic steroids. [3]

Estrogen - Class of predominantly female sex hormones important for the development and growth of the female reproductive tract, secondary sex characteristics, the female reproductive cycle, and the maintenance of pregnancy [2]

Exocrine (gland) - Group of epithelial cells that secrete substances through ducts that open to the skin or to internal body surfaces that lead to the exterior of the body. [6]

Fallopian tubes (uterine tubes or oviducts) - Ducts that facilitate transport of an ovulated oocyte to the uterus. [2]

Fertilization - Fertilization occurs when sperm and an oocyte combine. Because each of these reproductive cells is a haploid cell containing half of the genetic material needed to form a human being, their combination forms a diploid cell. This new single cell is called a zygote. [1]

Fimbriae - Fingerlike projections on the distal uterine tubes. [2]

Flagellum - Appendage on certain cells formed by microtubules and modified for movement

Follicle - Ovarian structure of one oocyte and surrounding granulosa (and later theca) cells. [2]

Follicular phase - Period of the **menstrual cycle** representing follicular growth, increase in ovarian estrogen (**estrogens**) production, and epithelial proliferation of the **endometrium**. Follicular phase begins with the onset of **menstruation** and ends with **ovulation** [3]

Folliculogenesis - Development of ovarian follicles from primordial to tertiary under the stimulation of gonadotropins. [2]

Follicle-stimulating Hormone (FSH) - Anterior pituitary hormone that stimulates the production and maturation of sex cells. [2]

Fundus - Dome-shaped region of the stomach above and to the left of the cardia. [2]

Gonadotropin-releasing hormone (GnRH) - A decapeptide that stimulates the synthesis and secretion of both pituitary gonadotropins, **luteinizing hormone** and **follicle-stimulating hormone**. GnRH is produced by neurons in the septum **preoptic area** of the **hypothalamus** and released into the pituitary portal blood, leading to stimulation of **gonadotrophs** in the **anterior pituitary gland**. [3]

Granulosa - Supportive cells in the ovarian follicle that produce estrogen. [2]

Haploid ovum - contains a single copy of each chromosome with the sex chromosome always an X chromosome.

Human chorionic gonadotropin (HCG) - A gonadotropic glycoprotein hormone produced primarily by the **placenta**. Similar to the pituitary **luteinizing hormone** in structure and function, chorionic gonadotropin is involved in maintaining the **corpus luteum** during pregnancy. CG consists of two noncovalently linked subunits, alpha and beta. [3]

Hypothalamus - Major region of the diencephalon that is responsible for coordinating autonomic and endocrine control of homeostasis. [2]

Infundibulum (of the uterine tube) - the wide, distal portion of the uterine tube terminating in fimbriae. [2]

Inhibin - Hormone secreted by the gonads that inhibits FSH production by the anterior pituitary ischemia. [2]

Ischemia - insufficient blood flow to the tissues [2]

Isthmus - narrow, medial portion of the uterine tube that joins the uterus portion of the uterine tube terminating infimbriae. [2]

Lamina propria - areolar connective tissue underlying a mucous membrane. [6]

Luteal phase - The period in the **menstrual cycle** that follows **ovulation**, characterized by the development of the **corpus luteum**, an increase in **progesterone** production by the **ovary,** and secretion by the glandular epithelium of the **endometrium**. The luteal phase begins with ovulation and ends with the onset of **menstruation**. [3]

Luteinization - Formation of the **corpus luteum**. This process includes capillary invasion of the ruptured **ovarian follicle**, hypertrophy of the **granulosa cells** and the **theca cells**, and the production of **progesterone**. **Luteinization** is regulated by **luteinizing hormone**. [3]

Luteinizing hormone (LH) - The anterior pituitary hormone that triggers ovulation and the production of ovarian hormones in females and the production of testosterone in males. [2]

Lumen - The interior of a tubular structure such as a blood vessel or a portion of the alimentary canal through which blood, chyme, or other substances travel luteinization meiosis. [2]

Meiosis - A type of **cell nucleus** division, occurring during maturation of the GERM CELLS. Two successive cell nucleus divisions following a single chromosome duplication (**S phace**) result in daughter cells with half the number of **chromosomes** as the parent cells. [3]

Menarche - First menstruation in a pubertal female. [2]

Menses - Shedding of the inner portion of the endometrium out trhough the vagina; also referred to as menstruation. [2]

Mesovarium - Extension of the peritoneum that connects the ovaries to the broad ligament. [2]

Myometrium - The smooth muscle layer of uterus that allows for uterine contractions during labor and expulsion of menstrual blood. [2]

Oocyte - A cell that results from the division of the oogonium and undergoes meiosis I at the LH surge and meiosis II at fertilization to become a haploid ovum [2]

Oogonia - Ovarian stem cells that undergo mitosis during female fetal development to form primary oocytes. [2]

Oogenesis - Process by which oogonia divide by mitosis to primary oocytes, which undergo meiosis to produce the secondary oocyte and, upon fertilization, the ovum. [2]

ovarian medulla

Ovary - female gonad that produces oocytes and sex steroid hormones (notably estrogen and progesterone). [2]

Ovum - A mature haploid female germ cell extruded from the **ovary** at **ovulation**. [6]

Ovulation - Release of a secondary oocyte and associated granulosa cells from an ovary. [2]

Oxytocin - Oxytocin injection is used to begin or improve contractions during labor. Oxytocin also is used to reduce bleeding after childbirth. It also may be used along with other medications or procedures to end a pregnancy. Oxytocin is in a class of medications called oxytocic hormones. It works by stimulating uterine contractions. [5]

Paraventricular nucleus (PVN) - Nucleus in the anterior part of the **hypothalamus**. [3]

Perimetrium - The outer epithelial layer of the uterine wall. [2]

Peritoneal cavity - The space enclosed by the peritoneum, divided into two portions, the greater sac and the lesser sac or omental bursa, which lies behind the **stomach**. The foramen of Winslow, or epiploic foramen, connects the two sacs. [3]

Pituitary gland (neuroohypophysis) - A bean-sized organ suspended from the hypothalamus that produces, stores, and secretes hormones in response to hypothalamic stimulation (also called hypophysis). [2]

Plasminogen activators - A heterogeneous group of proteolytic enzymes that convert **plasminogen** to **fibrinolysin**. They are concentrated in the lysosomes of most cells and in the vascular endothelium, particularly in the vessels of the microcirculation. [3]

Primordial follicles - Least developed ovarian follicles that consist of a single oocyte and a single layer of flat (squamous) granulosa cells. [2]

Progesterone - A sex hormone important in regulating the reproductive cycle in those with ovaries and the maintenance of pregnancy. [2]

Saccular - Having the form of a sac

Serous (gland) - A group of cells within the serous membrane that secrete a lubricating substance onto the surface. [6]

Serous (membrane) - A type of tissue membrane that lines body cavities and lubricates them with serous fluid. [6]

Serous membrane (serosa) - A thin lining of closed cavities of the body, consisting of a single layer of squamous epithelial cells (**mesothelium**) resting on a thin layer of **connective tissue** and covered with secreted clear fluid from blood and lymph vessels. Major serous membranes in the body include the **pericardium, peritoneum,** and **pleura**. [3]

Somatotrophs (Growth Hormone (GH)) - Anterior pituitary cells that produce **growth hormone**. [3]

Sperm (also, spermatozoon) - The male gamete. [2]

Stratum basale - The deepest layer of the epidermis, made of epidermal stem cells. [6]

Stratum functionalis - a highly vascularized mucosal layer that undergoes monthly cyclical changes and is lost during menstruation

Stromal cells - Connective tissue cells of an organ found in the loose connective tissue. These are most often associated with the uterine mucosa and the ovary as well as the hematopoietic system and elsewhere.

Supraoptic nucleus (SO) - Hypothalamic nucleus overlying the beginning of the **optic tract**. [3]

Tertiary follicle (also, antral follicles) - Ovarian follicles with a primary or secondary oocyte, multiple layers of granulosa cells, and a fully formed antrum. [2]

Theca cells - Estrogen-producing cells in a maturing ovarian follicle. [2]

Tonic inhibition - A form of neurotransmission usually thought to reduce the excitability of all neurons

Tunica albuginea - the fibrous-elastic sheath of connective tissue that surrounds the shaft and glans of the clitoris

Uterine tubes (also, fallopian tubes or oviducts) - Ducts that facilitate transport of an ovulated oocyte to the uterus. [2]

Uterus - The muscular hollow organ in which a fertilized egg develops into a fetus. [2]

Vagina - The tunnel-like organ that provides access to the uterus for the insertion of semen and from the uterus for the birth of a baby. [2]

Zygote - The fertilized **ovum** resulting from the fusion of a male and a female gamete. [3]

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CHAPTER OVERVIEW

3: Pathologies of the Female Reproductive System

3.1: Uterine Pathologies

3.1.1: Uterine Malformations

3.1.2: Abnormal Uterine Bleeding (AUB)

3.1.3: Endometritis

3.1.4: Adenomyosis

3.1.5: Endometriosis

3.1.6: Endometrial Hyperplasia

3.1.7: Endometrial Carcinoma (EC)

3.1.8: Endometrial Polyps

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3.2: Cervical Pathologies

3.2.1: Cervicitis

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3.3: Vulvovaginal Pathologies

3.3.1: Inflammatory Disorders of the Vulva

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3.3.3: Neoplastic Disroders of the Vulva and Vagina

3.4: Ovarian Pathologies

3.4.1: Non-Neoplastic Lesions

3.4.2: Ovarian Tumors (WHO Classification)

3.5: Breast Pathologies (Forthcoming)

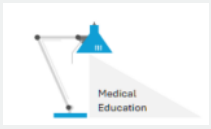
3.6: Pathologies of Pregnancy (Forthcoming)

3.7: Glossary

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About this Chapter

The content of this chapter is appropriate for, or easily adapted for the following audiences:





Learning Objectives

By the end of this chapter, learners will be able to

- Discuss the etiological factors, pathogenesis, and clinicopathological features of common female reproductive pathologies
- Identify abnormal histologic findings of the endometrium and compare the pathology of adenomyosis with endometriosis
- Discuss the histology of benign smooth muscle tumors of the uterus compared to malignancy.
- Identify the histologic changes of HPV infection, cervical dysplasia, and cervical cancer, and explain the role of Gardasil in prevention.
- Identify the most common pathogens and symptoms of pelvic infections and the risk of transmission and treatment.
- Describe the histologic findings of ovarian neoplasms, including those derived from epithelium, sex-cord stromal, and germ cell neoplasms.

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3.1: Uterine Pathologies

In this Section:

3.1.1 Uterine Malformations

3.1.2 Abnormal Uterine Bleeding (AUB)

3.1.3 Endometritis

3.1.4 Adenomyosis

3.1.5 Endometriosis

3.1.6 Endometrial Hyperplasia

3.1.7 Endometrial Carcinoma (EC)

3.1.8 Endometrial Polyps

3.1.9 Uterine Leiomyoma (uLM)

3.1.10 Leiomyosarcoma

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3.1.1: Uterine Malformations

3.1.1.1 Definition and Clinical Presentation

These are malformations that occur during **embryogenesis** due to abnormal development of the **Müllerian duct(s)**. Based on the type of malformation, the clinical presentations are variable. These include **amenorrhea**, infertility, recurrent miscarriages/abortions, pain, preterm birth, cervical insufficiency, premature rupture of membranes, fetal malpresentation, fetal growth restriction, **placental abruption**, **placenta previa**, **placental retention**, and cesarean birth 1. Women with **canalization defect unification defect** are less likely to achieve clinical pregnancy and live birth; they were more likely to experience spontaneous early pregnancy loss after In-Vitro Fertilization Embryo Transfer (IVF-ET) when compared with women with normal uterus.[1]

3.1.1.2 Types

The following is based on the American Fertility Society (AFS). The following malformations are recognized (Figure 3.1.1).[2]

- Class I

Müllerian agenesis (absent uterus): Hypoplasia (marked reduction in the size of the uterus) or agenesis (complete absence) of parts of the uterus. The latter includes

- Vaginal hypoplasia or agenesis
- Cervical hypoplasia or agenesis
- Fundal hypoplasia or agenesis
- Tubal hypoplasia or agenesis
- Combined hypoplasia and agenesis of different parts of the uterus

Mayer-Rokitansky-Kuster-Hauser syndrome is a congenital aplasia of the uterus and the upper part (2/3) of the vagina in women showing normal development of secondary sexual characteristics and a normal 46, XX karyotype. It affects at least 1 out of 4500 women and presents with primary amenorrhea.[3]

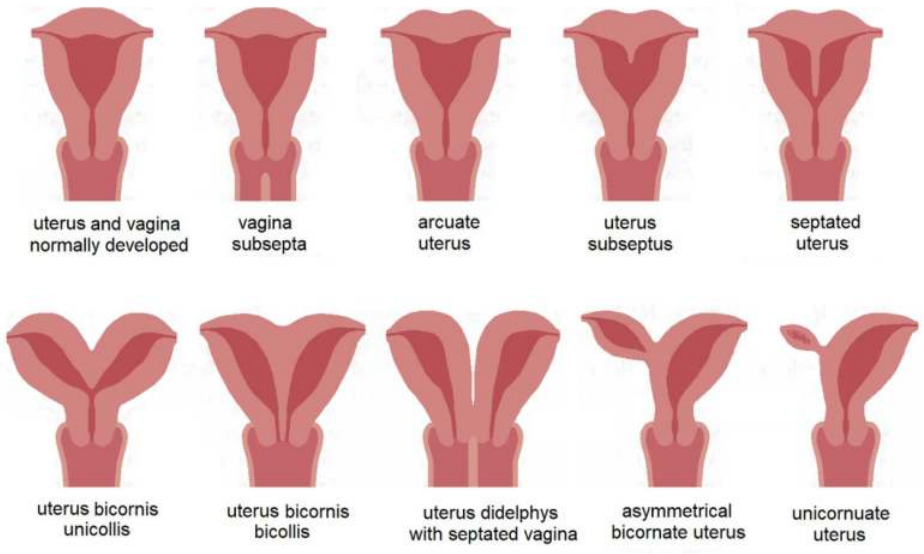


Figure 3.1.1. Diverse uterine malformations in humans.
Image Source: Sciencia58. "Uterine malformation". (2023) This work is openly licensed via CC0 Creative Commons license. Available from Wikimedia Commons.

- Class II

Unicornuate uterus: There is a partial or complete lack of one Müllerian duct, leading to an imaging abnormality, a "banana-shaped uterus." One Müllerian duct gives rise to one half of the uterus, which fuses with the other half, developing from the other Müllerian duct to form a normal uterus. Several subtypes of the unicornuate uterus (Figure 3.1.2) include

- A hemiuterus without a rudimentary horn
- A hemiuterus with a non-functional rudimentary horn (no cavity in the rudimentary horn)
- A hemiuterus with a functional, communicating rudimentary horn
- A hemiuterus with a functional, non-communicating rudimentary horn

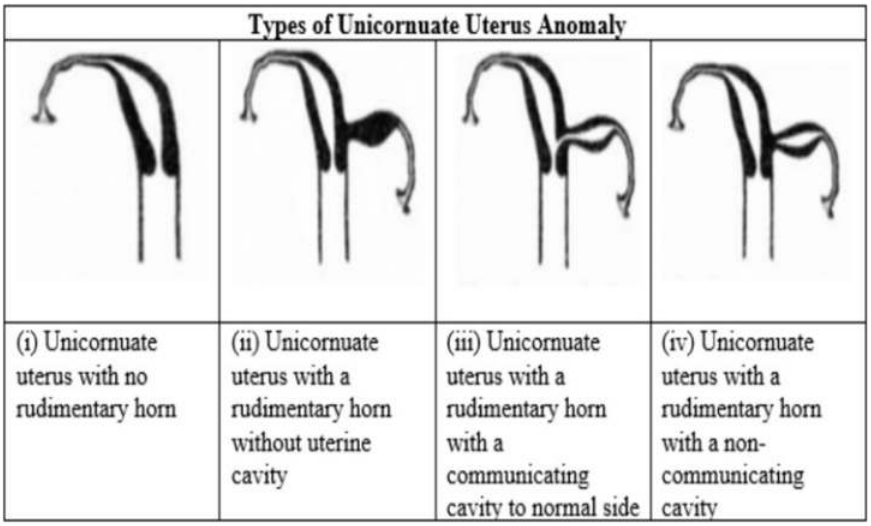


Figure 3.1.2 Types of unicornuate uterus anomaly.
Image Source: Ladke, Pooja, Ashish N Ambhore, Avinash Dhok, Kajal Mitra, and Vrushali Dalvi. “A Unique Case of Unicornuate Uterus With a Non-Communicating Rudimentary Horn and Hematometra.” *Cure*us 14, No. 12 (2022): e32640. This work is openly licensed via CC-BY license. doi.org/10.7759/cureus.32640

- Class III

Uterus didelphys/didelphis (double uterus): This anomaly results from the failure of fusion of both Müllerian ducts, leading to the formation of a "double uterus." It might also be associated with a double cervix and a vaginal partition.

- Class IV

Bicornuate uterus (uterus with two horns): This anomaly results from the failure of fusion of only the upper parts of the Müllerian system, leading to a bifurcated upper part of the uterus. The caudal (lower) part of the uterus is normal.

- Class V

Septate uterus (uterine septum or partition): After the fusion of the two Müllerian ducts, the septum between them persists, leading to the splitting of the uterine cavity. The persistent septum could be complete or partial.

- Class VI

DES drug-related uterus: Diethylstilbestrol (DES) exposure during pregnancy can cause uterine abnormalities, including

- Uterine shape: T-shaped or hypoplastic cavity
- Uterine muscle layers: disruption of the development of the uterine muscle layers
- Uterotubal junction: maldevelopment of the uterotubal junction
- Vaginal epithelium non-stratification and lack of vaginal glands resorption leading to vaginal adenosis

Note

The American Society for Reproductive Medicine (ASRM) Task Force on Mullerian Anomalies Classification updated the original AFS classification to include additional anomalies. For further details, please refer to ASRM mullerian anomalies classification 2021.

Glossary Terms

Embryogenesis

Complicated process by which a fertilized egg develops into an embryo

Müllerian ducts

Pair of ducts near the **Wolffian ducts** in a developing embryo. In the male embryo, they degenerate with the appearance of testicular **anti-Müllerian hormone**

Placental abruption

Premature separation of the normally implanted **placenta** from the **uterus**

Placenta previa

Abnormal placentation in which the **placenta** implants in the lower segment of the **uterus** (the zone of dilation) and may cover part or all of the opening of the **cervix**

Placental retention

Occurs when the placenta fails to be expelled after the **birth** of the **fetus**. A **placenta** is retained when the **uterus** fails to contract after the delivery of content, or when the placenta is abnormally attached to the **myometrium**

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3.1.2: Abnormal Uterine Bleeding (AUB)

3.1.2.1 Definitions

- Abnormal uterine bleeding: Non-gestational bleeding during the reproductive years. Involves any alteration in the normal frequency, regularity, duration, or volume of menstrual bleeding (heavy menstrual bleeding) as well as intermenstrual bleeding and unscheduled bleeding with pharmaceutical agents designed to suppress menstrual function
- Heavy menstrual bleeding (menorrhagia): An AUB symptom—excessive menstrual blood loss that interferes with a woman's physical, social, emotional and/ or material quality of life
- Intermenstrual irregular bleeding (metrorrhagia): An AUB symptom—uterine bleeding between regular menstrual periods
- Irregular menstruation: An AUB symptom—menstrual cycle lengths that vary by more than 7 (ages of 18–25 and 42–45 years) to 9 days (ages of 26–41 years)
- Prolonged menstrual bleeding: An AUB symptom—a menstrual period lasting more than 8 days
- Frequent menstrual bleeding: An AUB symptom—menstrual cycle of less than 24 days
- Infrequent menstrual bleeding: An AUB symptom—menstrual cycle length of more than 38 days
- Dysfunctional uterine bleeding: A clinical term for uterine bleeding without any underlying structural abnormality, caused mainly by hormonal imbalances[4]

3.1.2.2 Etiologies

The International Federation of Gynecologists and Obstetricians (FIGO) classification system of AUB (Figure 3.1.3) aimed to facilitate clinical care and research. The system used the "PALM-COEIN" nomenclature (**polyp**; **adenomyosis**; **leiomyoma**; **malignancy** and **hyperplasia**; **coagulopathy**; **ovulatory dysfunction**; **endometrial; iatrogenic**; and not yet classified). It systematically classifies AUB into groups with distinctively different structural and functional causes.[5]

- Structural Uterine Causes
  - Polyps
  - Adenomyosis
  - Leiomyoma
  - Malignancy and hyperplasia
- Non-Structural Causes
  - Coagulation disorders
  - Ovulatory disorders
  - Endometrial disorders
  - Iatrogenic
  - Not otherwise classified

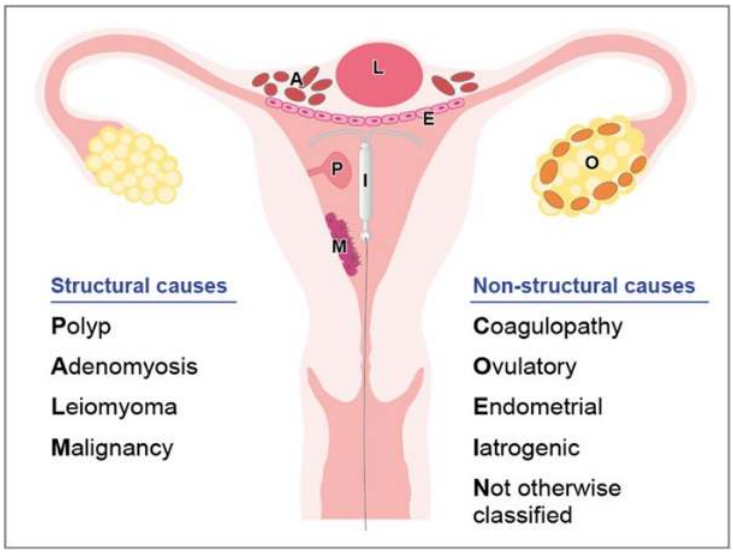


Figure 3.1.3 FIGO classification of causes of AUB; “PALM-COEIN.”
Image Source: Chodankar, Rohan, Hilary O.D. Critchley, and Carlos Simón. “Biomarkers in Abnormal Uterine Bleeding.” Biology of Reproduction 101, no. 6 (2019). This work is openly licensed via CC BY 4.0. license. doi.org/10.1093/biolre/ioy231

FIGO developed a new classification of ovulatory disorders (Figures 3.1.4 and 3.1.5) using a three-level multi-tiered system. The primary level of the system is based on an anatomic model (**Hypothalamus**, **Pituitary**, **Ovary**) that is completed with a separate category for polycystic ovary syndrome (PCOS). The system uses the acronym HyPO-P. Each anatomic category is stratified in the second layer of the system to provide granularity for investigators, clinicians, and trainees using the "GAIN-FIT-PIE" mnemonic (Genetic, **Autoimmune**, Iatrogenic, **Neoplasm**; **Functional, Infectious** and **Inflammatory**, **Trauma** and **Vascular**; **Physiological, Idiopathic**, **Endocrine**). The tertiary level of the system allows for specific diagnostic entities.[6]

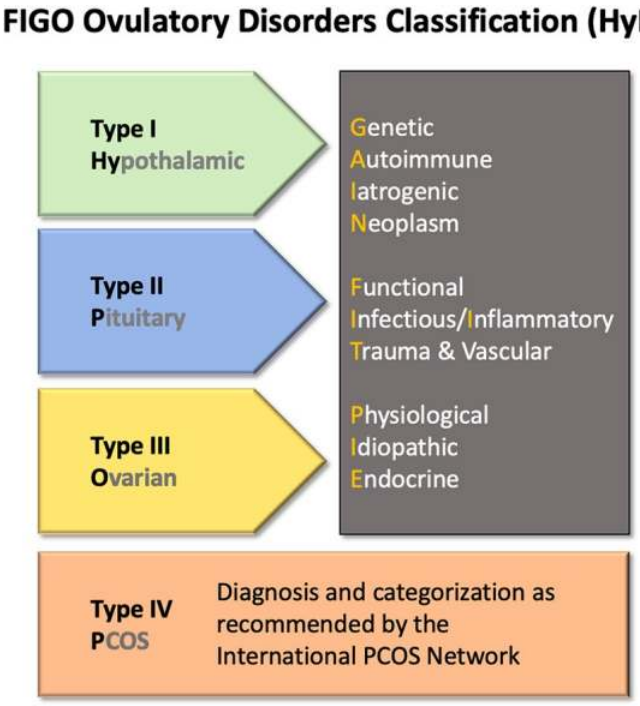


Figure 3.1.4 Graphical depiction of the proposed FIGO Ovulatory Disorders Classification System. Note: After the individual is diagnosed with an ovulatory disorder, the core or first level of the system is allocation to type I, II, or III disorders according to their presumed primary source: hypothalamus, pituitary gland, or ovary, respectively. PCOS comprises the type IV category, and the criteria proposed by WHO are to be used to determine this categorization. The second level stratifies each anatomic category (types I–III) into the known or presumed mechanism according to the 'GAIN-FIT-PIE' mnemonic as appropriate and applicable. FIGO, International Federation of Gynecology and Obstetrics; GAIN-FIT-PIE, Genetic, Autoimmune, Iatrogenic, Neoplasm; Functional, Infectious and Inflammatory, Trauma and Vascular; Physiological, Idiopathic, Endocrine; PCOS, polycystic ovary syndrome; WHO, World Health Organization.

Image Source: Munro, Malcolm G, Adam H Balen, SiHyun Cho, Hilary O D Critchley, Ivonne Díaz, Rui Ferriani, Laurie Henry, Edgar Mocanu, and Zephne M van der Spuy. FIGO Committee on Menstrual Disorders and Related Health Impacts, and FIGO Committee on Reproductive Medicine, Endocrinology, and Infertility. "The FIGO Ovulatory Disorders Classification System," *Human Reproduction*, 37, No. 10 (October 2022):2446–2464. Distributed under the terms of the Creative Commons CC BY license. doi.org/10.1093/humrep/deac180

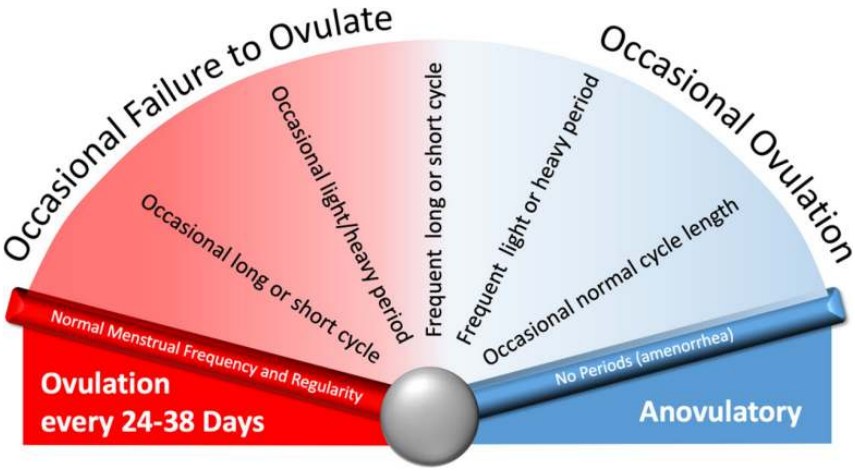


Figure 3.1.5 Disorders of ovulation exist on a spectrum that ranges from occasional failure to ovulate to chronic anovulation. Note: Typically, but not always these disorders manifest abnormalities in menstrual parameters, such as frequency, regularity, duration and volume of bleeding, and, in the case of chronic anovulation with amenorrhea. It is apparent that the luteinized unruptured follicle (LUF) and luteal out of phase (LOOP) disorders exist on a similar spectrum of varying frequency.

Image Source: Munro, Malcolm G, Adam H Balen, SiHyun Cho, Hilary O D Critchley, Ivonne Díaz, Rui Ferriani, Laurie Henry, Edgar Mocanu, and Zephne M van der Spuy. FIGO Committee on Menstrual Disorders and Related Health Impacts, and FIGO Committee on Reproductive Medicine, Endocrinology, and Infertility. "The FIGO Ovulatory Disorders Classification System," *Human Reproduction*, 37, No. 10 (October 2022):2446–2464. Distributed under the terms of the Creative Commons CC BY license. doi.org/10.1093/humrep/deac180

Glossary Terms

Adenomyosis

Relating to, affecting, or consisting of a vessel or vessels, especially those which carry blood.

Autoimmune

Disorders in which the immune system overreacts and begins to attack itself

Coagulopathy

(also called a bleeding disorder) A condition in which the blood's ability to coagulate (form clots) is impaired

Endocrine

Cells, tissues, and organs that secrete hormones as a primary or secondary function and play an integral role in normal bodily processes

Endometrial

Related to the inner lining of the uterus, part of which builds up during the secretory phase of the menstrual cycle and then sheds with menses

Hyperplasia

Abnormal growth due to the production of cells

Hypothalamus

Major region of the diencephalon that is responsible for coordinating autonomic and endocrine control of homeostasis

Iatrogenic

Relating to illness caused by medical examination or treatment (e.g., "Drugs may cause side effects which can lead to iatrogenic disease")

Idiopathic

something that is unknown

Infectious

transmission of **infectious** disease or pathogens. When transmission is within the same species, the mode can be horizontal or vertical (**infectious disease transmission, vertical**)

Inflammatory

Basic innate immune response characterized by heat, redness, pain, and swelling

Leiomyoma

Benign tumor derived from smooth muscle tissue, also known as a fibroid tumor. They rarely occur outside of the **uterus** and the **gastrointestinal tract** but can occur in the **skin** and **subcutaneous tissue**, probably arising from the smooth muscle of small blood vessels in these tissues

Malignancy

Cancerous

Neoplasm

New abnormal growth of tissue. Malignant neoplasms show a greater degree of anaplasia and have the properties of invasion and metastasis, compared to benign neoplasms

Ovary

female gonad that produces oocytes and sex steroid hormones (notably estrogen and progesterone)

Ovulatory dysfunction

Regular, infrequent (less than nine per year) menstrual periods or does not ovulate at all, she is said to have ovulatory dysfunction

Physiological

relating to the way in which a living organism or bodily part functions

Pituitary

Bean-sized organ suspended from the hypothalamus that produces, stores, and secretes hormones in response to hypothalamic stimulation (also called hypophysis)

Polyp

Growth that protrudes from a mucous membrane (National Cancer Institute)

Trauma

Physical injury

Vascular

Relating to, affecting, or consisting of a vessel or vessels, especially those which carry blood

Footnotes

4. Munro, Malcolm G, Adam H Balen, SiHyun Cho, Hilary O D Critchley, Ivonne Díaz, Rui Ferriani, Laurie Henry, Edgar Mocanu, and Zephne M van der Spuy. FIGO Committee on Menstrual Disorders and Related Health Impacts, and FIGO Committee on Reproductive Medicine, Endocrinology, and Infertility. "The FIGO Ovulatory Disorders Classification System," *Human Reproduction*, 37, No. 10 (October 2022):2446–2464. Distributed under the terms of the Creative Commons CC BY license. doi.org/10.1093/humrep/deac180
5. Munro et al, 2022
6. Munro et al, 2022

Image Acknowledgements

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- Munro, Malcolm G, Adam H Balen, SiHyun Cho, Hilary O D Critchley, Ivonne Díaz, Rui Ferriani, Laurie Henry, Edgar Mocanu, and Zephne M van der Spuy. FIGO Committee on Menstrual Disorders and Related Health Impacts, and FIGO Committee on Reproductive Medicine, Endocrinology, and Infertility. "The FIGO Ovulatory Disorders Classification System," *Human Reproduction*, 37, No. 10 (October 2022):2446–2464. Distributed under the terms of the Creative Commons CC BY license. doi.org/10.1093/humrep/deac180

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3.1.3: Endometritis

3.1.3.1 Definition

Inflammation of the **endometrium** is classified into acute or chronic based on the **inflammatory cellular infiltrate** (**neutrophilic** or **lymphoplasmacytic**). **Lymphocytes** are normally present in the endometrium; the presence of **plasma cells** is diagnostic for chronic endometritis.[7]

3.1.3.2 Etiology

Acute endometritis is less common than chronic and is mainly caused by postpartum bacterial infections due to placental or abortive residues. It could also be associated with other urogenital inflammatory conditions caused by bacterial or viral infections.

Chronic endometritis could follow acute inflammation or happen as subtle inflammation without an initial acute stage. It occurs as part of the **pelvic inflammatory disease**. The most frequent causative agents are **pyogenic** pathogens such as streptococci, staphylococci, enterococci, and Escherichia coli, as well as bacteria such as *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, *Mycoplasma*, and *Ureaplasma urealyticum*. Viruses such as herpes simplex virus (HSV) and cytomegalovirus (CMV) infections can cause postpartum endometritis, particularly in patients with HIV. Mechanical and chemical factors such as intrauterine devices can also cause chronic endometritis. **Granulomatous endometritis** is caused by tuberculosis and is usually associated with **tuberculous salpingitis** and **peritonitis**. These are usually seen in **immunocompromised** women.

3.1.3.3 Clinicopathological Features

- Clinical Picture

All types of acute endometritis present with fever, abdominal pain, and menstrual abnormalities. Chronic endometritis is often clinically silent. Some cases present with infertility, recurrent miscarriage, and repeated abortions. Endometrial inflammation seems to interfere with the physiological mechanisms of oocyte fertilization and embryonic implantation. Therefore, **hysteroscopy** should be a part of the diagnostic work-up of infertile women complaining of unexplained repeated miscarriage or repeated implantation failure.

Other symptoms include abnormal uterine bleeding (intermenstrual spotting or **metrorrhagia**), **dysmenorrhea**, **dyspareunia, leucorrhea** (malodorous, purulent vaginal discharge), urinary symptoms, and mild fever.

Tubercular endometritis always occurs secondary to respiratory or abdominal localization, with **adnexal** localization. It generally affects young women of childbearing age and is rare in menopausal women. Symptoms are variable, including changes in menstrual flow (**polymenorrhea** to **amenorrhea**) and infertility.

3.1.3.4 Diagnosis

- Imaging and Hysteroscopy

Two-dimensional transvaginal sonography (TVS) is difficult to diagnose chronic endometritis due to the absence of pathognomonic signs associated with the condition. Sonography signs include **hematometra**, endometrium with **hyperechogenic spots**, and increased endometrial thickness that mismatches the menstrual cycle phase.

A **hysteroscopy**, performed in the **proliferative phase** of the menstrual cycle, allows the identification of signs of endometrial inflammation. The pathognomonic hysteroscopic findings (Figures 3.1.6, 3.1.7, 3.1.8) include:

- Hyperemia: Accentuated vascular network, especially at the peri glandular level.
- Stromal edema: Pale and thickened endometrium
- Micropolyps: Small pedunculated, vascularized protrusions of the uterine mucosa (<1 mm) covered by endometrium and characterized by an accumulation of inflammatory cells (lymphocytes, plasma cells, and eosinophils) intermingled with normal stromal cells.

In tuberculous endometritis, suggestive diagnostic signs include the presence of a thin, uneven, and pale endometrium with irregular whitish spots scattered over the uterine walls. Intrauterine adhesions are common.



Figure 3.1.6 Hysteroscopic view of chronic endometritis in a 30-year-old infertile woman. Saline used as distension medium does not affect endometrial microcirculation, making it easier to identify the characteristic signs of chronic endometritis. Note the micropolyps, which appear as small pedunculated, vascularized protrusions (<1 mm) on the uterine mucosa (A). The close-up view clearly shows a marked accentuation of the vascular network at the level of the uterine fundus (B). To right, an overt stromal edema is evident (C), though the examination was carried out in the early proliferative phase.
Image Source: Sardo, Attilio Di Spiezio, Federica Palma, Gloria Calagna, Brunella Zizolfi, Giuseppe Bifulco, Attilio Di Spiezio Sardo, Federica Palma, Gloria Calagna, Brunella Zizolfi, and Giuseppe Bifulco. “Chronic Endometritis.” Arkhiv Patologii 62, no. 3 (June 29, 2016): 48–52. Distributed under the terms of the CC BY 3.0 license. doi.org/10.5772/63023

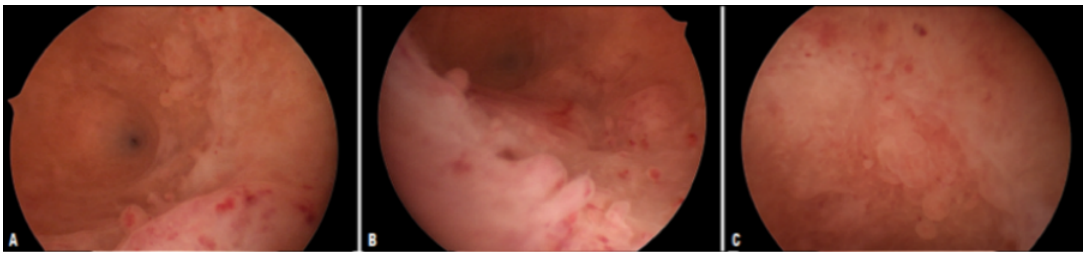


Figure 3.1.7 Hysteroscopic view of chronic endometritis in a 34-year-old woman with a positive anamnesis of three early spontaneous abortions (A–C). The stromal edema is clearly evident on the posterior wall (A) and micropolyps are detected on any of the uterine walls (A–C).
Image Source: Sardo, Attilio Di Spiezio, Federica Palma, Gloria Calagna, Brunella Zizolfi, Giuseppe Bifulco, Attilio Di Spiezio Sardo, Federica Palma, Gloria Calagna, Brunella Zizolfi, and Giuseppe Bifulco. “Chronic Endometritis.” Arkhiv Patologii 62, no. 3 (June 29, 2016): 48–52. Distributed under the terms of the CC BY 3.0 license. doi.org/10.5772/63023

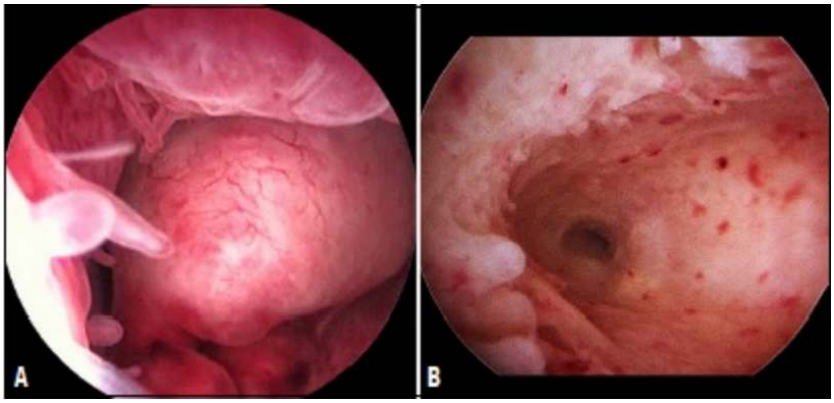


Figure 3.1.8 Detail of micropolyps under hysteroscopic examination using a liquid distension medium: the micropolyps, which appear with a varied morphology, are scattered over the uterine wall and may often be encountered with polyps (A) and/or pseudopolyps.
Image Source: Sardo, Attilio Di Spiezio, Federica Palma, Gloria Calagna, Brunella Zizolfi, Giuseppe Bifulco, Attilio Di Spiezio Sardo, Federica Palma, Gloria Calagna, Brunella Zizolfi, and Giuseppe Bifulco. “Chronic Endometritis.” Arkhiv Patologii 62, no. 3 (June 29, 2016): 48–52. Distributed under the terms of the CC BY 3.0 license. doi.org/10.5772/63023

Other morphological features include increased B lymphocytes; normally, these are less than 1% of the leukocyte count.

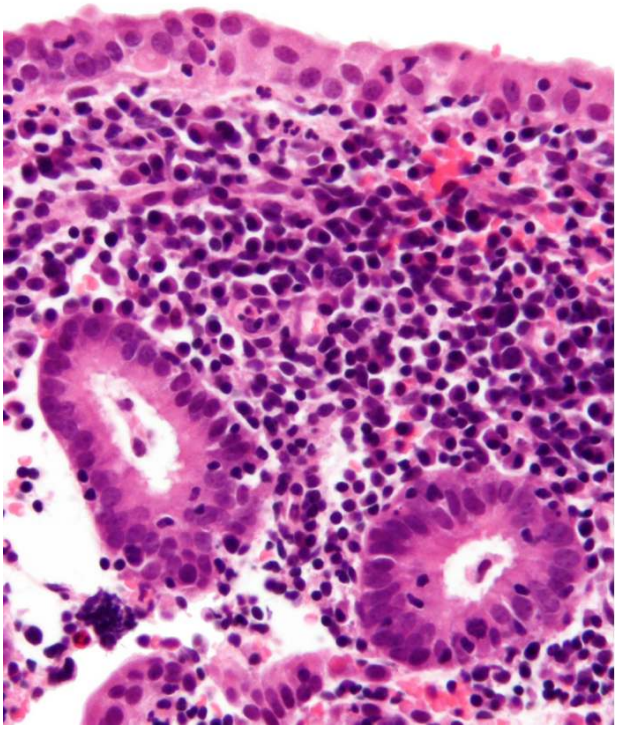


Figure 3.1.9 Very high magnification micrograph of endometritis. H&E stain. Images show endometrium with abundant plasma cells (blue arrows) (diagnostic for chronic endometritis).
Image Source: Neprhon. "Endometriosis -2-cropped". (2012). Own work, licensed under the CC SA 3.0. Available from Wikimedia Commons.

3.1.3.5 Treatment

Broad-spectrum antibiotics are the first line of treatment. Doxycycline is the drug of choice, administered in doses of 100 mg every 12 hours for 14 days. Cephalosporins, macrolides, or quinolones could also be used. It is preferable that the partner also undergoes the same antibiotic treatment. An endometrial culture should be performed in case of persistent endometritis, and an appropriate antibiotic treatment must be prescribed. In cases of tuberculous endometritis, the patient should be given a specific antibiotic therapy for tuberculosis (isoniazid, ethambutol, rifampicin, and pyrazinamide for 2 months, followed by isoniazid and rifampicin for another 4 months).

Glossary Terms

Adnexal

Relating to the uterine appendages (**adnexa uteri**), including diseases involving the **ovary**, the **fallopian tubes**, and ligaments of the uterus (**broad ligament**; **round ligament**)

Amenorrhea

Absence of menstruation

Dysmenorrhea

Painful menstruation

Dyspareunia

Genital pain before, during, or after intercourse

Endometrium

Inner lining of the uterus, part of which builds up during the secretory phase of the menstrual cycle and then sheds with menses

Granulomatous endometrititis

A defect of leukocyte function in which phagocytic cells ingest but fail to digest bacteria, resulting in recurring bacterial infections with granuloma formation. When chronic granulomatous disease is caused by mutations in the CYBB gene, the condition is inherited in an X-linked recessive pattern. When chronic granulomatous disease is caused by CYBA, NCF1, NCF2, or NCF4 gene mutations, the condition is inherited in an autosomal recessive pattern

Hematometra

Blood-filled UTERUS

Hyperechogenic spots

ddd

Hysteroscopy

Endoscopic examination of the uterus

Immunocompromised

human or animal whose immunologic mechanism is deficient because of an immunodeficiency disorder or other disease or as the result of the administration of immunosuppressive drugs or radiation

Leucorrhea

ccc

Lymphocytes

Agranular leukocytes of the lymphoid stem cell line, many of which function in specific immunity

Lymphoplasmacytic

ccc

Metrorrhagia

Excessive bleeding from the uterus not related to menstruation

Neutrophilic

Related to granulocytes that stain with a neutral dye and are the most numerous of the leukocytes; especially active against bacteria

Pelvic inflammatory disease

Spectrum of inflammation involving the female upper genital tract and the supporting tissues

Peritonititis

Inflammation of the peritoneum

Plasma cells

A type of B lymphocyte that produces antibodies, which bind to specific foreign or abnormal antigens in order to destroy them

Polymenorrhea

Variations of **menstruation** which may be indicative of disease

Proliferative phase

Phase of the menstrual cycle in which the endometrium proliferates

Pyogenic

ccc

Tuberculous salpingitis

inflammation of the uterine salpinx, the trumpet-shaped **fallopian tubes**, usually caused by ascending infections of organisms from the lower reproductive tract. Salpingitis can lead to tubal scarring, hydrosalpinx, tubal occlusion, **infertility**, and ectopic pregnancy (**pregnancy, ectopic**)

Footnotes

7. Sardo, Attilio Di Spiezio, Federica Palma, Gloria Calagna, Brunella Zizolfi, Giuseppe Bifulco, Attilio Di Spiezio Sardo, Federica Palma, Gloria Calagna, Brunella Zizolfi, and Giuseppe Bifulco. “Chronic Endometritis.” *Arkhiv Patologii* 62, no. 3 (June 29, 2016): 48–52. doi.org/10.5772/63023

Image Acknowledgements

- Neprhon. "Endometriosis -2-cropped". (2012). Own work, licensed under the CC SA 3.0. Available from Wikimedia Commons.
- Sardo, Attilio Di Spiezio, Federica Palma, Gloria Calagna, Brunella Zizolfi, Giuseppe Bifulco, Attilio Di Spiezio Sardo, Federica Palma, Gloria Calagna, Brunella Zizolfi, and Giuseppe Bifulco. “Chronic Endometritis.” *Arkhiv Patologii* 62, no. 3 (June 29, 2016): 48–52. doi.org/10.5772/63023

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3.1.4: Adenomyosis

3.1.4.1 Definition and Morphological Features

Adenomyosis is the presence of ectopic endometrial tissue (endometrial glands and stroma) in the **myometrium** (Figure 3.1.10).[8] Adenomyosis causes the uterus to enlarge (i.e., globular shape) due to the thickening of the uterine walls. This thickness is caused by reactive **hypertrophy** of the myometrium induced by the ectopic endometrial tissue.

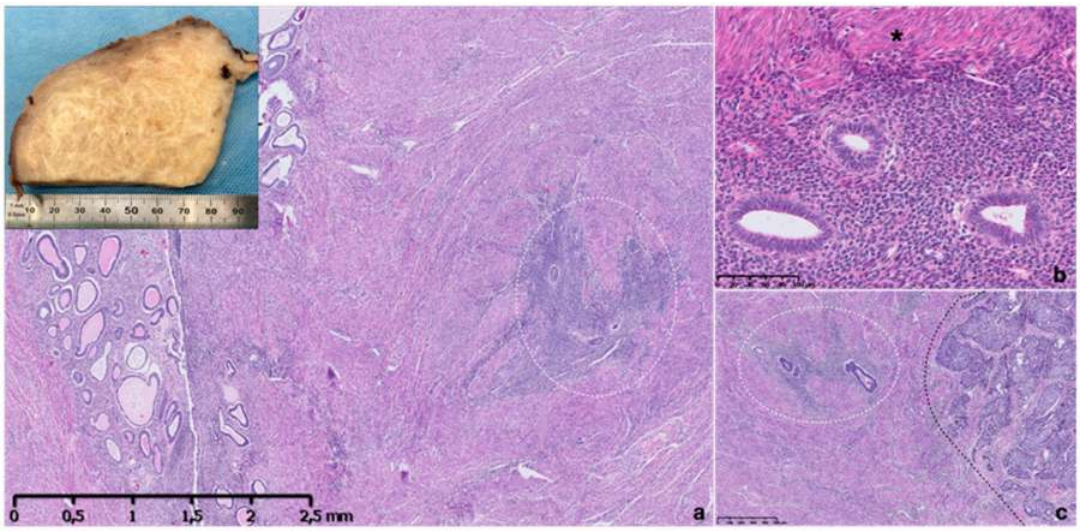


Figure 3.1.10 Macroscopic and microscopic appearance of adenomyosis. Thickened and trabeculated appearing myometrial wall with ill-defined hypertrophic swirls of smooth muscle of sectioned uterus with adenomyosis (a, inset). Histopathological image of uterine adenomyosis observed in hysterectomy specimen, with endometrial glandular and stroma invading the muscular myometrium (within circle) (a). Higher-power view showing ectopic endometrial glands and stroma surrounded by hyperplastic myometrium (asterisk) (b). Ectopic glandular epithelium is proliferative type and stroma is inactive, non-mitotic and composed of monotonous cells (b). A specimen showing an endometroid carcinoma infiltrating myometrial wall on the right (black line) and adenomyosis foci on the left (within line) (c). Hematoxylin and eosin stain.
Image Source: Camboni, Alessandra, and Etienne Marbaix. "Ectopic Endometrium: The Pathologist's Perspective" *International Journal of Molecular Sciences* 22, no. 20 (2021): 0974. This work is openly licensed via CC BY 4.0 license. doi.org/10.3390/ijms222010974

3.1.4.2 Differential Diagnosis

It is important to differentiate adenomyosis from **leiomyoma** because the latter could be treated via uterine-conserving therapy, whereas hysterectomy is the definitive treatment for severe adenomyosis. Cystic adenomyosis needs to be differentiated from a leiomyoma with central **hemorrhagic degeneration.** MRI could accurately differentiate between these conditions.[9] Adenomyosis and endometriosis can coexist.

3.1.4.3 Pathogenesis

Several theories exist regarding the pathogenesis of adenomyosis:[10]

- The invagination of the endometrial **basalis** into the myometrium due to a process of tissue injury and repair (TIAR).
- **De novo** development from **metaplasia** of displaced embryonic **pluripotent Müllerian** or **epithelial** remnants and differentiation of adult endometrial stem cells within the myometrium.

Several mechanisms are involved in adenomyosis pathogenesis. The endocrine mechanisms include steroid imbalances, pituitary influences, and genetic and epigenetic contributions. Several environmental factors are potential endocrine disrupters (Figure 3.1.11). Other mechanisms include **dysregulation** of **cell proliferation**, resistance to **apoptosis**, inflammatory responses, **neurogenesis**, **angiogenesis,** and **fibrosis**.

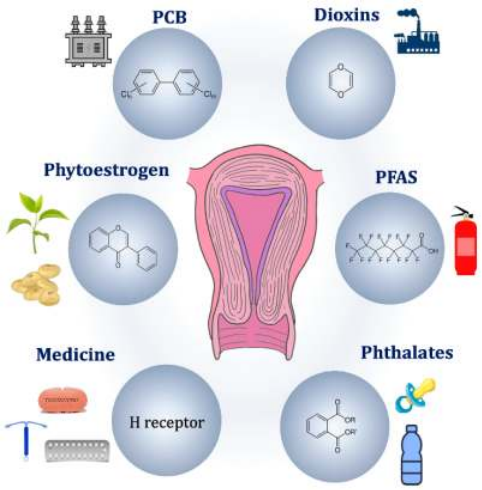


Figure 3.1.11 Potential endocrine pathogenic causes of adenomyosis.
Image Source: d'Otreppe, Juliette, Daniel Patino-García, Patryk Piekos, Matthieu de Codt, Diego D. Manavella, Guillaume E. Courtoy, and Renan Orellana. "Exploring the Endocrine Mechanisms in Adenomyosis: From Pathogenesis to Therapies." *Endocrines* 5, no. 1 (2024). This work is distributed under CC BY license. doi.org/10.3390/endocrines5010004

Note

For more details on pathogenesis, please refer to Juliette d'Otreppe et al., "Exploring the Endocrine Mechanisms in Adenomyosis: From Pathogenesis to Therapies."

d'Otreppe, Juliette, Daniel Patino-García, Patryk Piekos, Matthieu de Codt, Diego D. Manavella, Guillaume E. Courtoy, and Renan Orellana. "Exploring the Endocrine Mechanisms in Adenomyosis: From Pathogenesis to Therapies." *Endocrines* 5, no. 1 (2024). This work is distributed under CC BY license. doi.org/10.3390/endocrines5010004

3.1.4.4 Clinicopathological Features

The condition presents clinically with abnormal uterine bleeding [menorrhagia (prolonged menstrual bleeding) and/or dysmenorrhea (pain caused by menstrual periods)], pelvic pain, and infertility.

3.1.4.5 Treatment

There are several therapeutic options for treating adenomyosis (Figure 3.1.12); most of these are off-label medications. Therapeutic options include NSAIDS, combined oral contraceptives and progestin, Gonadotropin-releasing hormone agonists and antagonists, hormonal targeting therapies (selective receptor modulators, aromatase inhibitors, sulfatase inhibitors, and 17β-hydroxysteroid dehydrogenase type 1 inhibitors), and off-label medications (Metformin, Vit D, Linsitinib, and others).

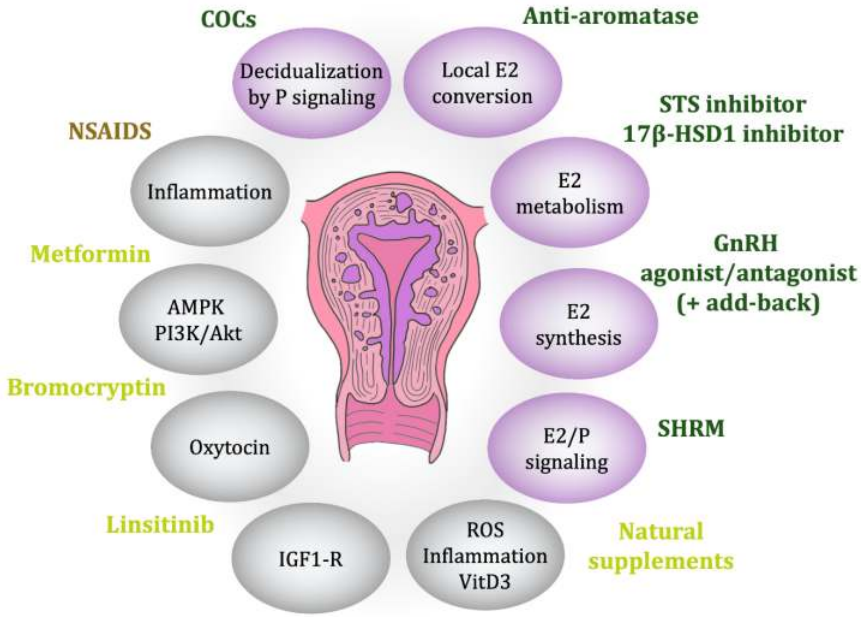


Figure 3.1.12 Existing and promising therapies. Ellipses denote the targeted action mode, with purple indicating steroid-related functions, primarily regarding estrogen. Family compound colors: brown represents family compounds with at least one approved drug for symptom management, green denotes at least one approved for disease control, and yellow signifies drugs currently under investigation.
Image Source: d'Otreppe, Juliette, Daniel Patino-García, Patryk Piekos, Matthieu de Codt, Diego D. Manavella, Guillaume E. Courtoy, and Renan Orellana. "Exploring the Endocrine Mechanisms in Adenomyosis: From Pathogenesis to Therapies." *Endocrines* 5, no. 1 (2024). This work is distributed under CC BY license. doi.org/10.3390/endocrines5010004

Note

For more details on treatment, please refer to Juliette d'Otreppe et al. "Exploring the Endocrine Mechanisms in Adenomyosis: From Pathogenesis to Therapies."

d'Otreppe, Juliette, Daniel Patino-García, Patryk Piekos, Matthieu de Codt, Diego D. Manavella, Guillaume E. Courtoy, and Renan Orellana. "Exploring the Endocrine Mechanisms in Adenomyosis: From Pathogenesis to Therapies." *Endocrines* 5, no. 1 (2024). This work is distributed under CC BY license. doi.org/10.3390/endocrines5010004

Angiogenesis

Development of new blood vessels from existing vessels

Apoptosis

Programmed cell death

Basalis

The basal part of the endometrium that is not shed during menstruation

Cell proliferation

All of the processes involved in increasing **cell number**, including **cell division**

De novo

The first occurrence of cancer in the body

Dysregulation

Abnormality or impairment in the regulation of a metabolic, physiological, or psychological process

Epithelial

Sheets of cells that cover the exterior surfaces of the body

Fibrosis

A process in which muscle fibers are replaced by scar tissue

Hemorrhagic degeneration

Hemorrhagic infarction of leiomyomas that often occurs during pregnancy

Hypertrophy

Enlargement of muscles

Leiomyoma

Benign tumor derived from smooth muscle tissue, also known as a fibroid tumor. They rarely occur outside of the **uterus** and the **gastrointestinal tract** but can occur in the **skin** and **subcutaneous tissue**, probably arising from the smooth muscle of small blood vessels in these tissues

Metaplasia

Condition in which there is a change of one adult cell type to another similar adult cell type

Myometrium

Smooth muscle layer of uterus that allows for uterine contractions during labor and expulsion of menstrual blood

Müllerian

Pair of ducts near the **Wolffian ducts** in a developing embryo. In the male embryo, they degenerate with the appearance of testicular **anti-Müllerian hormone**. In the absence of anti-Müllerian hormone, Mülerian ducts give rise to the female reproductive tract, including the **oviducts, uterus, cervix,** and **vagina**

Neurogenesis

Formation of **neurons** which involves the differentiation and division of **stem cells** in which one or both of the daughter cells become neurons

Pluripotent

Capable of giving rise to several different cell types

Footnotes

8. Chapron, Charles, Silvia Vannuccini, Pietro Santulli, Mauricio S Abrão, Francisco Carmona, Ian S Fraser, Stephan Gordts, et al. “Diagnosing Adenomyosis: An Integrated Clinical and Imaging Approach.” *Human Reproduction Update* 26, no. 3 (2020): 392–411. doi.org/10.1093/humupd/dmz049
9. Kinkel, Karen, Susan M Ascher, and Caroline Reinhold. “Benign Disease of the Uterus.” IDKD Springer Series, 2018. doi.org/10.1007/978-3-319-75019-4_3
10. Tempest, Nicola, Christopher J. Hill, Alison Maclean, Kathleen Marston, Simon G. Powell, Hannan Al-Lamee, and Dharani K. Hapangama. “Novel Microarchitecture of Human Endometrial Glands: Implications in Endometrial Regeneration and Pathologies.” *Human Reproduction Update* 28, no. 2 (2022). doi.org/10.1093/humupd/dmab039.; d’Otreppe, Juliette, Daniel Patino-García, Patryk Piekos, Matthieu de Codt, Diego D. Manavella, Guillaume E. Courtoy, and Renan Orellana. “Exploring the Endocrine Mechanisms in Adenomyosis: From Pathogenesis to Therapies.” *Endocrines* 5, no. 1 (2024). CC BY doi.org/10.3390/endocrines5010004

Image Acknowledgements

Camboni, Alessandra, and Etienne Marbaix. "Ectopic Endometrium: The Pathologist’s Perspective" *International Journal of Molecular Sciences* 22, no. 20 (2021): 0974. This work is openly licensed via CC BY 4.0 license. doi.org/10.3390/ijms222010974

d’Otreppe, Juliette, Daniel Patino-García, Patryk Piekos, Matthieu de Codt, Diego D. Manavella, Guillaume E. Courtoy, and Renan Orellana. “Exploring the Endocrine Mechanisms in Adenomyosis: From Pathogenesis to Therapies.” *Endocrines* 5, no. 1 (2024). This work is distributed under CC BY license. doi.org/10.3390/endocrines5010004

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3.1.5: Endometriosis

3.1.5.1 Definition

Endometriosis is the presence of **extrauterine** functional **endometrium**-like tissue (**glands** and **stroma**). The extrauterine structures commonly involved are the **ovaries**, **pouch of Douglas**, **uterine ligaments**, **fallopian tubes**, the **presacral nerves,** the anterior abdominal wall, and/or the **diaphragm**. It could also involve the **peritoneal cavity**, **periumbilical tissue**, and **laparotomy scars.** When located elsewhere than in the ovary or on the **superficial peritoneum**, endometriosis is referred to as being deep, usually lying 5 mm below the peritoneum within the bladder, vaginal, or bowel wall.[11]

3.1.5.2 Morphological Features

Gross **morphological** features of endometriosis depend on the duration of the disease, depth of penetration of **lesions**, **localization**, and timing of the menstrual cycle. Implants range from small (usually less than 2 cm) to **cystic**, **nodular,** or **polypoid masses**. Lesions vary in color based on the evolution of the disease due to the accumulation of **hemosiderin**. They could be unpigmented or red, then progress to mature blue or dark-pigmented lesions. They could also become white **fibrotic** scars. Lesions become more swollen and congested under hormonal stimulation during the menstrual cycle. In severe cases, **hemorrhages** and the resulting iron accumulation trigger **inflammation,** leading to **fibrosis**, scarring, and **adhesions**, distorting the normal pelvic anatomy and a frozen pelvis. Ovarian endometriotic cysts (endometriomas) are filled with blood and are commonly known as ‘chocolate cysts.’ In more than half of cases, endometriomas are bilateral and typically do not exceed 15 cm in diameter. Endometriomas have fibrotic walls, a smooth lining, and dense, dark brown cyst contents, often adherent to adjacent organs (Figures 3.1.13 and 3.1.14).[12]

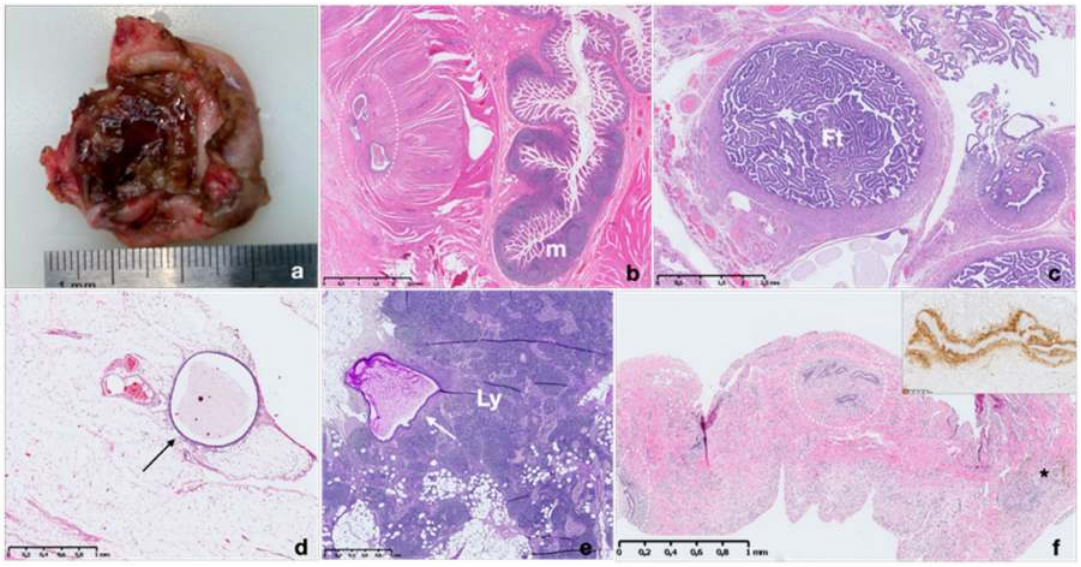
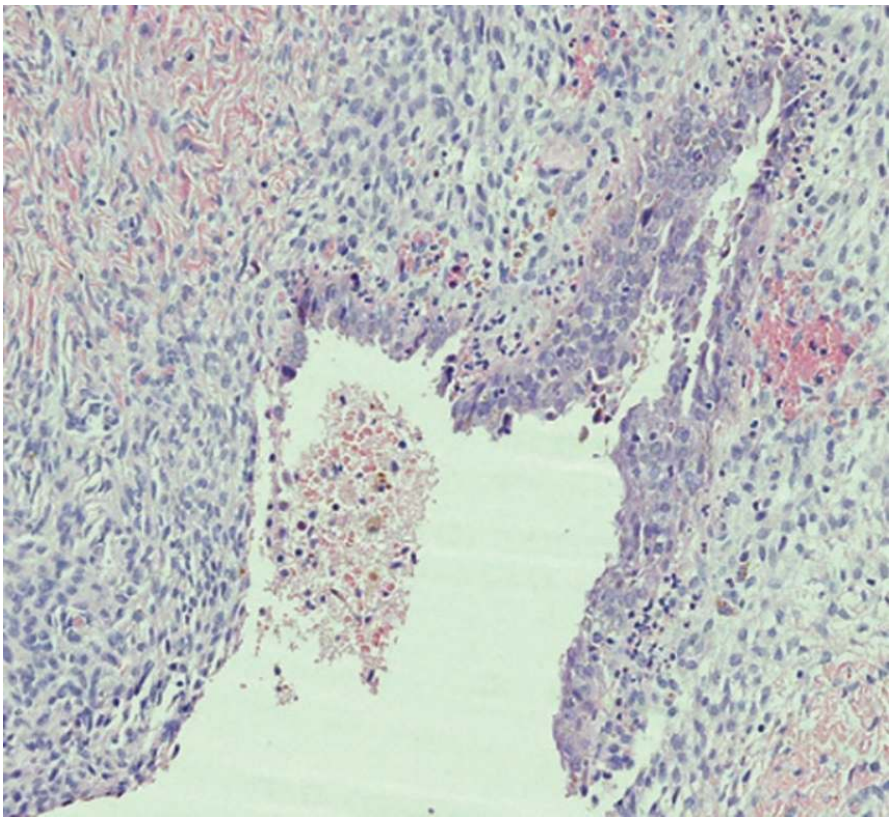


Figure 3.1.13 Macroscopic and microscopic appearance of endometriosis in different sites. Macroscopic picture of ovarian endometrioma with fibrotic wall and a dense, dark brown content (chocolate cyst) (a).

Histopathological images of endometriotic implants in intestinal wall, fallopian tube, mesenteric adipose tissue, lymph node and diaphragm (b–f); m: intestinal mucosa; Ft: Fallopian tube; Ly: lymph node. The withe circles and the arrows highlight endometrial implants composed by several endometrial glands and stroma (b–f). Note the presence of hemosiderin-laden macrophages (asterisk) (f). Immunohistochemistry for CD10 shows strong expression in stroma surrounding an ectopic endometrial gland in the diaphragm (f inset). Hematoxylin and eosin stain.

Image Source: Camboni, Alessandra, and Etienne Marbaix. "Ectopic Endometrium: The Pathologist's Perspective" International Journal of Molecular Sciences 22, no. 20 (2021): 0974. This work is openly licensed via CC BY 4.0 license. doi.org/10.3390/ijms222010974



3.1.14 Histopathology of ovarian endometrioma. The cyst wall is lined by cylindrical endometrial-type epithelium. (H&E) staining method (×10 magnification). Notice the brown hemosiderin deposits.

Image Source: Zucchini, Cinzia, Paola de Sanctis, Chiara Facchini, Nadine di Donato, Giulia Montanari, Valentina Bertoldo, Antonio Farina, Alessandra Curti, and Renato Seracchioli. "Performance of Circulating Placental Growth Factor as a Screening Marker for Diagnosis of Ovarian Endometriosis: A Pilot Study." *International Journal of Fertility and Sterility* 9, no. 4 (2016). This work is distributed under a CC BY 2.5 license. ce of Circulating Placental Growth Factor as a Screening Marker for Diagnosis of Ovarian Endometriosis: A Pilot Study." International Journal of Fertility and Sterility 9, no. 4 (2016). CC BY 2.5

3.1.5.3 Pathogenesis

The exact pathogenesis of the condition is not fully understood. It is proposed that endometriosis originates from uterine endometrial cells through several theories (Figure 3.1.15), including the following:[13]

- **Retrograde** menstruation (i.e., regurgitation theory) causes shed endometrial cells to pass through the **fallopian tubes** and be implanted in the pelvis. These cells demonstrate a cyclical response to ovarian hormones and resist **apoptosis** with sustained **proliferation**.
- Benign **metastasis** theory (lymphovascular dissemination): Endometrial tissue migrates to distant sites through blood vessels and **lymphatics**.

Alternatively, it is proposed that endometriosis originates from extrauterine cells that can form endometrial cells through the following theories:

3.1.5.3.1 Coelomic Metaplasia Theory

- The **mesothelium** of the abdomen or pelvis undergoes **metaplastic** changes to form endometrium. During embryologic development, the **Müllerian ducts** and the endometrium develop from the mesothelium.
- The mesonephric remnants can differentiate into ectopic endometrial tissue.

3.1.5.3.2 The extrauterine stem cell theory

Stem cells from the bone marrow can differentiate into endometrial tissue.

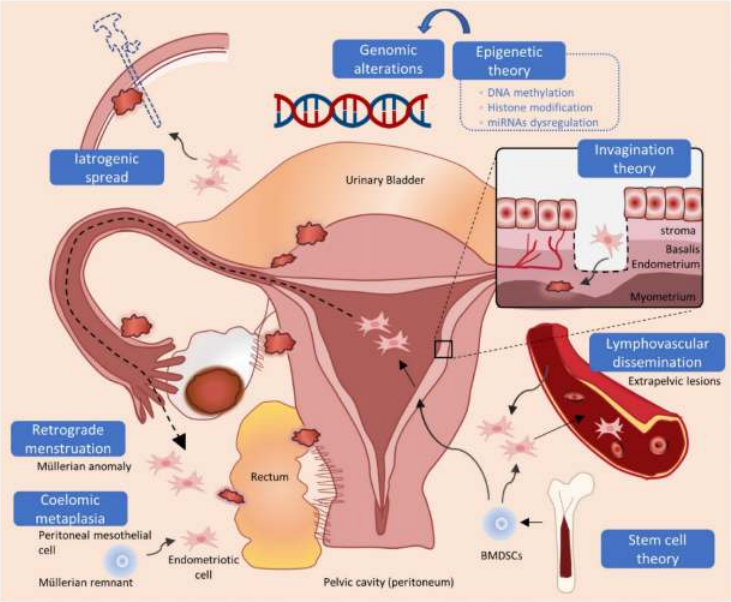


Figure 3.1.15 Theories of endometriosis pathogenesis. The potential origins of endometriotic lesions include traveling of endometrial tissue through retrograde menstruation and in situ by coelomic metaplasia of the peritoneal lining or from Müllerian remnants. Lymphovascular dissemination contributes to extra-pelvic lesions. Bone marrow-derived stem cells (BMDSCs) can directly differentiate into endometrial cells at ectopic locations in the peritoneal cavity and distant sites, further expanding the hypothesis of retrograde menstruation and lymphovascular dissemination. Invagination theory is characterized by altered endometrial basalis cells invading the uterine myometrium through disruption of the endometrial-myometrial interface (EMI), resulting in endometriosis of uterus. Epigenomic and genomic alterations further explain the aberrant gene expression in endometriotic lesions.
Image Source: Chen, Liang Hsuan, Wei Che Lo, Hong Yuan Huang, and Hsien Ming Wu. “A Lifelong Impact on Endometriosis: Pathophysiology and Pharmacological Treatment.” International Journal of Molecular

Sciences, *International Journal of Molecular Sciences* 24, no. 8 (2023: 7503. This work is openly licensed via CC BY 4.0 license. doi.org/10.3390/ijms24087503

3.1.5.4 Clinicopathological Features

Endometriosis presents with a variety of symptoms throughout the lifespan (Figure 3.1.16). Similar to adenomyosis, it presents with abnormal uterine bleeding, infertility (in approximately 40% of patients), and pelvic pain. Pelvic pain is mainly caused by intrapelvic bleeding and **adhesions** caused by organized blood.

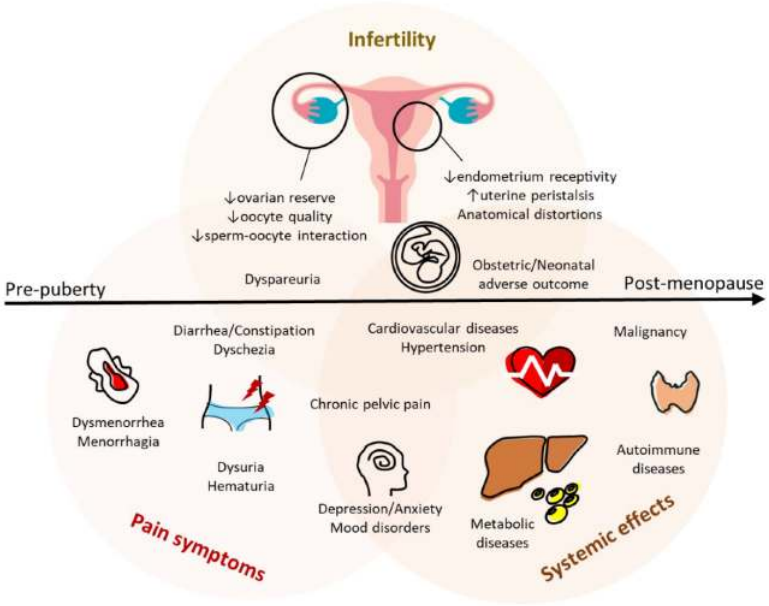


Figure3.1.16 Endometriosis across the life course. Summary of the symptoms associated with endometriosis, including pain, infertility, and systemic effects. They have a wide range of spectrum and can overlap with these other conditions. The upward arrows represent an increase, and the downward arrows represent a decrease.

Image Source: Chen, Liang Hsuan, Wei Che Lo, Hong Yuan Huang, and Hsien Ming Wu. “A Lifelong Impact on Endometriosis: Pathophysiology and Pharmacological Treatment.” International Journal of Molecular Sciences, *International Journal of Molecular Sciences* 24, no. 8 (2023: 7503. This work is openly licensed via CC BY 4.0 license. doi.org/10.3390/ijms24087503

3.1.5.5 Treatment

There is a variety of therapeutic options for endometriosis, including hormonal manipulation, surgical procedures, and assisted reproductive technology (ART) for infertility (Figure 3.1.17). COX-2 and aromatase inhibitors are effective treatments,[14] particularly because the endometriotic stromal cells produce **aromatase**, leading to increased local estrogen production from **androgens**.

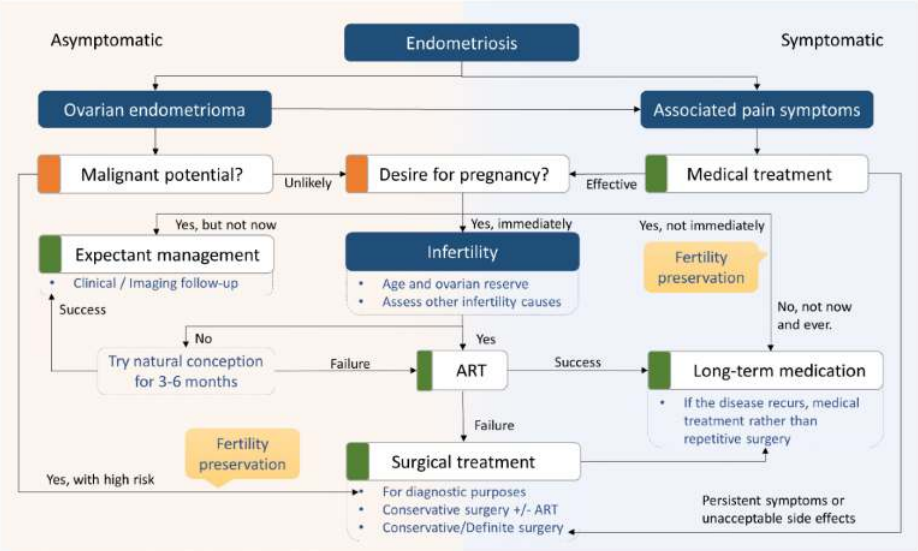


Figure 3.1.17 Treatment algorithm of endometriosis.
Image Source: Chen, Liang Hsuan, Wei Che Lo, Hong Yuan Huang, and Hsien Ming Wu. “A Lifelong Impact on Endometriosis: Pathophysiology and Pharmacological Treatment.” International Journal of Molecular Sciences, *International Journal of Molecular Sciences* 24, no. 8 (2023: 7503. This work is openly licensed via CC BY 4.0 license. doi.org/10.3390/ijms24087503

Note

For detailed treatment options, please refer to Chen, L et al. "A Lifelong Impact on Endometriosis: Pathophysiology and Pharmacological Treatment."[63]

Glossary Terms

Adhesions
a band of scar tissue that joins two surfaces of the body that are usually separate

Androgens
male sex hormones; for example, testosterone

Apoptosis
programmed cell death

Aromatase
enzyme that catalyzes the desaturation (aromatization) of the ring A of C19 androgens and converts them to C18 estrogens. In this process, the 19-methyl is removed

Cystic
relating to, formed of, or within a cyst; relating to the bladder or gall bladder

Diaphragm
skeletal muscle that separates the thoracic and abdominal cavities and is dome-shaped at rest

Endometrium
inner lining of the uterus, part of which builds up during the secretory phase of the menstrual cycle and then sheds with menses

Extrauterine
existing, formed, or occurring outside the uterus

Fallopian tubes

(uterine tubes or oviducts) ducts that facilitate transport of an ovulated oocyte to the uterus

Fibrosis

process in which muscle fibers are replaced by scar tissue

Gland

organ of the body that secretes/produces liquid chemicals that have various purposes

Hemorrhages

Excessive bleeding

Hemosiderin

type of protein that have one or more tightly bound metal ions forming part of their structure

Inflammation

basic innate immune response characterized by heat, redness, pain, and swelling

Laparotomy scars

scarring from surgical incision made in the wall of the abdomen

Lesions

areas of abnormal tissue

Localization

the fact of being or becoming located or fixed in a particular place

Lymphatics

the system of tubes that transport lymph arond the body

Metaplasia

condition in which there is a change of one adult cell type to another similar adult cell type

Metastasis

spread of cancer cells from a source to other parts of the body

Mullerian ducts

pair of ducts near the Wolffian ducts in a developing embryo

Nodule

growth or lump that may be malignant or benign

Ovaries

female gonads that produce oocytes and sex steroid hormones (notably estrogen and progesterone)

Peritoneal cavity

space enclosed by the peritoneum

Periumbilical

region of the body that immediately surrounds the umbilicus

Polypoid

organism whose genomes consist of more than two complete sets of chromosomes

Pouch of Douglas

(Douglas' Pouch) A sac or recess formed by a fold of the peritoneum

Presacral

presacral space is the area between the rectum and lowest part of your the spine, which is called the sacrum. The presacral space is inside the pelvis, behind the rectum and in front of the coccyx and sacrum

Proliferation

phase of the menstrual cycle in which the endometrium proliferates

Retrograde

a backward movement or a movement that is opposite to the usual direction of flow

Stroma

tissue that forms the structure of an organ or body part

Superficial (peritoneum)

describes a position nearer to the surface of the body

Uterine ligaments

strong bands of dense connective tissue

Footnotes

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13. Tempest, Nicola, Christopher J. Hill, Alison Maclean, Kathleen Marston, Simon G. Powell, Hannan Al-Lamee, and Dharani K. Hapangama. “Novel Microarchitecture of Human Endometrial Glands: Implications in Endometrial Regeneration and Pathologies.” *Human Reproduction Update* 28, no. 2 (2022). doi.org/10.1093/humupd/dmab039
14. Słopień, Radosław, and Błażej Męczekalski. "Aromatase inhibitors in the treatment of endometriosis". *Menopause Review/Przegląd Menopauzalny* 15 (1): 43-47. CC BY-NC-SA 4.0 doi:10.5114/pm.2016.58773

Image Acknowledgements

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3.1.6: Endometrial Hyperplasia

3.1.6.1 Definition

Endometrial **hyperplasia** (EH) is an irregular proliferation of the endometrial glands leading to an increase in the gland-to-stroma ratio in contrast to **proliferative** endometrium.[15]

3.1.6.2 Etiology and Pathogenesis

- A marked and prolonged increase of estrogen levels more than progesterone induces endometrial hyperplasia. Underlying causes include:
  - Obesity: Steroid precursors are converted into estrogens in **adipose** tissue. Excess adipose tissue promotes a chronic **proinflammatory** status, which stimulates the release of **cytokines** that are also involved in developing EH and EC
  - Polycystic ovarian syndrome: Chronic **anovulation** results in **hyperandrogenic** status with prolonged estrogen production that is not balanced by progesterone.
  - Estrogen-secreting ovarian tumors (granulosa and theca cell tumors)
  - **Exogenous/iatrogenic**: Prolonged estrogenic therapy with increasing doses not opposed by an adequate intake of progestins, especially in post-menopausal women. Tamoxifen is the most widely used among selective estrogen receptor modulators (SERMs) against breast cancer in both pre-and post-menopausal women.
- Genetic diseases such as Lynch Syndrome, also known as hereditary non-polyposis colonic cancer (HNPCC), caused by a mutation in one of the genes involved in the DNA repair system (MLH1, MSH2, MSH6, PMS2, and EP-CAM) are associated with increased risk of endometrial hyperplasia and **carcinoma**. Similar to endometrial carcinoma, endometrial hyperplasia with **atypia** has acquired mutations affecting the tumor suppressor gene PTEN.

3.1.6.3 Histopathology

- Endometrial Hyperplasia without atypia (Benign Hyperplasia): An increased endometrial gland-to-stroma ratio without nuclear atypia (Figure 3.1.18).
- Endometrial hyperplasia with atypia/Endometrial **Intraepithelial Neoplasia** (EIN): There is an increased endometrial gland-to-stroma ratio with complex proliferating glands with nuclear atypia (Figure 3.1.19). It is a premalignant lesion with an approximately 30% risk of progression to endometrial carcinoma. Because of the shared genetic mutations of PTEN with endometrial carcinoma, EIN is considered a precursor of endometrial carcinoma.

3.1.6.4 Treatment

Surgical removal of the uterus (total hysterectomy) is the treatment of choice for EIN in patients who no longer consider conception. In younger patients, the condition is treated by the administration of high-dose **progestins**.

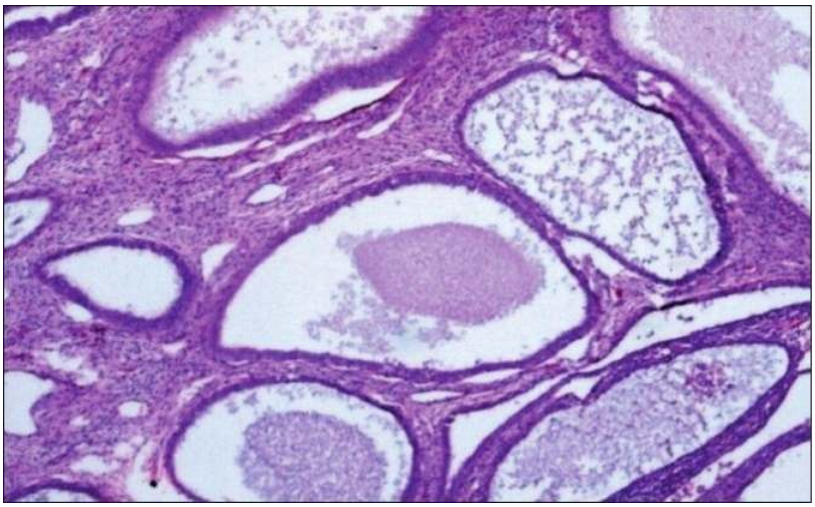


Figure 3.1.18 Histopathology of complex hyperplasia without atypia: Cystically dilated endometrial glands lined by a single layer of columnar epithelium (Hematoxylin and eosin stain, ×20)
Image Source: Rao, Shalinee, Sandhya Sundaram, and Raghavan Narasimhan. "Biological behavior of preneoplastic conditions of the endometrium: A retrospective 16-year study in south India". *Indian Journal of Medical and Paediatric Oncology* 30 (4): 131 (2009). doi.10.4103/0971-5851.65335. Distributed under the terms of the CC BY 2.0 license. Available from Wikipedia Commons.

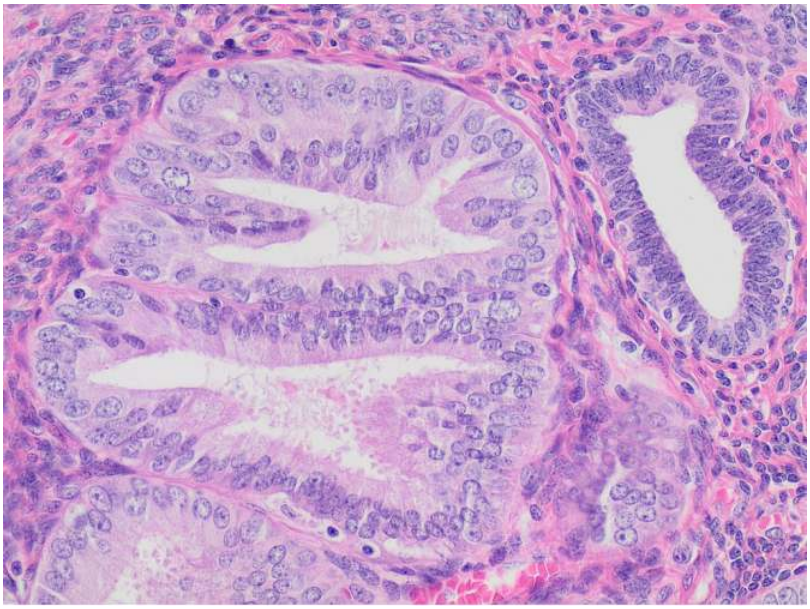


Figure 3.1.19 Endometrial Hyperplasia with Atypia: Atypia (mainly seen as signs of endometrial intraepithelial neoplasia (EIN), which has the following criteria: Architectural gland crowding - Altered cytology relative to background glands (rounded vesicular nuclei with prominent nucleoli) - Minimum size of 1 mm - Exclusion of adenocarcinoma.
Image Source: Haggstrom, Mikael. "Endometrial Intraepithelial Neoplasia". Image from *Archives of Pathology & Laboratory Medicine* 138, No. 4 (2014): 484–491. Distributed under the terms of the CCO license. doi.10.5858/arpa.2012-0709-RA

Glossary Terms

Adipose tissue

specialized areolar tissue rich in stored fat

Anovulation

suspension or cessation of OVULATION in animals or humans with follicle-containing ovaries (OVARIAN FOLLICLE). Depending on the etiology, OVULATION may be induced with appropriate therapy

Atypia

abnormality in cells in tissue

Carcinoma

condition in which abnormal cells that look like cancer cells under a microscope are found only in the place where they first formed and haven’t spread to nearby tissue

Cytokines

class of protein signaling molecules; in the cardiovascular system, they stimulate the proliferation of progenitor cells and help to stimulate both nonspecific and specific resistance to disease

Exogenous

describes substance made outside of the human body

Hyperandrogenic

when you have an excess amount of androgens (a group of sex hormones) in your body

Hyperplasia

abnormal growth due to the production of cells

Iatrogenic

adverse condition in a patient occurring as the result of treatment by a physician, surgeon, or other health professional, especially infections acquired by a patient during the course of treatment

Introepithelial neoplasia

term used to describe the presence of abnormal cells on the surface of or in the tissue that lines an organ, such as the cervix, breast, prostate, anus, vagina, vulva, penis, and mouth

Progestins

compounds that interact with PROGESTERONE RECEPTORS in target tissues to bring about the effects similar to those of PROGESTERONE

Proinflammatory

promoting inflammation : capable of causing inflammation

Proliferative

phase of the menstrual cycle in which the endometrium proliferates

Footnotes

15. Giannella, Luca, Camilla Grelloni, Marco Bernardi, Camilla Cicoli, Federica Lavezzo, Gianmarco Sartini, Leonardo Natalini, et al. “Atypical Endometrial Hyperplasia and Concurrent Cancer: A Comprehensive Overview on a Challenging Clinical Condition.” *Cancers* 16, no. 5 (2024): 914. Distributed under the terms of the CC BY 4.0 doi.org/10.3390/cancers16050914

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3.1.7: Endometrial Carcinoma (EC)

3.1.7.1 Definition

Primary malignant tumor of the endometrial glandular component (i.e., **endometrial epithelial** cells), not **stromal cell**s.[16]

3.1.7.2 Pathogenesis

Similar to endometrial **hyperplasia**, estrogen excess increases the risk of developing **endometrial carcinoma** (particularly the **endometroid** type, also known as type I ECs) in perimenopausal women. Non-endometroid (serous is the most common subtype) endometrial carcinoma (Type II ECs) occurs in postmenopausal women and arises from **atrophic** endometrium. In contrast, serous cancers originate in the setting of endometrial **atrophy** in older postmenopausal women.

As previously mentioned, EIN is the precursor lesion of endometroid endometrial carcinoma, representing most of endometrial carcinoma (80%). Several genetic mutations, including mutations of the mismatch repair genes and the tumor suppressor genes (e.g., PTEN), have been identified as early events in the stepwise **carcinogenesis** of endometrioid carcinoma. Most of these mutations are acquired **somatic** mutations; however, other **germ-line mutations** have also been identified, such as Cowden Syndrome (PTEN mutations) and Lynch Syndrome (DNA mismatch repair genes mutations).

The more aggressive non-endometroid endometrial carcinoma represents around (10%- 20%) of endometrial carcinoma cases. Contrary to the endometroid type, it is not associated with increased estrogen levels or endometrial hyperplasia. This type of tumor exhibits genetic mutations of the *TP53* tumor suppressor gene. Serous Endometrial **Intraepithelial Neoplasia** (SEIC) is believed to be the precursor **lesion** because of the *TP53* mutations.

3.1.7.3 Histopathology

Endometrioid endometrial carcinomas exhibit **morphological** features of normal endometrium glands. The irregular glands are lined by **columnar epithelium** with low **cytological atypia**. ECs can exhibit other architectural patterns (Figure 3.1.20). Invasion of the **myometrium** by malignant glands could be seen. To differentiate EIN from low-grade endometroid adenocarcinoma, the glands in EIN are crowded but not **confluent,** and endometrial stroma is preserved around the glands. (Figure 3.1.21, A and B).

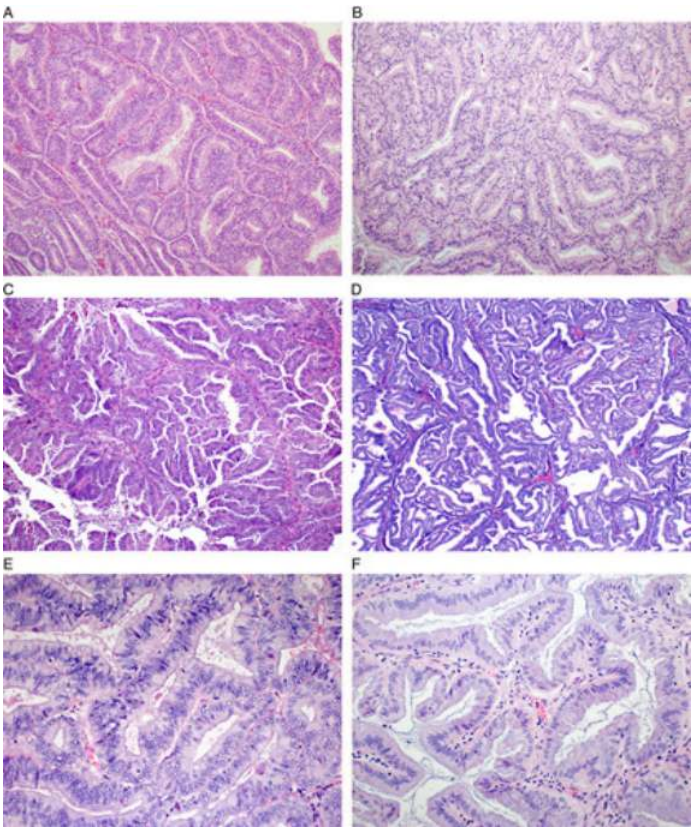


Figure 3.1.20 Architectural patterns that meet qualitative criteria for classifying an endometrial proliferation as grade 1 endometrioid carcinoma: confluent glandular growth (A); cribriform growth (B); confluent papillary growth (C); complex labyrinthine growth (D). There is no evidence-based consensus on the minimum size of these patterns needed to classify as endometrioid carcinoma. The absence of endometrial stroma between the glands is required for classification as endometrioid carcinoma (E); however, there may be other cell types in between the glands, such as lymphocytes, neutrophils, plasma cells, histiocytes, and/or endothelium of blood vessels (F).

Image Source: Rabban, Joseph T., C. Blake Gilks, Anais Malpica, Xavier Matias-Guiu, Khush Mittal, George L. Mutter, Esther Oliva, et al. “Issues in the Differential Diagnosis of Uterine Low-Grade Endometrioid Carcinoma, Including Mixed Endometrial Carcinomas: Recommendations from the International Society of Gynecological Pathologists.” *International Journal of Gynecological Pathology* 38 (January 2019):S25-S39. This work is distributed under a CC BY 4.0 license. doi.org/10.1097/PGP.0000000000000512

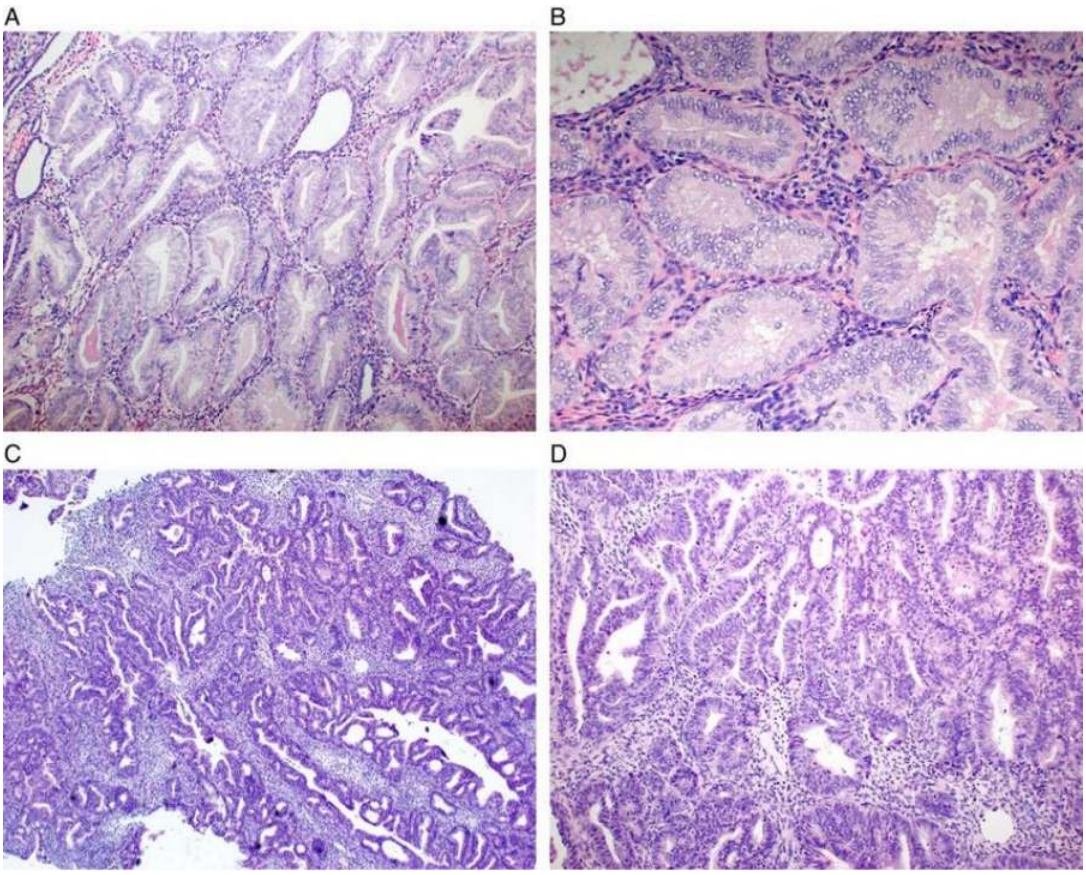


Figure 3.1.21 In endometrial atypical hyperplasia, the glands are crowded but not confluent (A), and endometrial stroma is preserved around the glands (B). On occasion, the presence of small foci suggestive of confluent architecture (C, D) within atypical hyperplasia may raise suspicion for small foci of grade 1 endometrioid carcinoma but may not be interpreted to meet the criteria for a definite diagnosis of malignancy. The interpretation of such cases can be problematic and subject to interobserver variation, especially since there are no evidence-based guidelines for the minimum size of confluent growth that predicts myoinvasive endometrioid carcinoma. If the findings are not deemed to meet criteria for cancer, it is recommended to report the diagnosis as atypical hyperplasia with features suspicious for grade 1 endometrioid carcinoma (or using equivalent wording).

Image Source: Rabban, Joseph T., C. Blake Gilks, Anais Malpica, Xavier Matias-Guiu, Khush Mittal, George L. Mutter, Esther Oliva, et al. “Issues in the Differential Diagnosis of Uterine Low-Grade Endometrioid Carcinoma, Including Mixed Endometrial Carcinomas: Recommendations from the International Society of Gynecological Pathologists.” *International Journal of Gynecological Pathology* 38 (January 2019):S25-S39. This work is distributed under a CC BY 4.0 license. doi.org/10.1097/PGP.0000000000000512

Serous endometrial carcinomas exhibit **papillary** growth and cellular atypia. Glandular arrangements can also be detected with more cellular atypia than endometroid carcinomas. Strong **immunohistochemistry** staining for p53 is characteristic (Figures 3.1.22 and 3.1.23).

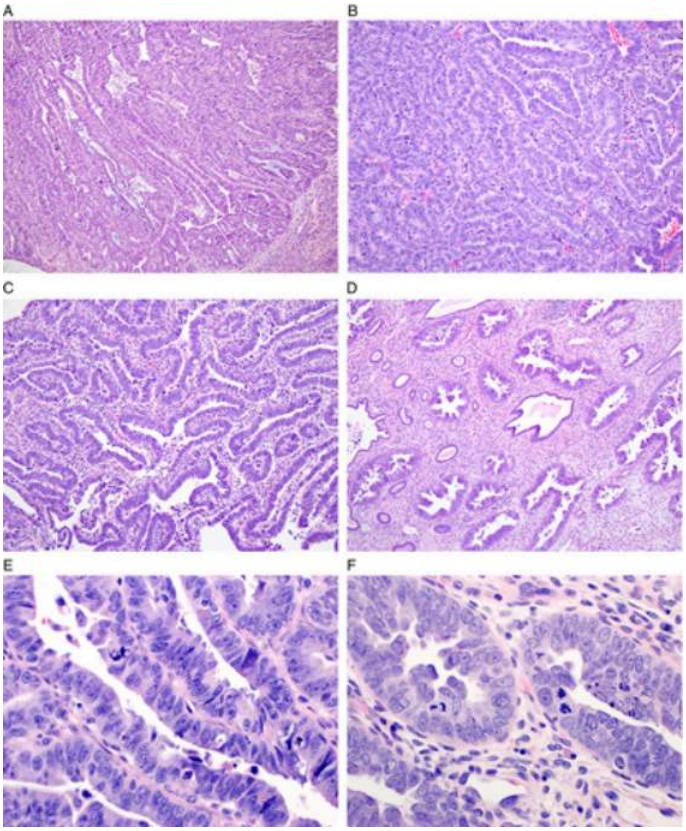


Figure 3.1.22 The glandular pattern of endometrial serous carcinoma may mimic the architecture of low-grade endometrioid carcinoma at low (A) and medium (B) magnification. Serous carcinoma may also mimic atypical hyperplasia (C), particularly within an endometrial polyp (D). However, at high magnification (E, F), serous carcinoma exhibits nuclear pleomorphism, high nuclear to cytoplasmic ratio, macronucleoli, high mitotic activity, and atypical mitotic figures. None of these features are expected in a low-grade endometrioid carcinoma.

Image Source: Rabban, Joseph T., C. Blake Gilks, Anais Malpica, Xavier Matias-Guiu, Khush Mittal, George L. Mutter, Esther Oliva, et al. “Issues in the Differential Diagnosis of Uterine Low-Grade Endometrioid Carcinoma, Including Mixed Endometrial Carcinomas: Recommendations from the International Society of Gynecological Pathologists.” *International Journal of Gynecological Pathology* 38 (January 2019):S25-S39. This work is distributed under a CC BY 4.0 license. doi.org/10.1097/PGP.0000000000000512

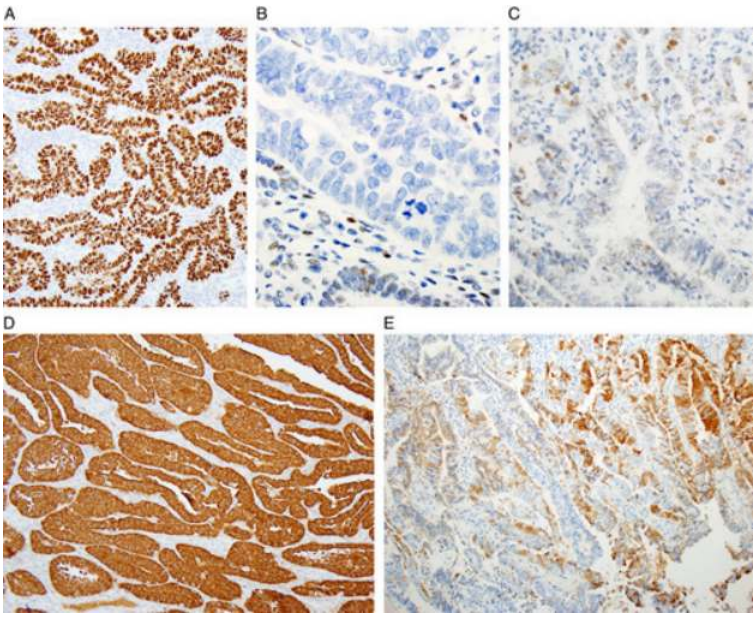


Figure 3.1.23 Mutation-type p53 immunoexpression in endometrial serous carcinoma is defined as either diffuse strong nuclear staining in >80% of tumor cells (A) or complete absence of any staining in tumor cells (B). In the latter setting, weak patchy p53 staining of lymphocytes, stroma, and normal endometrial glands serves as a positive internal control. p53 staining in grade 1 endometrioid carcinoma is weak and patchy (wild-type immunoreactivity) (C). p16 staining in serous carcinoma is typically diffuse and strong (D) and is typically patchy in grade 1 endometrioid carcinoma (E).
Image Source: Rabban, Joseph T., C. Blake Gilks, Anais Malpica, Xavier Matias-Guiu, Khush Mittal, George L. Mutter, Esther Oliva, et al. “Issues in the Differential Diagnosis of Uterine Low-Grade Endometrioid Carcinoma, Including Mixed Endometrial Carcinomas: Recommendations from the International Society of Gynecological Pathologists.” *International Journal of Gynecological Pathology* 38 (January 2019):S25-S39. This work is distributed under a CC BY 4.0 license. doi.org/10.1097/PGP.0000000000000512

3.1.7.4 Clinical Features

Carcinoma of the endometrium in women less than 40 years of age is associated with non-invasive cancers, less **lymph-vascular** space invasion, and a higher body mass index. However, more aggressive, higher grade, late-stage, non-endometrioid endometrial cancers are more prevalent in women >65 years of age. Endometrial carcinomas characteristically present with irregular or postmenopausal bleeding. Serous carcinoma is more prevalent in older (65 to 70 years of age) women with relatively lower body mass index. Generally, the prognosis of **serous carcinoma** is poor due to the tumor's aggressive behavior and higher-stage. [21]

Glossary Terms

Atrophy

loss of mass and function

Atypia

abnormality in cells in tissue

Carcinogenesis

the production of cancer

Carcinoma

condition in which abnormal cells that look like cancer cells under a microscope are found only in the place where they first formed and haven't spread to nearby tissue

Columnar

having a tall or long, narrow shape, like a column, as in columnar cells

Confluent

two things, such as areas of skin or cells that join or come together without any space between them, or flow together in the same direction

Cytological

elated to structure, function, or pathology of cells

Endometrium

inner lining of the uterus, part of which builds up during the secretory phase of the menstrual cycle and then sheds with menses

Epithelium

sheets of cells that cover the exterior surfaces of the body, line internal cavities and passageways, and form certain glands; also known as epithelial tissue

Germ-line mutation

detectable and heritable alteration in the lineage of germ cells

Hyperplasia

abnormal growth due to the production of cells

Immunochemistry

field of chemistry that pertains to immunological phenomena and the study of chemical reactions related to antigen stimulation of tissues. It includes physicochemical interactions between antigens and antibodies

Intraepithelial neoplasia

term used to describe the presence of abnormal cells on the surface of or in the tissue that lines an organ, such as the cervix, breast, prostate, anus, vagina, vulva, penis, and mouth

Lesion

area of abnormal tissue

Lymph-vascular

of, relating to, or containing lymphatic vessels

Morphology

form and structure of an organism or any of its parts

Myometrium

smooth muscle layer of uterus that allows for uterine contractions during labor and expulsion of menstrual blood

Papillary

of, relating to, being, or resembling a papilla or nipple-shaped projection, mass or structure; marked by the presence of papillae

Serous

having to do with serum, the clear liquid part of blood

Somatic

having to do with the body

Stromal cells

connective tissue cells of an organ found in the loose connective tissue. These are most often associated with the uterine mucosa and the ovary as well as the hematopoietic system and elsewhere

Footnotes

16. Zheng, Wenxin. "Molecular Classification of Endometrial Cancer and the 2023 FIGO Staging: Exploring the Challenges and Opportunities for Pathologists." *Cancers* 15, no. 16 (2023): 4101. Work is Distributed under the terms of the CC BY 4.0 license. doi.org/10.3390/cancers15164101; Baiden-Amissah, Regina Esi Mensimah,

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Image Acknolwedgements

Rabban, Joseph T., C. Blake Gilks, Anais Malpica, Xavier Matias-Guiu, Khush Mittal, George L. Mutter, Esther Oliva, et al. “Issues in the Differential Diagnosis of Uterine Low-Grade Endometrioid Carcinoma, Including Mixed Endometrial Carcinomas: Recommendations from the International Society of Gynecological Pathologists.” *International Journal of Gynecological Pathology* 38 (January 2019):S25-S39. This work is distributed under a CC BY 4.0 license. doi.org/10.1097/PGP.0000000000000512

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3.1.8: Endometrial Polyps

3.1.8.1 Definition

Endometrial **polyps** are abnormal growths of the endometrium that could be either **sessile** (a non-mobile polyp with a broad base with no stalk) or **pedunculated** (projecting into the uterine cavity and attached by a stalk). Histologically, they resemble the **stratum basalis** of the endometrium (i.e., **cystically dilated** glands with small muscular arteries) (Figure 3.1.24, A and B). The endometrial polyp **stroma** is more **collagenous** than the normal endometrial stroma (more cellular) (Figure 3.1.24 C). An endometrial polyp may be diagnosed in the presence of 2 of the following 3:

- Thick-walled vessels
- Collagenous stroma
- Epithelium on at least 3 sides

Endometrial polyps usually present with abnormal uterine bleeding. Although malignant transformation is rare, Endometrial carcinoma can arise in endometrial polyps (Figure 2B.44 D).

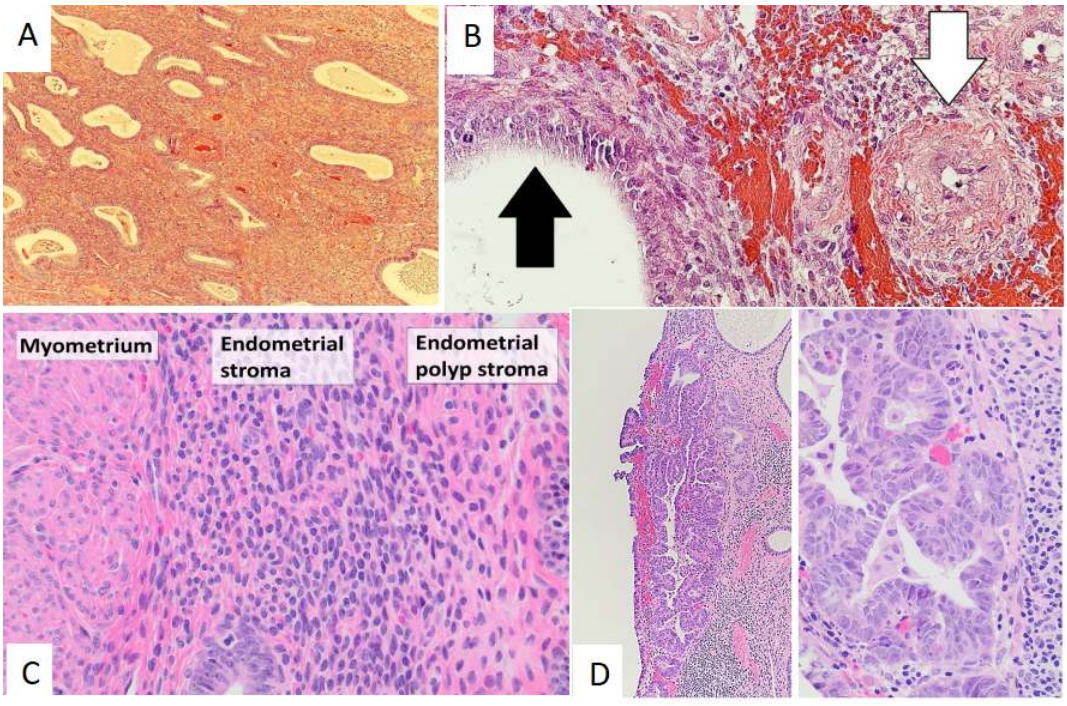


Figure 3.1.24 (A) Endometrial polyp (without atypia), with a thick-walled blood vessel in the middle - typical of endometrial polyps. Glands are regular. (B) Endometrial polyp (without atypia), with tubal metaplasia (black arrow, showing ciliated epithelium) and a thick-walled blood vessel (white arrow). The stroma is hemorrhagic in this case. (C) Myometrium (smooth muscle cells) versus endometrial stroma (more cellular) versus endometrial polyp stroma (more collagenous). (D) Endometrial adenocarcinoma arising in an endometrial polyp. These are most commonly endometrioid, in which case low-grade carcinoma is distinguished from hyperplasia with atypia by the presence of glandular crowding with endometrial stromal

exclusion and significant cribriform, confluent glandular, labyrinthine, papillary/villoglandular, or non-squamous solid architecture.

Image Source: Haggstrom, Mikael. "Endometrial Intraepithelial Neoplasia". Image from *Archives of Pathology & Laboratory Medicine* 138, No. 4 (2014): 484–491. Distributed under the terms of the CCO license. doi.10.5858/arpa.2012-0709-RA

Glossary Terms

Collagen

flexible fibrous proteins that give connective tissue tensile strength

Cystic

relating to, formed of, or within a cyst; relating to the bladder or gall bladder

Dilated

expanded, enlarged, or widened normally or abnormally in all dimensions

Pedunculated

having, growing on, or being attached by a peduncle (narrow stalk by which a tumor or polyp is attached)

Polyp

growth that protrudes from a mucous membrane

Sessile

attached permanently or established

Stratum Basale

deepest layers of the epidermis

Stroma

tissue that forms the structure of an organ or body part

Image Acknowledgements

Haggstrom, Mikael. "Endometrial Intraepithelial Neoplasia". Image from *Archives of Pathology & Laboratory Medicine* 138, No. 4 (2014): 484–491. Distributed under the terms of the CCO license. doi.10.5858/arpa.2012-0709-RA

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3.1.9: Uterine Leiomyoma (uLM)

3.1.9.1 Definition

It is a benign **neoplasm** arising from the uterine smooth muscles, also known as **fibroid.** Leio (smooth), myo (muscle), oma (tumor). It is the most common neoplasm of the female reproductive system.

3.1.9.2 Pathogenesis

Risk factors for developing fibroids include advanced reproductive age, smoking, contraceptive pill intake, African and Latin American ethnicity, family medical history, obesity, early **menarche**, **arterial hypertension**, chronic **inflammation,** exposure to **xenoestrogens** in early **ontogenesis**, sexually transmitted infections, and alcohol. The **pathogenetic** mechanisms are very complex, considering the interplay of all the previously mentioned factors (Figure 3.1.25).[18]

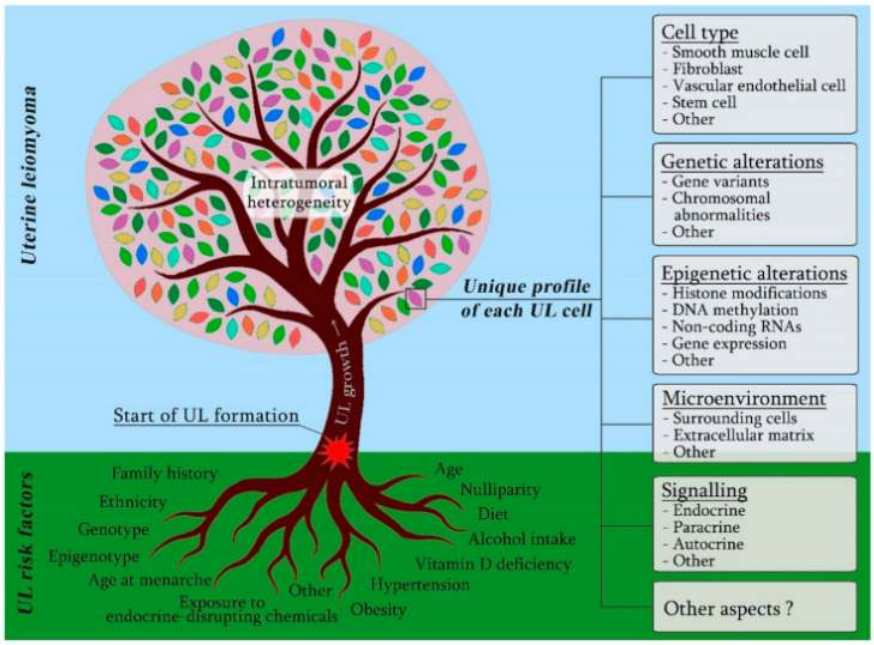


Figure 3.1.25 An illustration of predisposing factors intricacy and **intratumoral heterogeneity** complicating the search for key events of uterine leiomyoma (UL) genesis. UL formation is associated with a wide range of predisposing factors: family medical history, African or Latin American ethnicity, gene variants, epigenetic changes, early menarche, exposure to xenoestrogens, obesity, hypertension, vitamin D deficiency, alcohol intake, dietary habits, **nulliparity**, and advanced reproductive age. During UL growth, each cell acquires a unique set of parameters (cell type, genetic and **epigenetic** alterations, characteristics of **signaling,** and microenvironmental components), thus resulting in a pronounced **intratumoral** heterogeneity and complicating identification of the characteristics of initial UL cell(s).

Image Source: Koltsova, Alla S., Olga A. Efimova, and Anna A. Pendina. “A View on Uterine Leiomyoma Genesis through the Prism of Genetic, Epigenetic and Cellular Heterogeneity.” *International Journal of Molecular Sciences* 24, no. 6 (2023): 5752. This work is distributed under a CC BY license. doi.org/10.3390/ijms24065752

Leiomyomas are considered of **monoclonal** origin (i.e., they arise from a single transformed smooth muscle cell) and later differentiate into other cell types that contribute to the cellular components of fibroids (e.g., **fibroblasts** and vascular **endothelial** cells). Several tissue-

specific stem cells expressing stem markers (e.g., OCT4, NANOG, and others) have been detected and isolated from uterine **leiomyomas. Paracrine** signaling and interactions between stem cells and mature smooth muscle cells play a role in leiomyoma formation (Figure 3.1.26).[19] Several chromosomal abnormalities (chromosomes 6 and 12) and genetic mutations (*MED12* regulating RNA polymerase II-mediated transcription) have also been implicated.

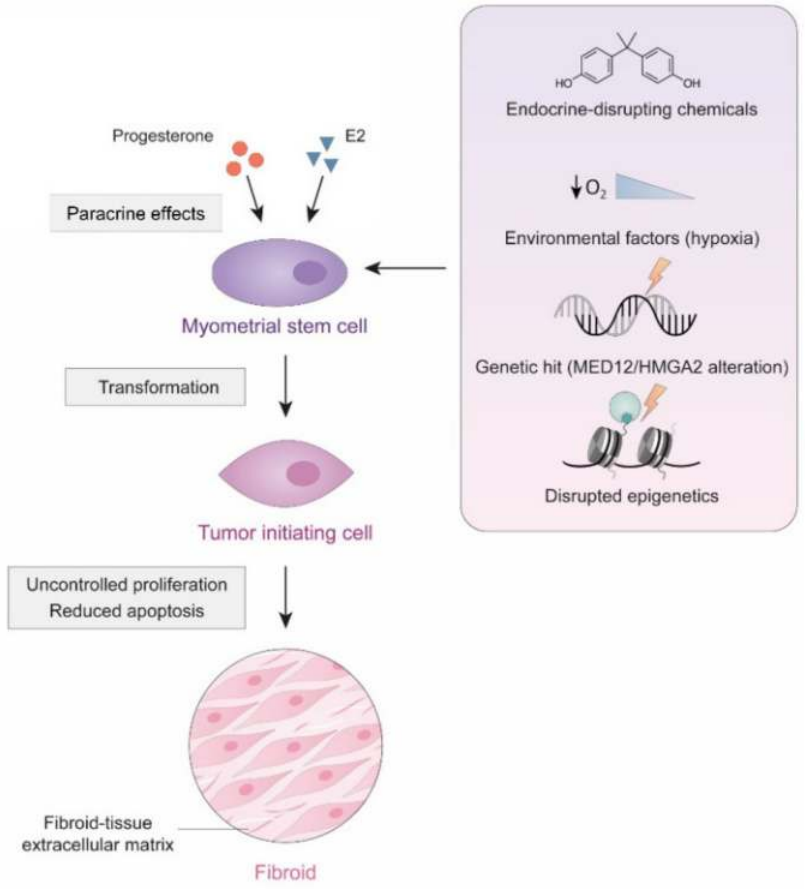


Figure 3.1.26 Cellular origin of uLM. Specific environmental and genetic changes may cause the transformation of myometrial stem cells into tumor initiating cells, that, through uncontrolled proliferation and reduced apoptosis, may eventually give rise to a uLM tumor

Image Source: Machado-Lopez, Alba, Carlos Simón, and Aymara Mas. “Molecular and Cellular Insights into the Development of Uterine Fibroids.” *International Journal of Molecular Sciences* 22, no. 16 (2021): 8483. This work is distributed under a CC BY license. doi.org/10.3390/ijms22168483

Note

For further details on leiomyoma pathogenesis and implicated mechanisms, refer to these articles:

- Machado-Lopez A, Simón C, Mas A. "Molecular and Cellular Insights into the Development of Uterine Fibroids." *International journal of molecular sciences*, 22, No. 16 (Aug 6, 2022):8483. doi: 10.3390/ijms22168483 PMID: 34445194

- Koltsova, Alla S et al. “A View on Uterine Leiomyoma Genesis through the Prism of Genetic, Epigenetic and Cellular Heterogeneity.” *International journal of molecular sciences* vol. 24, No. 6 (March 17, 2023):5752. doi:10.3390/ijms24065752 PMID: 34445194

3.1.9.3 Morphology

- Macroscopically

Fibroids are well-circumscribed, rubbery, firm, grey-white, non-encapsulated, spherical tumors. The cut surface is bulging, well **demarcated** from adjacent **myometrium**, and exhibits a **whorled** pattern (Figure 3.1.27). Areas of **mucoid** change, **hemorrhage**, **necrosis**, and **calcification** could be seen. There are three main types of fibroids with variable locations (Figure 3.1.28):

- Submucosal (bulge into the uterine cavity and covered by the endometrium)
- Intramural (grow within the muscular uterine wall)
- Subserosal (project to the outside of the uterus and covered by the peritoneum)

The latter may be attached to the uterus by a stalk and may attach to surrounding organs where it gets its blood supply from these organs (i.e., parasitic fibroid).

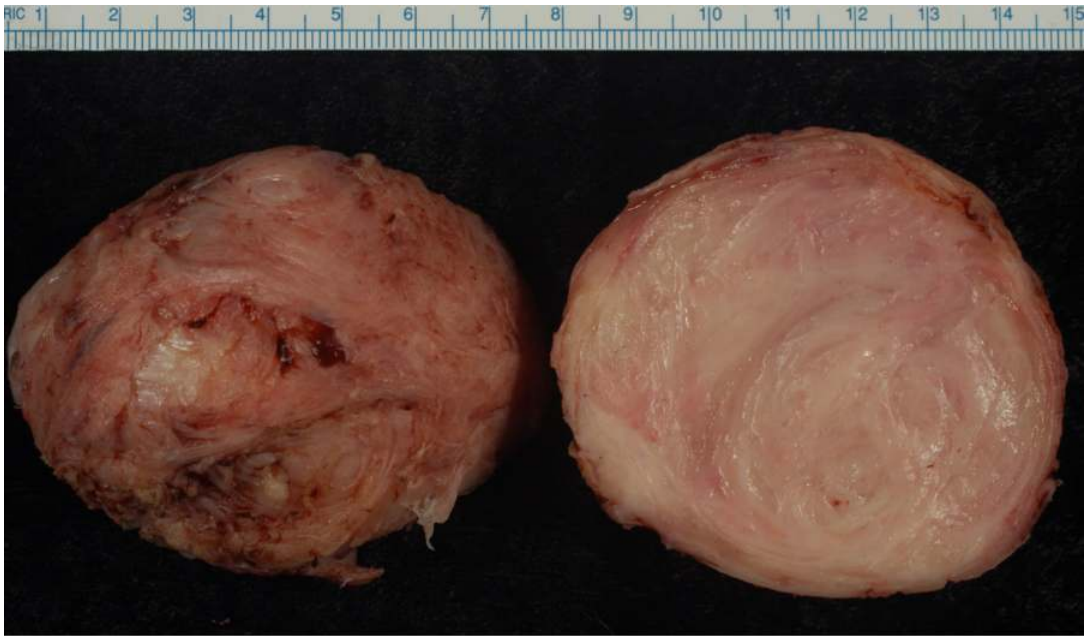


Figure 3.1.27 A well-circumscribed uterine fibroid. The cut surface demonstrates the characteristic whorled pattern.
Image Source: Uthman, Ed. "Leiomyoma from a uterine myomectomy." This work is distributed under a CC BY 2.0 license. Image available from Wikimedia Commons.

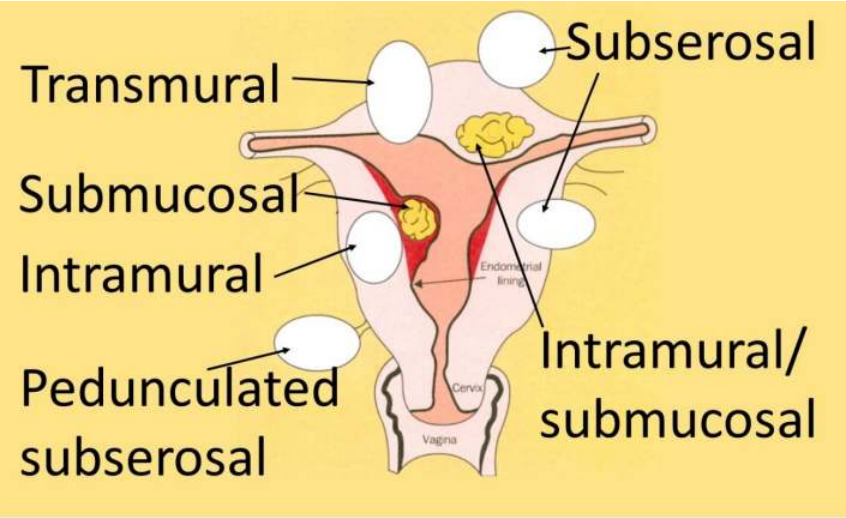


Figure 3.1.28 Fibroid Locations.
Image Source: Haggstrom, Mikael. "Fibroid locations." Image adpated from Anja Hirschelmann, Rudy Leon De Wilde. "Plastic and reconstructive uterus operations by minimally invasive surgery? A review on myomectomy". *GMS Interdisciplinary Plastic and Reconstructive Surgery DGPW* No. 1 (2012). This work is distributed under a CC BY 4.0 license. Image available from Wikimedia Commons.

Histologically, bundles of smooth muscle cells resembling normal myometrium are present (Figure 3.1.29, A). The **fascicular** pattern/arrangement is responsible for the whorled appearance. **Mitotic** activity may be observed, but there are usually less than 5 mitoses per 10 high-power fields (HPF). Tumor cellularity is variable, with some tumors being more cellular than others, and areas within the same tumor demonstrate variable cellularity (Figure 3.1.29, B). Areas of degenerative changes, fibrosis, hemorrhage, and calcification could also be detected.

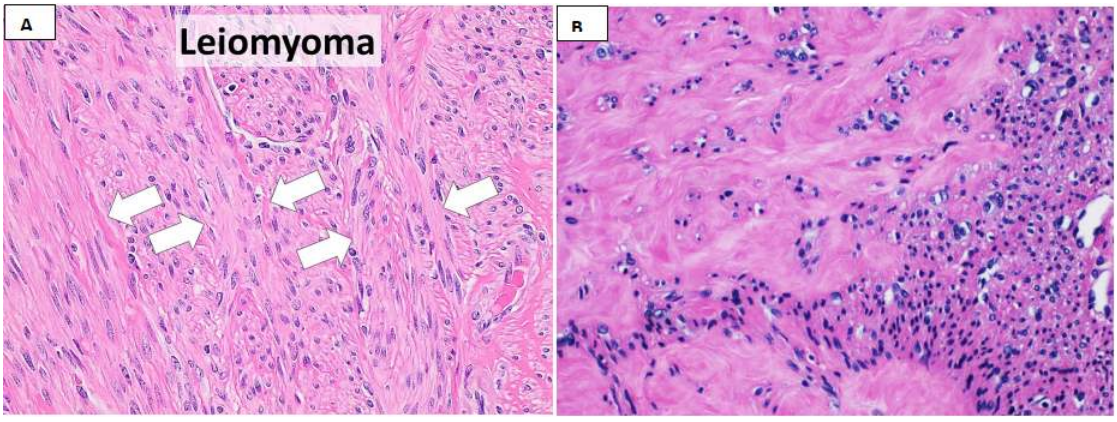


Figure 3.1.29 Leiomyomas typically show smooth muscle in a fascicular pattern (arrows point at fascicles) (A). Leiomyoma, with areas where the cellularity is relatively lower (left) and higher (right) (B). H&E stain.
Image Source: Haggstrom, Mikael. "Histopathology of a leiomyoma in a postmenopausal uterus". Intermediate magnification. Own work. (October 2020). This work is distributed under a CCO license. Image available from Wikimedia Commons.

3.1.9.4 Clinical Features and Treatment

Common presentations include abnormal uterine bleeding, pelvic pain, **dyspareunia**, pressure effects on the bladder or rectum, and infertility. Anemia results from excessive bleeding. Other consequences include spontaneous abortions, pre-term delivery, and Caesarean sections. Imaging techniques such as **transabdominal** or **transvaginal** ultrasound are the most commonly used diagnostic modalities. MRI may be used to delineate the number, size, and location of fibroids in certain cases, and **hysteroscopy** may be useful to distinguish between sub-endometrial fibroids and large endometrial polyps.

Surgical treatment includes **hysterectomy** or **myomectomy** depending on the size, number, and extent of fibroids and the patient's wishes about fertility. Myomectomy (i.e., surgical removal of fibroids) is performed by Hysteroscopy or **laparoscopy**. The latter is the standard surgical option in women who do not wish to retain fertility.

Non-surgical interventional treatments include uterine artery **embolization** (UAE) and high-frequency MR-guided focused ultrasound surgery. Medical management of fibroids using gonadotropin-releasing hormone (GnRH) analogs is indicated for symptomatic treatment of pain and bleeding. Other therapeutics, such as selective progesterone receptor modulators (SPRMs), effectively control heavy menstrual bleeding and correct anemia by reducing fibroids' size. Estrogen levels remain at around **mid-follicular** levels, and, as a consequence, menopausal symptoms and bone loss are not encountered regularly.[20]

Glossary terms

Arterial

related to or flowing in an artery

Calcification

process by which organic tissue becomes hardened by the physiologic deposit of calcium salts

Dyspareunia

genital pain before, during, or after intercourse

Embolization

action of deliberately blocking the flow of blood in a particular blood vessel by putting material into the blood

Endothelial

layer of epithelium that lines the heart, blood vessels (ENDOTHELIUM, VASCULAR), lymph vessels (ENDOTHELIUM, LYMPHATIC), and the serous cavities of the body

Fascicular

of, related to, or consisting of fasciculi (seldner bundle of anatomical fibers, nerve fibers)

Fibroblasts

most abundant cell type in connective tissue, secretes protein fibers and matrix into the extracellular space

Fibroid

benign tumor derived from smooth muscle tissue

Hemorrhage

excessive bleeding

Hypertension

blood pressure goes below the homeostatic set point when standing

Hysterectomy

surgery to remove the uterus and, sometimes, the cervix

Hysteroscopy

endoscopic examination of the uterus

Inflammation

basic innate immune response characterized by heat, redness, pain, and swelling

Laparoscopy

procedure that uses a laparoscope, inserted through the abdominal wall, to examine the inside of the abdomen

Leiomyoma

benign tumor derived from smooth muscle tissue, also known as a fibroid tumor. They rarely occur outside of the UTERUS and the GASTROINTESTINAL TRACT but can occur in the SKIN and SUBCUTANEOUS TISSUE, probably arising from the smooth muscle of small blood vessels in these tissues

Menarche

first menstruation in a pubertal female

Mitotic

of, related to, involving or occurring by cellular mitosis

Monoclonal

produce by, being, composed of, or caused by cells derived from a single cell

Mucoid

resembling mucus

Myomectomy

surgical removal of a LEIOMYOMA of the UTERUS

Myometrium

smooth muscle layer of uterus that allows for uterine contractions during labor and expulsion of menstrual blood

Necrosis

accidental death of cells and tissues

Ontogenesis

development of course of development of an organism

Paracine

cellular signaling in which a factor secreted by a cell affects other cells in the local environment

Pathogenic

causing or capable of causing disease

Transabdominal

passing through or performed by passing through the abdomen of the abdominal wall

Transvaginal

passing through or performed by way of the vagina

Whorled

having or arranged in whorls (arrangement of similar anatomical parts in a circule aruond a point or on an axis)

Xenoestrogens

foreign synthetic chemicals that mimic natural estrogens and can bind to estrogen receptors in the body

Footnotes

18. Koltsova, Alla S., Olga A. Efimova, and Anna A. Pendina. “A View on Uterine Leiomyoma Genesis through the Prism of Genetic, Epigenetic and Cellular Heterogeneity.” *International Journal of Molecular Sciences* 24, no. 6 (2023): 5752. This work is distributed under a CC BY license. doi.org/10.3390/ijms24065752
19. Koltsova, Efimova, and Pendina, 2023.
20. Machado-Lopez, Alba, Carlos Simón, and Aymara Mas. “Molecular and Cellular Insights into the Development of Uterine Fibroids.” *International Journal of Molecular Sciences* 22, no. 16 (2021): 8483. This work is distributed under a CC BY license. doi.org/10.3390/ijms22168483

Image Acknowledgements

- Koltsova, Alla S., Olga A. Efimova, and Anna A. Pendina. “A View on Uterine Leiomyoma Genesis through the Prism of Genetic, Epigenetic and Cellular Heterogeneity.” *International Journal of Molecular Sciences* 24, no. 6 (2023): 5752. This work is distributed under a CC BY license. doi.org/10.3390/ijms24065752
- Machado-Lopez, Alba, Carlos Simón, and Aymara Mas. “Molecular and Cellular Insights into the Development of Uterine Fibroids.” *International Journal of Molecular Sciences* 22, no. 16 (2021): 8483. This work is distributed under a CC BY license. doi.org/10.3390/ijms22168483

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3.1.10: Leiomyosarcoma

3.1.10.1 Definition

It is a primary malignant **mesenchymal** tumor of smooth muscle cells in both **visceral** organs and **non-visceral** structures. The most common primary sites of leiomyosarcomas include the uterus, retroperitoneum, gastrointestinal tract, and extremities. Uterine leiomyosarcoma is one of the rarest female genital tumors.[21]

3.1.10.2 Pathogenesis

They arise from the **myometrium** or the connective tissue elements of the **endometrium**. They have complex chromosomal abnormalities, including chromosomal deletions. Several genetic mutations have been identified, including TP53, RB1, and MED 12, among several others. Occasional cases have been reported with tamoxifen use.

3.1.10.3 Morphology

Macroscopically, leiomyosarcomas are soft tumors with areas of **hemorrhage** and **necrosis**.

Microscopically, there are three subtypes: spindle-cell type and the less common **myxoid** and **epithelioid** types. Spindle-cell type contains spindle cells with marked cellular **atypia**/nuclear **pleomorphism**, >10 mitoses per 10 high-power fields, and areas of necrosis (Figure 3.1.30 A); these features differentiate leiomyosarcoma from leiomyoma (at least two of these are required to diagnose leiomyosarcoma). Myxoid tumors have abundant myxoid **stroma.** Epithelioid tumor cells resemble epithelial cells (epithelial-like, hence the name); these cells are round or **polygonal** with **eosinophilic cytoplasm** (Figure 3.1.30 B).

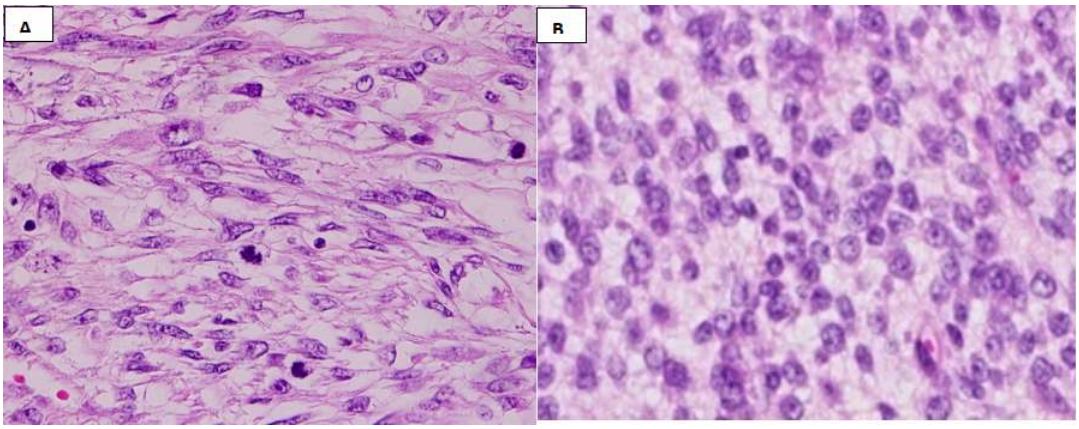


Figure 3.1.30 (A) Leiomyosarcoma: Variable atypia, often with cytoplasmic vacuoles at both ends of nuclei and frequent mitoses.
Image Source: Kobayashi, Eiji, Takuhei Yokoyama, Satoshi Nakagawa, Shinya Matsuzaki, Toshihiro Kimura, Yutaka Ueda, Kiyoshi Yoshino, Masami Fujita, Yumiko Hori, Eiichi Morii and Tadashi Kimura. " Histopathology of leiomyosarcoma of the uterus." (July 31, 2013). This work is distributed under a CC BY 4.0 license. Original Source: "Pedunculated Sub-Serous Leiomyosarcoma Mimicking Ovarian Cancer: Case Report and Review of Literature". *Gynecology & Obstetrics* 3, No. 3 (2012). This work is distributed under a CC BY 4.0 license. DOI:10.4172/2161-0932.1000157. Image available from Wikimedia Commons.

Figure 3.1.30 (B) Histopathology of epithelioid leiomyosarcoma of the uterus. 40x, H&E staining.
Image Source: King, Luke, Radhika P Gogoi, Christopher Hummel, Zongming Chen and Ashlee Smith. "Histopathology of epithelioid leiomyosarcoma of the uterus." 40x, H&E staining. (July 12, 2018). This work is distributed under a CC BY 4.0 license. Original Source: "High Grade Uterine Sarcoma with Concurrent Metastatic Adenocarcinoma to the Uterus: A Case Report". *Obstetrics and Gynaecology Cases - Reviews* 5, No. 4 (2018). This work is distributed under a CC BY 4.0 license. DOI:10.23937/2377-9004/1410127. Image available from Wikimedia Commons.

3.1.10.4 Clinical Presentation

They are usually diagnosed in the 6th decade of life, with an average age of 53 reported at diagnosis. These are aggressive tumors with a worse prognosis than endometrial endometrioid carcinoma. Typically presenting as a large pelvic mass (greater than 5 cm in diameter), its signs and symptoms include vaginal bleeding, pelvic pain, a sense of fullness in the pelvis or abdomen, **dyspareunia,** and **dysuria,** although some patients are asymptomatic. Survival outcomes are impacted by age at diagnosis, tumor size, and disease stage. An increase in each of these prognostic categories is associated with poorer prognosis. Diagnosis mainly depends on histopathological assessment since imaging techniques are not diagnostic.

Glossary terms

Atypia
abnormality in cells in tissue

Cytoplasm
internal material between the cell membrane and nucleus of a cell, mainly consisting of a water-based fluid called cytosol, within which are all the other organelles and cellular solute and suspended materials

Dyspareunia
genital pain before, during, or after intercourse

Dysuria
painful urination

Eopsinophils
granulocytes that stain with eosin; they release antihistamines and are especially active against parasitic worms

Epithelium
sheets of cells that cover the exterior surfaces of the body, line internal cavities and passageways, and form certain glands; also known as epithelial tissue

Hemorrhage
excessive bleeding [

Mesenchymal
refers to cells that develop into connective tissue, blood vessels, and lymphatic tissue

Myometrium
smooth muscle layer of uterus that allows for uterine contractions during labor and expulsion of menstrual blood

Necrosis
accidental death of cells and tissues

Pleomorphism
able to assume different forms

Stroma

tissue that forms the structure of an organ or body part

Visceral

pertaining to internal organs

Footnotes

21. Kim, Suyeon, Hyunsik Bae, and Hyun Soo Kim. “Dedifferentiated Leiomyosarcoma of the Uterine Corpus with Heterologous Component: Clinicopathological Analysis of Five Consecutive Cases from a Single Institution and Comprehensive Literature Review.” *Diagnostics* 14, no. 2 (2024): 160. This work is distributed under a CC BY license. doi.org/10.3390/diagnostics14020160; Dall, Genevieve V., Anne Hamilton, Gayanie Ratnayake, Clare Scott, and Holly Barker. “Interrogating the Genomic Landscape of Uterine Leiomyosarcoma: A Potential for Patient Benefit.” *Cancers* 14, no. 6 (2022): 1561. This work is distributed under a CC BY license. doi.org/10.3390/cancers14061561

Image Acknowledgements

King, Luke, Radhika P Gogoi, Christopher Hummel, Zongming Chen and Ashlee Smith. "Histopathology of epithelioid leiomyosarcoma of the uterus." 40x, H&E staining. (July 12, 2018). This work is distributed under a CC BY 4.0 license. Original Source: "High Grade Uterine Sarcoma with Concurrent Metastatic Adenocarcinoma to the Uterus: A Case Report". *Obstetrics and Gynaecology Cases - Reviews* 5, No. 4 (2018). This work is distributed under a CC BY 4.0 license. DOI:10.23937/2377-9004/1410127. Image available from Wikimedia Commons.

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3.2: Cervical Pathologies

In this section:

- 3.2.1 Cervicitis
- 3.2.2 Endocervical Polyp
- 3.2.3 Carcinoma of the Cervix

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3.2.1: Cervicitis

3.2.1.1 Definition and Types

Inflammation of the **ectocervix** that could be acute (mainly infectious) or chronic (mainly noninfectious).[22]

3.2.1.2 Etiology

- Infectious Causes
  - Sexually transmitted organisms (Chlamydia trachomatis, Ureaplasma urealyticum, T. vaginalis, Neisseria gonorrhoeae, HSV-2, and certain types of HPV)
  - Bacterial **vaginosis**[23]
- Noninfectious causes

These are mainly chemical and mechanical irritants. Chemical irritants include soaps, laundry products, spermicides, latex, vaginal douches, and contraceptive creams; they result in allergic reactions. Mechanical irritants include condoms, diaphragms, cervical caps, or tampons)[24]

- Other inflammatory conditions

Cervicitis can also be a part of systemic inflammatory diseases such as **lichen planus** and **Behcet syndrome**.[25]

3.2.1.3 Clinical Presentation

Clinically, it can be asymptomatic or present with **mucopurulent** vaginal discharge (i.e., **leukorrhea**), post-coital bleeding, and **dyspareunia**. It is usually associated with pelvic inflammatory disease and presents with abdominal pain and **adnexal** tenderness. If associated with inflammation of the urethra (urethritis), it presents with urinary symptoms. On pelvic examination, a yellowish **mucoid** discharge can be seen coming from the **cervical os**. The cervix appears swollen with small red spots indicating punctate hemorrhages (strawberry cervix); is usually associated with **trichomonas** infections. Cervical vesicles and ulcers are seen in cervicitis caused by HSV. Systemic symptoms of inflammation, such as high fever, can also be detected.[26]

3.2.1.4 Diagnosis

Nucleic acid amplification testing (NAAT) is the most sensitive and specific test for identifying the causative organisms in infectious cervicitis. Both vaginal discharge and urine samples are used for this test.[27]

3.2.1.5 Treatment

Treatment mainly targets the causative agents. Administration of **empiric** antibiotics is indicated whenever a causative pathogen is not detected on testing and for women at higher risk of sexually transmitted disease (less than 25 years of age, having a partner with STD, new partner, or multiple partners). These antimicrobials mainly target **chlamydia** and **gonorrhea**.[28]

For more information

For more details on cervical abnormalities secondary to cervicitis, please refer to World Health Organization (WHO) "VIA procedure - Examination before application of acetic acid," Atlas of visual inspection of the cervix with acetic acid for screening, triage, and assessment for treatment.

For more details on specific treatments based on detected pathogens, please refer to National Library of Medicine (NLM) "Cervicitis," StatPearls (2023).

Glossary Terms

Adnexal
: of the uterine appendages (ADNEXA UTERI) including diseases involving the OVARY, the FALLOPIAN TUBES, and ligaments of the uterus (BROAD LIGAMENT; ROUND LIGAMENT)

Behcet syndrome
: Rare chronic inflammatory disease involving the small blood vessels. It is of unknown etiology and characterized by mucocutaneous ulceration in the mouth and genital region and uveitis with hypopyon. The neuro-ocular form may cause blindness and death. SYNOVITIS; THROMBOPHLEBITIS; gastrointestinal ulcerations; RETINAL VASCULITIS; and OPTIC ATROPHY may occur as well

Cervical os
: neck portion of the UTERUS between the lower isthmus and the VAGINA forming the cervical canal

Chlamydia
: A genus of the family CHLAMYDIACEAE whose species cause a variety of diseases in vertebrates including humans, mice, and swine. **Chlamydia** species are gram-negative and produce glycogen

Dyspareunia
: genital pain before, during, or after intercourse

Ectocervix
: neck portion of the UTERUS between the lower isthmus and the VAGINA forming the cervical canal

Gonorrhea
: acute infectious disease characterized by primary invasion of the urogenital tract

Leukorrhea
: clear or white discharge from the VAGINA, consisting mainly of MUCUS

Lichen planus
: inflammatory, pruritic disease of the skin and mucous membranes, which can be either generalized or localized; characterized by distinctive purplish, flat-topped papules having a predilection for the trunk and flexor surfaces

Mucoid
: resembling mucus

Mucopurulent
: containing both mucus and pus

Trichomonas
: genus of parasitic flagellate EUKARYOTES distinguished by the presence of four anterior flagella, an undulating membrane, and a trailing flagellum

Vaginosis
: abnormal condition of the vagina

Footnotes

22. Groetsch, Stefan and James W. Keck. “Cervicitis,” *Clinics in Family Practice* 7, no. 1 SPEC. ISS. (September 4, 2023): 43–56. doi.org/10.1016/j.cfp.2005.01.002

23. Groetsch and Keck, 2023
24. Groetsch and Keck, 2023
25. Groetsch and Keck, 2023
26. Groetsch and Keck, 2023
27. Groetsch and Keck, 2023
28. Groetsch and Keck, 2023

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3.2.2: Endocervical Polyp

3.2.2.1 Definition and Overview

Polyps are abnormal growths that arise from the **ecto** or **endocervix**. They are usually **benign** (common in reproductive age) and, rarely, **malignant**. Malignant polyps are seen mainly in postmenopausal women.

They vary in shape, size, number (single or multiple), and color (degree of **vascularization**). Endocervical polyps are more common than ectocervical ones and occur in premenopausal women, while ectocervical polyps are more common in postmenopausal women.[29]

3.2.2.2 Etiology

The exact etiology is unknown. However, vascular congestion, infections, chronic inflammations, chemical irritants, and hormonal imbalances are hypothesized causes. Risk factors include premenopausal, **multigravida**, and STI.[30]

3.2.2.3 Histopathology

Microscopically, cervical polyps have a vascular connective tissue core covered by proliferating **epithelia**l cells. Endocervical polyps (Figure 3.2.1) are the most common type and have loose, **edematous stroma** with variably sized blood vessels. Chronic inflammatory infiltrate can be detected in the stroma. Epithelial cells demonstrate glandular **hyperplasia**.[31]

3.2.2.4 Clinical Picture

Cervical polyps are incidentally detected during routine gynecological examination. They can be asymptomatic or present with abnormal uterine bleeding, including heavy menstruation, intermenstrual bleeding, or postmenopausal bleeding. Other presentations include vaginal discharge and infertility (if polyps are large enough to block the cervical canal). **Histologic** examination of cervical polyps is essential for the diagnosis of underlying and associated pathologies and to rule out malignancy.[32]

3.2.2.5 Treatment

Usually, asymptomatic polyps don't need any intervention. Large symptomatic polyps require removal (i.e., polypectomy) using forceps, electrosurgical excision, or laser **ablation.**[33]

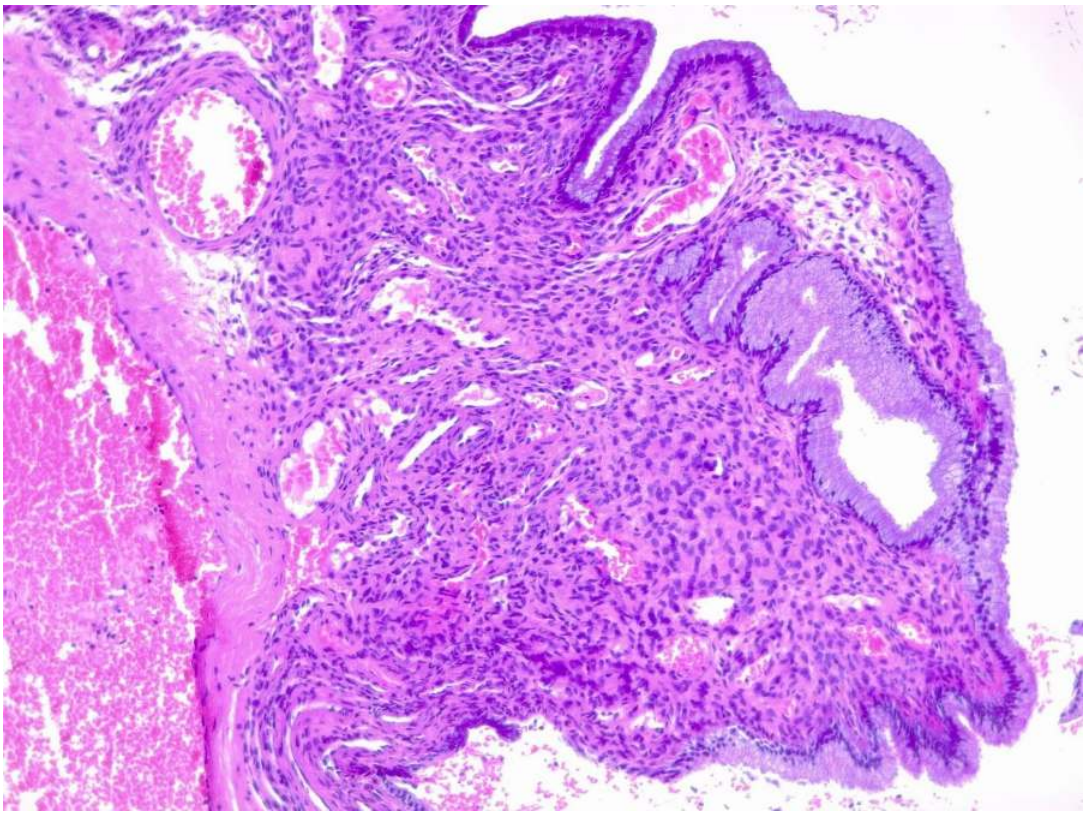


Figure 3.2.1 Endocervical polyp**:** With endocervical epithelium and glands (mucinous columnar linings), edematous stroma, and clear congestion. H&E stain.
Image Source: Aggarwal, Pearl and Anissa Ben Amor. "Cervical Ectropion," *StatPearls* (2024). This work is distributed under a CC BY-NC-ND license. Available from NIH National Library of Medicine (NLM) Bookshelf StatPearls.

Glossary Terms

Ablation

removal or destruction of a body part or tissue or its function; may be performed by surgery, hormones, drugs, radiofrequency, heat, or other methods

Benign

non-cancerous

Ectocervix

outer part of the neck portion of the UTERUS between the lower isthmus and the VAGINA forming the cervical canal

Edematous

ccc

Endocervix

inner part of the neck portion of the UTERUS between the lower isthmus and the VAGINA forming the cervical canal

Epithelial

relating to or affected with edema **:** abnormally swollen with fluid

Histology

The study of tissues

Hyperplasia

abnormal growth due to the production of cells

Malignant

cancerous

Multigravida

a woman who has been pregnant more than once

Stroma

tissue that forms the structure of an organ or body part

Vascularization

process of becoming vascular (channel for the conveyance of a body fluid (such as blood)

Footnotes

29. Alkilani, Yara G. and Irasema Apodaca-Ramos. “Cervical Polyps.” *The American Journal of Surgery* 36, no. 1 (September 4, 2023): 239. doi.org/10.1016/S0002-9610(37)90821-3.
30. Alkilani and Apodaca-Ramos, 2023
31. Alkilani and Apodaca-Ramos, 2023
32. Alkilani and Apodaca-Ramos, 2023
33. Alkilani and Apodaca-Ramos, 2023

Image Acknowledgements

Aggarwal, Pearl and Anissa Ben Amor. "Cervical Ectropion," *StatPearls* (2024). This work is distributed under a CC BY-NC-ND license. Available from NIH National Library of Medicine (NLM) Bookshelf StatPearls.

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3.2.3: Carcinoma of the Cervix

3.2.3.1 Definition

This is a malignant tumor of the **cervix** mainly caused by **oncogenic** strains of HPV. The tumors commonly arise from the transformation zone.

3.2.3.2 Transformation Zone

The **ectocervix** (i.e., the part of the cervix protruding into the vagina) is lined with **squamous epithelium** (Figure 3.2.2 A). The epithelial lining of the **endocervical canal** is columnar mucous-secreting glandular epithelium (Figure 3.2.2 B).

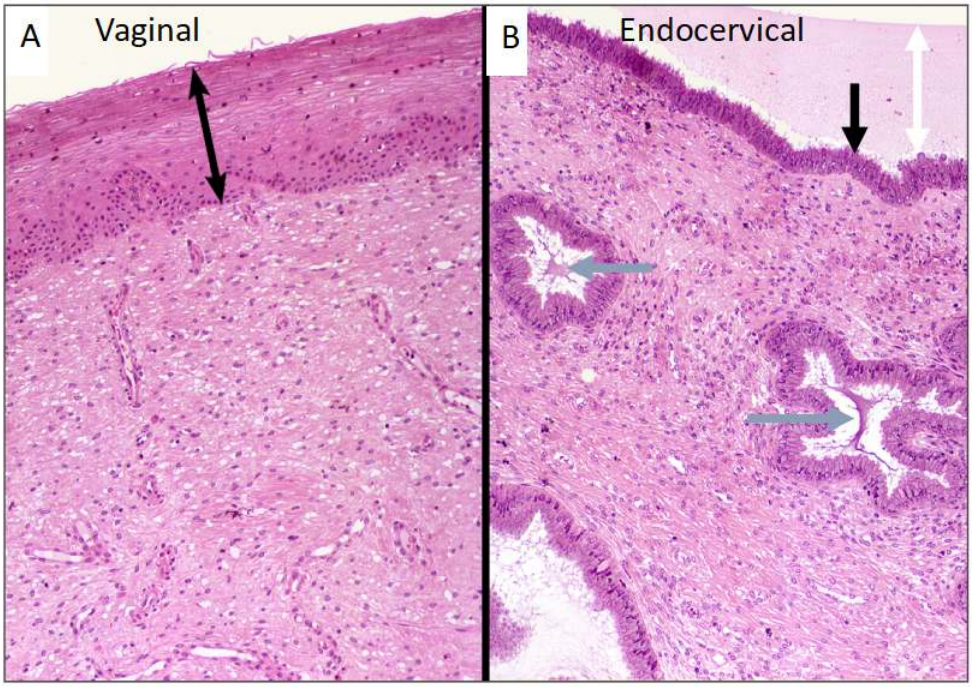


Figure 3.2.2 Ectocervix (A): The ectocervix, like the vagina, is lined by a stratified squamous moist epithelium (Black double-headed arrow). **Endocervix (B):** The tall, simple columnar epithelium lining the endocervical canal (black arrow) secretes mucus (blue double-headed arrow and grey arrows). Infolds of this epithelium form plicae palmatae ("palm folds"); these are known as cervical crypts or glands. In the presence of high estrogen levels at ovulation, the cells lining he crypts secrete abundant alkaline secretions (grey arrows). This mucus lubricates the vagina and nourishes spermatozoa. Some of this mucus is seen on the surface of the epithelium.
Image Source: Pakurar, Alice S. and John W. Bigbee. Carole W. Christman, Ph.D, Medical Illustrator. *Digital Histology,* (ND). This work is openly licensed via CC BY SA Creative Commons License. Available from Virginia Commonwealth University. Used with permission.

The **squamocolumnar junction** SCJ is where the squamous epithelium meets the glandular epithelium. The anatomical location of the SCJ keeps changing, and this is dependent on age, hormonal status, and pregnancy (Figure 3.2.3). Before puberty, the SCJ is located in the endocervical canal above the **external os**; this is referred to as the original SCJ because it

represents the junction between the original two types of epithelia formed during **embryogenesis**. After puberty and during the reproductive period, elongation of the endocervical canal occurs secondary to hormonal effects resulting in **eversio**n of the columnar epithelium of the lower part of the endocervix (i.e., the columnar epithelium shifts towards the ectocervix). This shift makes the SCJ located on the ectocervix, away from the external os. Due to exposure of the columnar epithelium of the SCJ to the acidic vaginal secretions, it undergoes **squamous metaplasia**. The metaplastic changes start at the original SCJ and proceed towards the external os, resulting in the formation of a new SCJ between the newly formed **metaplastic squamous** epithelium and the columnar epithelium. These metaplastic changes occur throughout the reproductive period and until menopause. They are dynamic and vary in rates and cell maturation based on hormonal status and pregnancy. Therefore, the location of the newly formed SCJ keeps changing until it becomes completely invisible in postmenopausal women as it becomes entirely endocervical. The metaplastic epithelium closer to the SCJ is composed of immature metaplastic cells, and the mature metaplastic epithelium is closer to the original SCJ. The area between the original SCJ and the newly formed SCJ is known as the transformation Zone (TZ). The immature squamous cells in the TZ are the most susceptible to Human Papilloma Virus (HPV) oncogenesis, and these are the cells of origin of cervical carcinomas.[34]

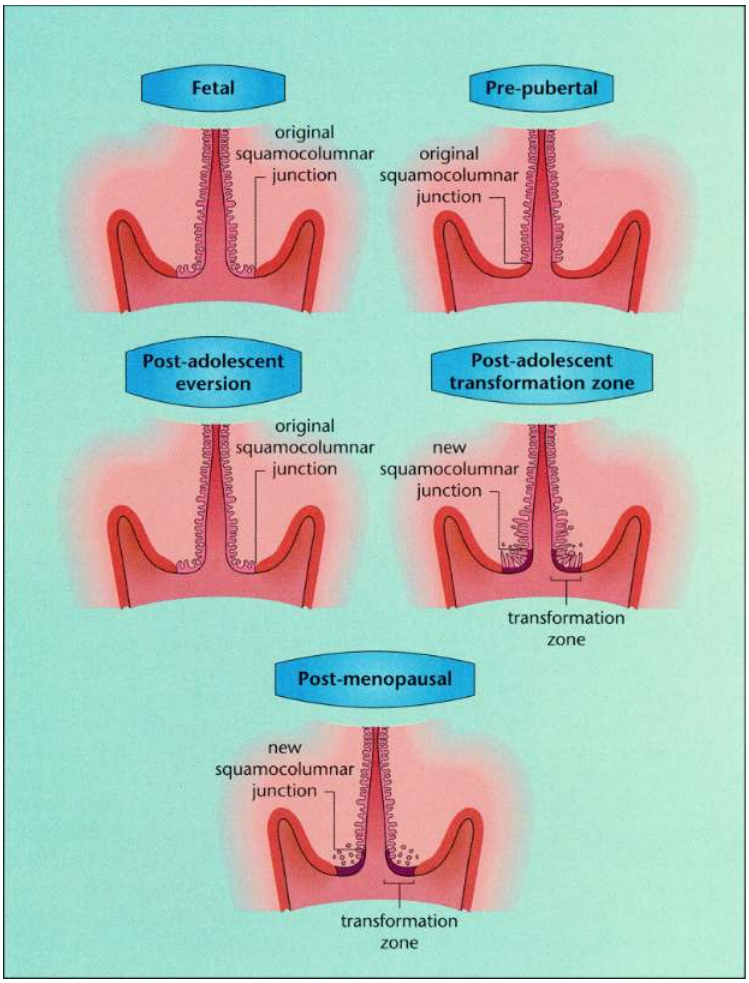


Figure 3.2.3 Development of the transformation zone from fetal life to postmenopausal life. Prendiville W, Ritter J, Tatti SA, Twiggs LB (2003). Colposcopy: management options. Amsterdam: Elsevier Limited.
Image Source: Prendiville, Walter, and Rengaswamy Sankaranarayanan. "Chapter 2. Anatomy of the Uterine Cervix and the Transformation Zone," in *Colposcopy and Treatment of Cervical Precancer,* IARC Technical Report, No. 45 (2017). Openly available from NIH National Library of Medicine (NLM) Bookshelf.

3.2.3.3 Pathogenesis

Cervical Intraepithelial Neoplasia (CINs) are the precursor **lesions** of cervical carcinomas. These lesions arise from normal cervical epithelium and are categorized into low-grade and high-grade CINs. The most important factor in the pathogenesis of all types of cervical cancer (squamous and **adenocarcinomas**) is the High-risk HPV (hrHPV). HPVs are DNA viruses that are categorized into low oncogenic risk (types 6 and 11) and high oncogenic risk (types 16 and 18) based on their genotypes. Infections with hrHPV take a longer time to clear and are usually associated with the formation of precursor lesions (CIN). High-risk HPVs are the main pathogenic factors of squamous cell carcinomas of other tissues (e.g., **oropharynx**, tonsils, anus, vagina, vulva, and penis). Risk factors associated with HPV infections are early age at first intercourse, multiple sexual partners, and persistent infection with high-risk strains of HPV.[35]

The hrHPV infection into the cervical epithelium results in host genome alterations, leading to the silencing of various tumor-suppressor factors on one hand and inducing aberrant functioning of various tumor-promoting factors on the other (Figure 3.2.4). The imbalance and instability caused by various hrHPV-derived oncogenic factors in the host genome of the cervical epithelial cells drive neoplastic progression over the course of years. HPV infection causes cervical carcinoma in a small percentage of individuals; other factors contributing to the persistence of this viral infection play a role in HPV-mediated carcinogenesis. These include cigarette smoking and **host immune status**. [36]

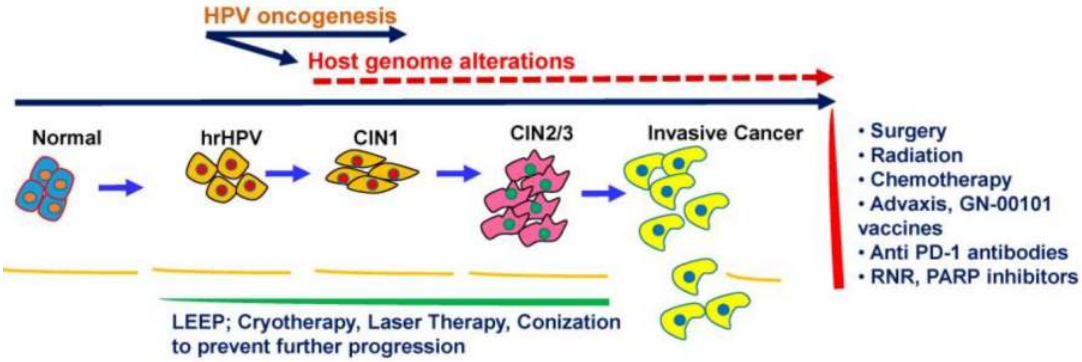


Figure 3.2.4 Cervical cancer development, prevention, and treatment. Invasive cervical cancer development from normal to progressive cervical intraepithelial neoplasia (CIN) through high-risk human papilloma virus (hrHPV) oncogenesis and host genome alterations. Available interventions in preventing and treating cervical cancer have also been shown. LEEP: loop electrosurgical excision procedure; RNR: ribonucleotide reductase; PARP: Poly (adenosine diphosphate [ADP]-ribose) polymerase.
Image Source: Olusola, Patti, Hirendra Nath Banerjee, Julie V. Philley, and Santanu Dasgupta. "Human Papilloma Virus-Associated Cervical Cancer and Health Disparities." *Cells* 8, no. 6 (2019):622 This work is openly licensed via CC BY license. doi.org/10.3390/cells8060622.88

The major **oncoproteins** E5, E6, and E7 encoded by the HPV genome are the major drivers of oncogenesis in normal cervical epithelium. They disrupt the normal functioning of the major **histocompatibilit**y complex I (MHC class I), p53 and Rb, Notch1, Wnt, MAPK, mTOR, and STAT-associated pathways, which are central players controlling normal cellular growth, differentiation, and immune function (Figure 3.2.5). HPVs induce carcinogenesis through dysregulation of the activity of tumor suppressor proteins such as p53 and RB by the viral E6 and E7 proteins, respectively. HPV infects immature squamous cells of the TZ, and when these cells mature, the viral infection prevents the normal arrest of these cells in the G1 phase of the cell cycle. Hence, viral replication takes place in mature cells. viral genome and for productive shedding of the virus. The viral E6 **upregulates telomerase** and binds to p53, leading to its destruction. E7 binds to the RB protein, leading to the release of the E2F transcription factors from the inhibitory effect of RB. This results in progression through the cell cycle. High-risk HPVs also integrate into the host cell genome. This integration results in increased expression of the viral E6 and E7 proteins. Also, the integration into the host cell genome increases the

genomic instability of these cells, leading to the acquisition of prooncogenic mutations. Low-risk HPVs do not integrate into the host genome.[37]

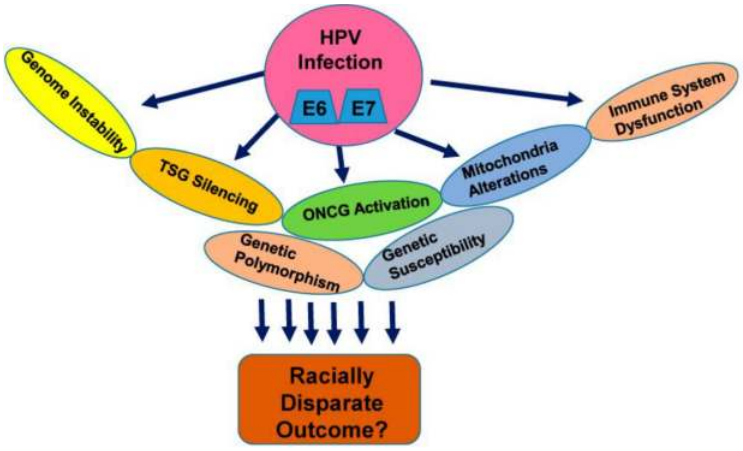


Figure 3.2.5 Molecular pathogenesis of HPV-associated cervical cancer. Multiple nuclear and mitochondrial genetic alteration pathways leading to cervical cancer progression and racial health disparities. E6, E7: oncogenic HPV molecules. TSG: tumor suppressor gene; ONCG: oncogene.
Image Source: Olusola, Patti, Hirendra Nath Banerjee, Julie V. Philley, and Santanu Dasgupta. "Human Papilloma Virus-Associated Cervical Cancer and Health Disparities." *Cells* 8, no. 6 (2019):622 This work is openly licensed via CC BY license. doi.org/10.3390/cells8060622.

Periodic surveillance for hrHPV and Pap smear-based testing resulted in a remarkable reduction in the incidence of cervical carcinomas in the USA and globally. However, there is still great variability in the occurrence and outcome of cervical cancer in various ethnic populations. Moreover, several social determinants of health, including lack of adequate health insurance, pose a socioeconomic burden for cervical cancer preventive screening in a timely manner. This results in disparate cervical cancer incidence and health outcomes. Therefore, understanding the underlying molecular mechanism and genetic basis behind these disparities is warranted through further research studies.[38]

For more information

For further details on the molecular pathogenic mechanisms associated with disparities, please refer to Olusola, Patti, Hirendra Nath Banerjee, Julie V. Philley, and Santanu Dasgupta. "Human Papilloma Virus-Associated Cervical Cancer and Health Disparities." *Cells* 8, no. 6 (2019):622.

3.2.3.4 Squamous Intraepithelial Lesion (SIL) and Cervical Intraepithelial Neoplasia (CIN)

Precancerous cervical lesions caused by HPV infections are known as SIL and usually occur years before invasive carcinoma. Based on cell biology, these lesions are classified into low-grade SIL (LSIL) and high-grade SIL (HSIL). Another classification system categorizes them into three categories: CIN I, CIN II, and CIN III. The LSIL corresponds to CIN I, and the HSIL

corresponds to CIN II and III. HSIL has a high risk for progression to carcinoma. Risk factors associated with progression include cigarette smoking and **immunocompromised** status.[39]

3.2.3.5 Screening and Diagnostic Testing

The Papanicolaou (Pap) test is the gold standard for screening for cervical cancer. It detects the cytological abnormalities associated with cervical precancerous lesions. The test is performed by scraping the cervical TZ and examining the cells microscopically.[40]

Detection of hrHPV DNA in the scraped cells is an additional step in cervical cancer screening. The Food and Drug Administration (FDA) approved HPV testing for women aged 25 and older. This test detects HPV types 16, 18, and 26 and additional hrHPV types. HPV testing of women younger than 25 years of age is less useful because these infections are usually cleared by the immune system and never progress to SIL.[41]

3.2.3.6 Morphology

- Morphologic features of SIL/CIN

The morphological features of SIL/CIN are illustrated in (Figure 3.2.6). LSIL (CIN I) demonstrates **dysplastic** changes in the lower third of the squamous epithelium with **koilocytosis** (i.e., cells with halo or **vacuolated cytoplasm** or empty space cytoplasm) in the superficial layers of the epithelium. In HSIL, the dysplastic changes involve the lower two-thirds (CIN II) or all layers (CIN III). The dysplastic changes include variation in cell and nuclear size, heterogeneity of nuclear **chromatin**, and the presence of **mitoses**. In CIN III, in addition to the previously described dysplastic changes, there is also disordered cellular orientation. [42]

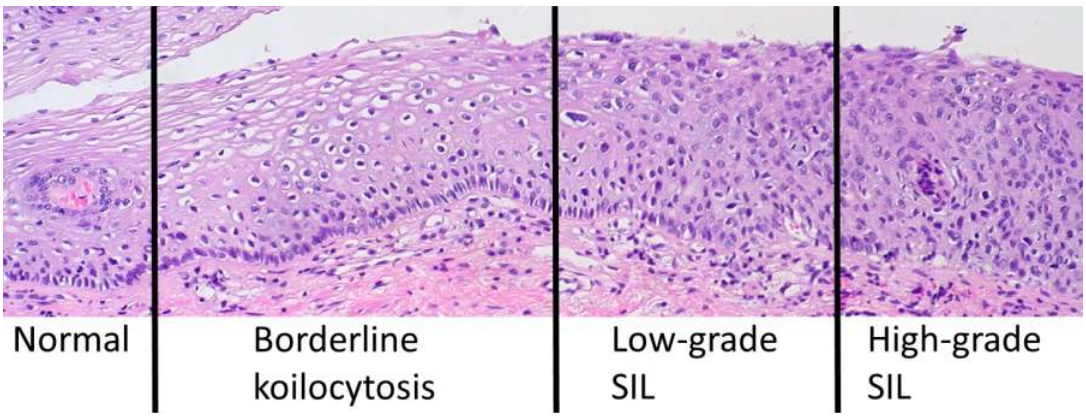


Figure 3.2.6 Spectrum from normal to high-grade SIL.
Image Source: Ed Uthman (December 23, 2021). This work is openly licensed via CC BY 2.5 license. Available from Wikimedia Commons

The cytological changes of cells collected via Pap smear are illustrated in (Figure 3.2.7). The superficial squamous cells stain either red or blue. The increase in the nuclear/cytoplasmic ratio in both LSIL and HSIL indicates the progressive loss of cellular differentiation.

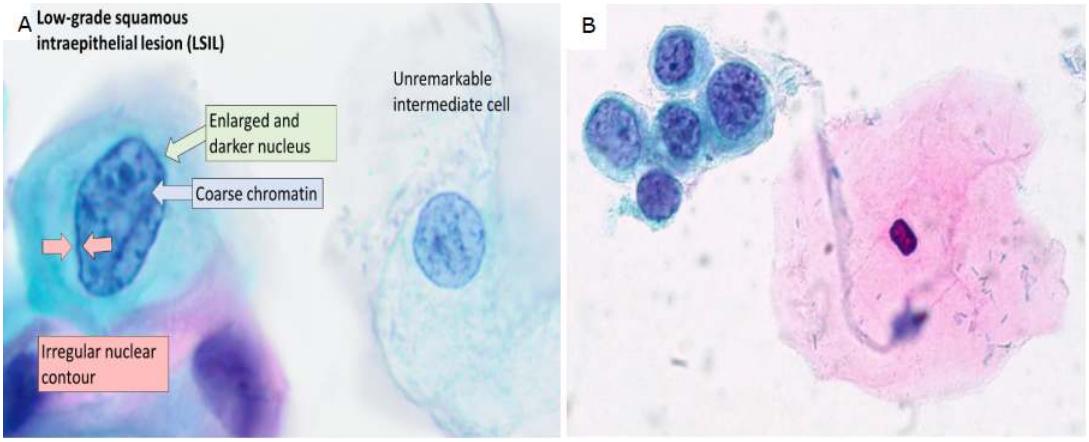


Figure 3.2.7 Low-grade squamous intraepithelial lesion (LSIL) (A), here compared to an unremarkable intermediate squamous cell.

Image Source: Mikael Häggström (August 29, 2022). This work is openly licensed via CC0 Public Domain license. Available from Wikimedia Commons.

High-grade squamous intraepithelial lesion (HSIL) (B), showing even more prominent features, and decreased cytoplasm, causing a high nuclear/cytoplasmic ratio (The group of cells at the upper left corner of the photomicrograph). Pap smear from a 35-year-old, with no previous Pap on file. Biopsy confirmed the presence of carcinoma in situ, extending over the surfaces of all the biopsy fragments. The endocervical curettage specimen also had numerous fragments of CIS.

Image Source: Ed Uthman (January 26, 2010). This work is openly licensed via CC BY 2.0 License. Available from Wikimedia Commons.

- Morphologic features of Invasive Carcinoma

The morphological features of Invasive Carcinoma of the Cervix are illustrated in (Figure 3.2.8). Cervical carcinomas develop in the TZ. Squamous cell carcinoma is the most common type; other less common types include adenocarcinoma**, adenosquamous carcinoma**, and small-cell **neuroendocrine** carcinoma. The invasive tumors consist of nests of squamous cells that induce a **desmoplastic stromal** response (i.e., an inflammatory response in the stroma that leads to scar tissue formation and **fibrosis)**. Tumor grading is based on the degree of tumor cell differentiation (i.e., the degree the tumor cells resemble the cells of origin). Well-differentiated tumors demonstrate **keratin pearls**. Less differentiated, neuroendocrine tumors look like small cell carcinoma of the lungs.[43]

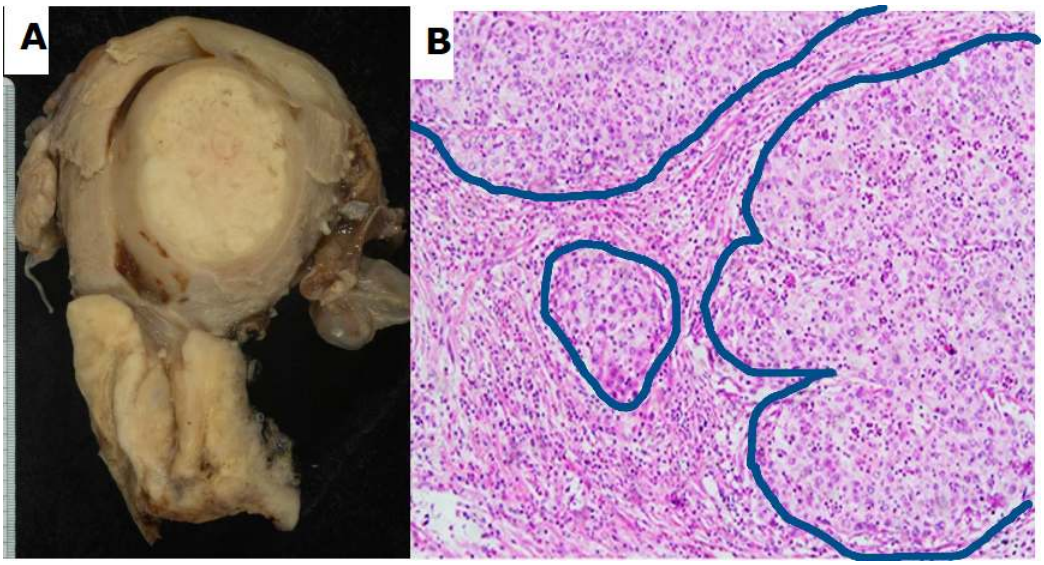


Figure 3.2.8 Invasive Squamous Cell Carcinoma of the Cervix. Large squamous carcinoma (bottom of the picture) has obliterated the cervix and invaded the lower uterine segment (A). The uterus also has a round leiomyoma up higher.
Image Source: Ed Uthman (March 28, 2006). This work is openly licensed via a CC BY 2.0 license. Available from Flickr.
Histopathology of a poor-differentiated squamous cell carcinoma of the cervix (B). Nests of malignant cells (marled by blue free lines). Note the stromal desmoplastic reaction between the nests.
Image Source: Li H, Jing X, Yu J, Liu J, Zhang T, and Chen S. (August 26, 2020). This work is licensed under a CC BY 4.0 license. Available from Wikimedia Commons.

3.2.3.7 Clinical Features, Treatment and Prevention

SILs are usually asymptomatic and are detected in Pap smears. These lesions are managed conservatively through follow-up. HSILs are treated by cone biopsy (cervical excision). Follow-up is required due to the increased risk of invasive carcinomas. The gold standard for early detection of invasive cervical tumors is Pap tests and biopsy of suspicious lesions.[44]

Invasive cervical cancer usually presents with abnormal vaginal bleeding and/or discharge **(leukorrhea)**, painful coitus (**dyspareunia**), or **dysuria**. **Hysterectomy** with lymph node removal is the first line of treatment for invasive cervical carcinomas. **Adjuvant** treatments in the form of radiation or chemotherapy are helpful in case surgery is not curative. The prognosis for invasive carcinoma greatly depends on the stage and tumor grade at the time of diagnosis. High-grade tumors such as neuroendocrine tumors generally have poor prognosis.[45]

Vaccination against high-risk HPV plays a great role in preventing the development of cervical carcinomas. The recommended age for vaccination is 11 to 12 years for boys and girls and 26 for young men and women; they provide approximately 10 years of protection. The quadrivalent HPV vaccine for types 6, 11, 16, and 18, and the more recently introduced 9-valent vaccine, are effective in preventing HPV infections. Due to the fact that current vaccines

do not protect against all oncogenic HPV types, vaccines don't substitute for regular cervical cancer screening.[46]

Glossary Terms

Adenocarcinoma

A malignant epithelial tumor with a glandular organization

Adenosquamous

mixed adenocarcinoma and squamous cell or epidermoid carcinoma

Adjuvant

augment, stimulate, activate, potentiate or modulate action or response of medical treatment

Cervix

elongate inferior end of the uterus where it connects to the vagina

Chromatin

substance consisting of DNA and associated proteins

Cytoplasm

internal material between the cell membrane and nucleus of a cell, mainly consisting of a water-based fluid called cytosol, within which are all the other organelles and cellular solute and suspended materials

Desmoplastic

characterized by the formation of fibrous tissue

Dyspareunia

genital pain before, during, or after intercourse

Dysplastic

abnormal growth or development (as of organs or cells)

Dysuria

painful urination

Ectocervix

neck portion of the UTERUS between the lower isthmus and the VAGINA forming the cervical canal

Embryogenesis

human embryogenesis is a complicated process by which a fertilized egg develops into an embryo

Endocervical

neck portion of the UTERUS between the lower isthmus and the VAGINA forming the cervical canal.

Epithelium

sheets of cells that cover the exterior surfaces of the body, line internal cavities and passageways, and form certain glands; also known as epithelial tissue

Eversion

foot movement involving the intertarsal joints of the foot in which the bottom of the foot is turned laterally, away from the midline

External os

the opening of the uterine cervix into the vagina

Fibrosis

process in which muscle fibers are replaced by scar tissue

Histocompatability

state of mutual tolerance that allows some tissues to be grafted effectively to others

Hysterectomy

surgery to remove the uterus and, sometimes, the cervix

Immunocompromised

human or animal whose immunologic mechanism is deficient because of an immunodeficiency disorder or other disease or as the result of the administration of immunosuppressive drugs or radiation

Keratin pearls

formed by local squamous epithelium accumulation which is easily recognized under a microscope [5] and is considered a marker of well-differentiated squamous cell carcinoma

Koilocytosis

the presence of koilocytes (vacuolated pyknotic epithelial cell that has either a clear cytoplasm or a perinuclear halo and that tends to be associated with certain human papillomavirus infections) usually in the anogenital region or the uterine cervix

Lesions

areas of abnormal tissue

Leukorrhea

clear or white discharge from the VAGINA, consisting mainly of MUCUS

Metaplasia

condition in which there is a change of one adult cell type to another similar adult cell type

Mitosis

type of CELL NUCLEUS division by means of which the two daughter nuclei normally receive identical complements of the number of CHROMOSOMES of the somatic cells of the species

Neuroendocrine

of, relating to, or being a hormonal substance that influences the activity of nerves

Oncogene

gene that is a mutated form of a gene involved in normal cell growth and may cause the growth of cancer cells (National Cancer Institute, n.d.)

Oncoproteins

proteins coded by oncogenes; they include proteins resulting from the fusion of an oncogene and another gene (ONCOGENE PROTEINS, FUSION)

Oropharynx

part of the pharynx continuous with the oral cavity that functions in respiration and digestion

Squamocolumnar junction (SCJ)

the region in the uterine cervix in which the squamous lining of the vagina is replaced by the columnar epithelium typical of the body of the uterus and which is a common site of neoplastic change

Squamous

of, relating to, or being a stratified epithelium that consists at least in its outer layers of small scalelike cells

Stroma

the tissue that forms the structure of an organ or body part

Telomerase

essential ribonucleoprotein reverse transcriptase that adds telomeric DNA to the ends of eukaryotic CHROMOSOMES

Upregulation

the process by which a cell increases its response to a substance or signal from outside the cell to carry out a specific function. For example, a cell may increase the number or activity of protein receptors or other molecules on its surface to make it more sensitive to a hormone or drug

Vacuolated (cytoplasm)

containing one or more vacuoles (small cavity or space in the tissues of an organism containing air or fluid)

Footnotes

34. Prendiville, Walter and Rengaswamy Sankaranarayanan. “Chapter 2. Anatomy of the Uterine Cervix and the Transformation Zone,” in *Colposcopy and Treatment of Cervical Precancer,* IARC Technical Report, No. 45 (2017).

Openly available from NIH National Library of Medicine (NLM) Bookshelf.
35. Olusola, Patti, Hirendra Nath Banerjee, Julie V. Philley, and Santanu Dasgupta. “Human Papilloma Virus-Associated Cervical Cancer and Health Disparities.” *Cells* 8, no. 6 (2019):622 This work is openly licensed via CC BY license. doi.org/10.3390/cells8060622.
36. Olusa et al, 2019
37. Olusa et al, 2019
38. Olusa et al, 2019
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45. Olusa et al, 2019
46. Olusa et al, 2019

Image Acknowledgements

- Olusola, Patti, Hirendra Nath Banerjee, Julie V. Philley, and Santanu Dasgupta. “Human Papilloma Virus-Associated Cervical Cancer and Health Disparities.” *Cells* 8, no. 6 (2019):622 This work is openly licensed via CC BY license. doi.org/10.3390/cells8060622.
- Pakurar, Alice S. and John W. Bigbee. Carole W. Christman, Ph.D, Medical Illustrator. *Digital Histology,* (ND). This work is openly licensed via CC BY SA Creative Commons License. Available from Virginia Commonwealth University.
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3.3: Vulvovaginal Pathologies

In this section:

- 3.3.1 Inflammatory Disorders of the Vulva
- 3.3.2 Inflammatory Disorders of the Vagina
- 3.3.3 Neoplastic Disorders of the Vulva and Vagina

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3.3.1: Inflammatory Disorders of the Vulva

Note

Inflammatory disorders of the Vulva are a miscellaneous group of non-infectious conditions affecting the vulvar area and are characterized mainly by inflammation.[1] This section will cover Vulva lichen sclerosis (VLS) since it is one of the most common pathologies present in clinics.

For details on other inflammatory conditions affecting the vulva, including atopic dermatitis, contact dermatitis, lichen simplex chronicus (LSC; squamous cell hyperplasia) and vulvar psoriasis, please refer to Prabhu, Smitha and Swathy Krishna. "Vulvar inflammatory disorders: A review". Journal of Skin and Sexually Transmitted Diseases. 4 No. 2 (July-December 2022). 189-195. DOI. 10.25259/SSTD_11_2021 This open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial-Share Alike 4.0 License. https://jsstd.org/view-pdf/?article=ddef97141e2f1afa86fb2029d051544fvPLQsgFIo5Q=.

3.3.1.1 Vulvar Lichen Sclerosus

- Overview and Definition

Lichen sclerosis is a chronic progressive inflammatory auto-immune, non-contagious, and non-neoplastic dermatosis of the genital skin. It presents with white, atrophic plaques often forming a “figure-of-eight” configuration around the vulva and perianal region, and can lead to scarring and functional impairment. The current International Society for the Study of Vulvovaginal Disease (ISSVD) classification includes this disease entity with vulvar dermatoses, which are nonneoplastic and non-infectious. There is a potential for lichen Sclerosis to transform into vulvar intraepithelial neoplasia (VIN) and keratinizing vulvar carcinoma. Also, VIN associated with LS is differentiated (dVIN); cancer seems always to be preceded by dVIN in the context of LS.[2]

- Epidemiology, Etiology, Risk Factors, and Pathogenesis

VLS has a bimodal age distribution, primarily affecting prepubertal girls and postmenopausal women, with an estimated prevalence of 1:30 in the latter. Incidence has doubled over two decades, possibly due to increased awareness. The etiology of LS remains unknown, but several mechanisms have been studied for this noncontagious disease. Studies suggest multiple etiologies, including a genetic (Up to 12% report a first-degree relative with VLS; HLA-DQ7, -DQ8, -DQ9, and -DR12 associated with increased susceptibility; HLA-DR17 may be protective), autoimmune (High co-occurrence with autoimmune disorders such as thyroiditis, type 1 diabetes, and systemic sclerosis and presence of activated T cells in the subepithelial infiltrate), hormonal (More common in hypoestrogenic states; theories on local androgen

deficiency), local trauma (Koebner phenomenon—lesions arising at sites of chronic irritation), and infectious (*Borrelia burgdorferi, HPV, and HCV*) background.[3]

- Pathogenesis

Autoimmune-driven inflammation involves T-cell infiltration and basal keratinocyte damage leading to collagen hyalinization and tissue sclerosis. Overexpression of miR-155 inhibits Treg function and promotes autoimmunity. Th1 cytokines and oxidative stress promote chronic inflammation. Details on the pathogenic mechanisms are outlined in Figure 3.3.1.[4]

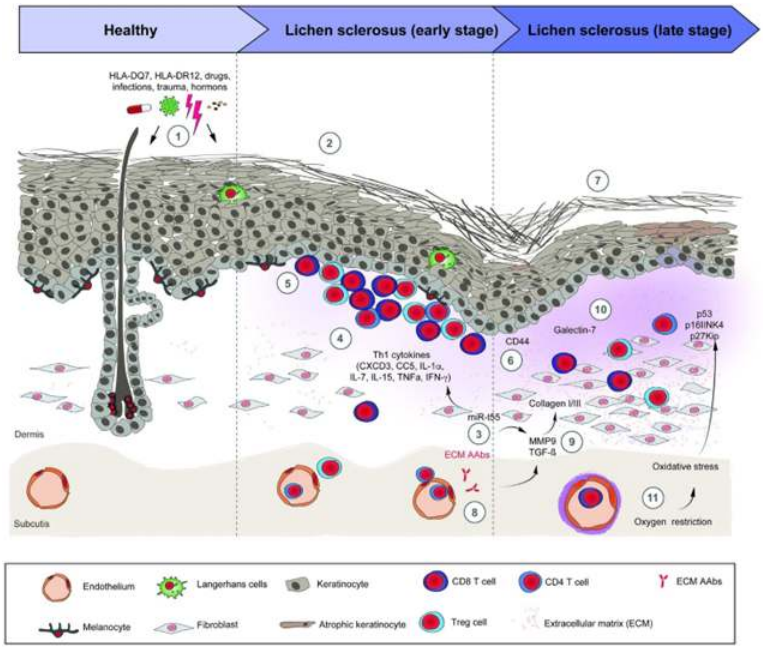


Figure 3.3.1. Schematic overview of lichen sclerosus pathogenesis. (1) Risk factors for LS; (2) The inflammatory early stage of LS is unspecific and shows a dermoepidermal interface band of mostly T-cells. (3) miR-155 is overexpressed in LS, stimulates the Th1 profile and the dermal sclerosis. (4) Th1 cytokines implicated in the pathogenesis of LS. (5) Lichenoid infiltrate of TCD4+, TCD8+, and Tregs cells in the upper dermis. (6) Abnormal expression of CD44 in the epidermis and lichenoid infiltrate. (7) The sclerotic late stage of LS presents an atrophic epidermis, with comedo-like plugs and a cleft in the stratum corneum, dermal sclerosis, reduction and dilation of dermal vessels and the appendages disappear. (8) The autoantibodies against EMC1 may activate MMP9, which subsequently activates TGF-β. (9) TGF-β and BMP2 induce the synthesis of collagen I and III in fibroblasts. (10) Galectin-7 induces the synthesis of collagen I and III. (11) Along with inflammation, the vessel sclerosis contributes to the oxidative stress in LS, leading to downregulation of tumor suppressors genes and overexpression of p53 in the skin, factors related with the development of skin carcinomas. The precise sequence of events and their interactions are only incompletely understood. References: BMP2: bone morphogenetic protein 2; EMC1: extracellular matrix protein 1; LS: lichen sclerosus; MMP9: metalloproteinase 9; TGF-β: tumor growth factor beta. TNF-α: Tumor necrosis factor alpha.
Source: De Luca DA, Papara C, Vorobyev A, et al. "Lichen sclerosus: The 2023 update." *Front Med (Lausanne)*. 10 (Feb 16 2023) doi:10.3389/fmed.2023.1106318. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY).

- Morphology

Grossly, lesions are smooth, porcelain-white plaques. There is marked hyperkeratosis (excessive keratinization), thinning of the epidermis (epidermal atrophy), degeneration of the

basal layer, loss of rete pegs (finger-like extensions of the epidermis into the dermis), papillary dermal edema and sclerotic changes, hyalinization and homogenization of collagen in the upper dermis, and chronic inflammatory infiltrate in the dermis around blood vessels (lichenoid or band like) (Figure 3.3.2). Early LS may be histologically misdiagnosed as eczema or “nonspecific vulvitis.” [5]

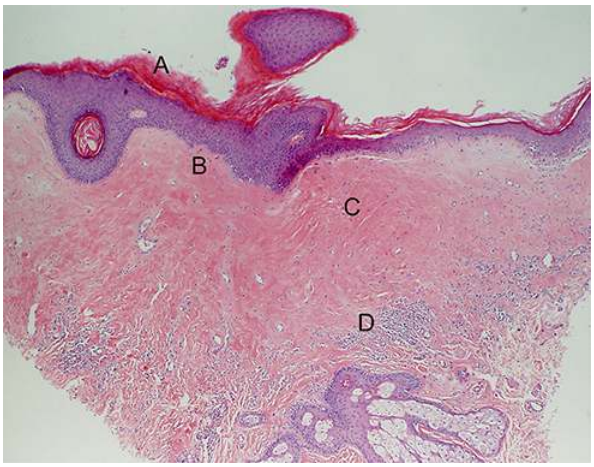


Figure 3.3.2. Classic histology of vulvar LS includes hyperkeratosis of the epidermis (A), epidermal atrophy with loss of rete ridges (B), homogenization of the collagen below the dermal-epidural junction (C), and lichenoid T-lymphocyte infiltrate near the basement membrane (D). This work is published and licensed by Dove Medical Press Limited.
Source: Krapf, Jill M., Leia Mitchell, Michelle A. Holton, and Andrew T. Goldstein. “Vulvar Lichen Sclerosus: Current Perspectives.” International Journal of Women’s Health, 2020. https://doi.org/10.2147/IJWH.S191200.This work is published and licensed by Dove Medical Press Limited. The full terms of this license are available at https://www.dovepress.com/terms.php and incorporate the Creative Commons Attribution – Non-Commercial (unported, v3.0) License http://creativecommons.org/licenses/by-nc/3.0/.

- Clinical Picture and Diagnosis

The diagnosis of LS is usually clinical. Careful history-taking and clinical examination are essential for diagnosis. The condition presents with patchy, thin, glistening, smooth, white areas affecting the labia and perineum with subsequent atrophy of the labia, and vulvar skin and constriction of the vaginal orifice leading to significant pain and sexual dysfunction. Diagnosis is mainly based on clinical features, and biopsy is reserved for cases if there is a doubt in diagnosis, a suspicion for preneoplastic and neoplastic change such as vulvar intraepithelial neoplasia and vulvar cancer, resistance to adequate treatment, or atypical extragenital presentations. Biopsy should be performed from the interface between normal and abnormal areas. A biopsy should also be performed on the hyperkeratotic areas and erosions that do not improve with treatment or sites with altered pigmentation. Assessment should also include workup for autoimmune diseases such as type 1 diabetes mellitus, thyroid disease, scleroderma, and rheumatoid arthritis, as there is an association between VLS and autoimmune diseases.[6]

- Differential Diagnosis

VLS is commonly misdiagnosed as Candida albicans vulvitis, thrush, or postmenopausal atrophy. The differentials also include lichen planus, localized scleroderma, leukoplakia, and vitiligo, and immunobullous disorders such as cicatricial pemphigoid, cutaneous patch of Lyme disease and vulvar intraepithelial neoplasia (VIN).[7]

- Treatment

Early and adequate treatment, ensuring restoration of normal skin color and texture, is essential for lowering the risk of malignant transformation. The first line of treatment is topical corticosteroids. Second-line treatment includes topical calcineurin inhibitors. Systemic immunosuppressives (cyclosporine and methotrexate) and oral acitretin can be used in resistant cases. Other therapies include fractional CO2 laser therapy, platelet-rich plasma, and high-intensity focused ultrasound. However, no evidence supports the role of these emerging therapies in preventing malignant transformation. Surgical techniques for restoring vulvar anatomy and treating clitoral phimosis, introital stenosis, and vulvar granuloma fissuratum lead to improved sexual dysfunction and satisfactory outcomes.[8]

3.3.1.2 Juvenile Vulvar Lichen Sclerosus (JVLS)

- Definition and Epidemiology

JVLS is a chronic inflammatory, autoimmune dermatosis of the anogenital region occurring in girls in childhood and adolescence. Affects approximately 1 in 900 girls aged 2–16. It is clinically similar to adult VLS, but with additional psychosocial and diagnostic challenges, including being underreported (misattribution to abuse or infection) and often persisting beyond puberty (complete remission is rare).[9]

- Etiology and Pathogenesis

Similar to adult VLS, with an autoimmune basis. Histological features (Th1-dominant inflammation with features of autoimmune attack) are consistent across age groups, suggesting immune-mediated mechanisms. Early-onset JVLS has not been associated with neoplastic progression but necessitates long-term surveillance. No reported cases of differentiated valvular intraepithelial neoplasia or valvular squamous cell carcinoma in juveniles, but adult sequelae are possible; hence, long-term surveillance is recommended.[10]

- Clinical Features and Morphology

Symptoms include pruritus, pain, constipation, and perineal involvement. Histologically, JVLS demonstrates general features of VLS, including epidermal thinning, loss of rete ridges, hyperkeratosis, dermal sclerosis, papillary edema, melanophages, and lymphocytic infiltrate. Some features (e.g., basal vacuolar change) are more prevalent in younger children.[11]

- Treatment and Prognosis

Management parallels adult protocols. Regular follow-up is critical due to the risk of architectural distortion and chronicity.[12]

3.3.1.3 Other Vulvar Inflammatory Dermatoses

- Valvular Dermatitis

Vulvar dermatitis typically presents with redness, skin breakdown, erosions, and thickened skin (lichenification), often accompanied by itching. It may arise from internal (endogenous) conditions such as atopic dermatitis, seborrheic dermatitis, or lichen simplex chronicus (LSC), or from external (exogenous) triggers like irritant and allergic contact dermatitis. These forms can coexist or overlap. Diagnosis is primarily clinical. Histopathology helps distinguish dermatitis from other conditions, as well as confirming atypical cases or those unresponsive to treatment. Key microscopic features include marked spongiosis with a lymphohistiocytic infiltrate. Acute dermatitis may show intraepidermal vesicles, while chronic cases often exhibit hyperkeratosis and epidermal thickening (acanthosis). A comprehensive clinical history is warranted for accurate diagnosis. Therapy aims to reduce the inflammatory process to culminate symptoms like itching and help restore the skin barrier. Treatment aims to control inflammation, stop the itch-scratch cycle, and restore the skin barrier. Avoiding known irritants and allergens is essential. First-line therapy includes topical corticosteroids (TCS) twice daily for a week and then gradually reduced to once weekly. The regular use of emollients supports skin barrier repair and relieves itching. Sedating antihistamines may be beneficial for nocturnal itch control. For cases unresponsive to corticosteroids, topical calcineurin inhibitors (such as tacrolimus 0.03% or 0.1% or pimecrolimus 0.1%) serve as second-line options. Addressing underlying factors such as stress, tight clothing, obesity, and excessive cleansing practices can improve outcomes. Patients should be advised against overzealous genital hygiene routines.[13]

- Atopic Dermatitis

Usually presents with a picture similar to eczema during childhood and is associated with a family history of atopy.[14]

- Lichen Simplex Chronicus (LCS)

Occurs either as a primary disease or secondary to other valvular conditions. Chronic scratching secondary to chronic pruritus aggravated by heat, moisture, menstruation, and tight clothing results in breaking skin barriers with subsequent susceptibility to infections. Mainly affects hair-bearing areas, leading to hair loss in chronic cases, and may affect the perineum and mucous surfaces. Lesions are thickened and lichenified. Histology reveals acanthosis, hyperkeratosis, hypergarnulosis, papillomatosis, inflammatory infiltrate, and lamellar dermal thickening. Neural fibrosis may be seen.[15]

- Contact Dermatitis

Triggered by direct injury caused by irritants or allergens (menstrual pads, excessive washing, and hair removal). Irritant contact dermatitis is more frequent than allergic forms and results from disruption of the skin barrier by substances like urine, feces, vaginal discharge, sweat, semen, topical medications, soaps, and depilatory creams. It commonly affects older women with urinary incontinence and those who practice excessive genital cleansing. Allergic contact dermatitis arises from sensitization to allergens such as fragrances, preservatives, local anesthetics, antiseptics, wet wipes, condoms, nail polish, and nickel. Clinical features of both types include erythema, scaling, vesiculation, oozing, and crusting. Irritant dermatitis typically presents with more pronounced rawness and weeping.Chronic inflammation may lead to secondary lichen simplex chronicus due to persistent scratching and skin thickening. Diagnosis is clinical or via patch testing.[16]

- Lichen Planus (LP)

LP is an immune-mediated condition affecting mucocutaneous surfaces. It may present as an isolated disease or part of a generalized syndrome (e.g., vulvovaginal-gingival). Clinical variants include the classical papulosquamous, hypertrophic, and erosive subtypes. **Classical papulosquamous VVLP** appears as papules or plaques with characteristic white, lacy striae over the vulva and periclitoral skin. This form is generally responsive to topical corticosteroids and may even resolve spontaneously. **Erosive LP** (most common) primarily affecting the introitus and labia minora, particularly in perimenopausal women. It may coexist with oral lichen planus. Presents as glazed erosions with white reticulated borders, leading to vaginal stenosis and scarring. Complications may include abnormal vaginal discharge, bleeding, tissue adhesions (synechiae), and progressive scarring, potentially resulting in significant anatomical changes. These changes include introital narrowing or agglutination, vaginal shortening, and clitoral hood phimosis, resulting in dyspareunia and distress. There is a risk of malignant transformation. Patients often report pain, burning, and irritation symptoms more prevalent than itching and experienced by up to 92% of those affected. Diagnosis is largely clinical and supported by dermoscopy (showing Wickham's striae). **Hypertrophic VVLP** is intensely pruritic and often resistant to standard therapies. [17]

- Histologically

Hypertrophic lichen planus is characterized by marked and irregular thickening of the epidermis (acanthosis). In contrast, erosive lichen planus is defined by areas of surface erosion accompanied by a dense inflammatory infiltrate, with hallmark features of lichen planus most prominently seen at the periphery of the lesion. For accurate diagnosis, it is essential that biopsies include the edge of the affected area.

The differential diagnosis for these forms includes other erosive or sclerotic vulvar conditions such as lichen sclerosus, drug-induced eruptions, cicatricial pemphigoid, vaginal intraepithelial neoplasia, and graft-versus-host disease.

The primary goals of treatment are to reduce symptoms and prevent disease progression. Ultrapotent topical corticosteroids are considered the first-line therapy and have shown clinical improvement in up to 71% of cases. Once the active disease is under control, the dosage is typically tapered. Systemic treatment options for severe VVLP include oral corticosteroids (e.g., prednisolone at 0.5 mg/kg/day) and intralesional corticosteroid injections (e.g., triamcinolone acetonide 10 mg/mL). For patients with vaginal stenosis, maintenance strategies such as tapering doses of hydrocortisone cream or suppositories and the regular use of corticosteroid-coated vaginal dilators help preserve vaginal patency. Weekly fluconazole (150 mg) is sometimes used to prevent secondary candidal infections. In advanced cases presenting with labial fusion, clitoral phimosis, or vaginal stenosis, surgical intervention may be necessary to relieve symptoms and restore urinary or sexual function.[18]

- Psoriasis

Lesions can be induced by mechanical friction in the vulvar region through the Koebner phenomenon. Common presentations include plaque-type and inverse psoriasis, though pustular forms may also occur. Classic plaque psoriasis typically affects hair-bearing areas such as the labia majora and mons pubis, appearing as well-defined, red plaques covered with silvery scales. In contrast, inverse psoriasis affects skin folds, presenting as smooth, shiny, red plaques with little to no scaling and occasional fissuring. Frequently reported symptoms include itching and burning in the majority of patients, pain, and dyspareunia. Psoriasis in other body areas or associated nail changes can aid diagnosis. Due to overlapping features, it can be mistaken for other dermatoses such as lichen simplex chronicus, lichenoid disorders, candidiasis, or contact dermatitis.

Histopathological examination usually shows characteristic features of psoriasis; concurrent dermatitis or secondary infections necessitate correlation with clinical findings. Dermoscopic examination often reveals red dot capillaries against an erythematous background.

Treatment is centered on the use of high-potency topical corticosteroids. Other options include coal tar preparations, topical calcipotriol, retinoids, and tacrolimus. In cases that are widespread, severe, or resistant to topical therapy, systemic medications such as methotrexate or dapsone may be considered.[19]

Footnotes

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3.3.2: Inflammatory Disorders of the Vagina

3.3.2.1 Etiology

Vaginitis encompasses both infectious and noninfectious causes. Infectious etiologies include bacterial vaginosis (BV), vulvovaginal candidiasis (VVC), and trichomoniasis, while noninfectious types include atrophic vaginitis, allergic reactions, foreign body, chemical irritation, desquamative inflammatory vaginitis, and lichen planus. Disruption in the normal vaginal microbiota, particularly the reduction of hydrogen peroxide-producing Lactobacillus, is a key factor, often replaced by anaerobic and facultative bacteria such as Gardnerella vaginalis in BV or overgrowth of Candida species in VVC. Contributing factors include hormonal changes, antibiotics, douching, irritants, and tight clothing.[20]

3.3.2.2 Epidemiology

Vaginitis is one of the most frequent gynecological complaints worldwide, with BV being the most common, followed by VVC and trichomoniasis. BV affects around 20–30% of reproductive-aged women in the U.S., and candidiasis affects over 30% of women in this age group. Trichomoniasis is the most common non-viral STI globally. Its incidence varies by age, hormonal status, sexual activity, hygiene, and healthcare access. Incidence is higher in low-resource settings and among individuals with risk factors such as poor hygiene, multiple sexual partners, and immunosuppression. Many women use over-the-counter remedies, which makes it difficult to evaluate the incidence of vaginitis accurately. [21]

3.3.2.3 Pathogenesis

The pathogenesis of vaginitis differs based on the underlying cause. In bacterial vaginosis (BV), the depletion of protective *Lactobacillus* species permits the overgrowth of anaerobic bacteria such as *Gardnerella vaginalis*. Vulvovaginal candidiasis (VVC) results from the transformation of *Candida* from a commensal organism to a pathogen, often triggered by hormonal fluctuations, antibiotic use, or immune suppression. Trichomoniasis arises from direct infection by the protozoan *Trichomonas vaginalis*. Noninfectious forms may be associated with estrogen deficiency, hypersensitivity reactions, or mechanical irritation. Oxidative stress has emerged as a central mechanism across multiple vaginitis types. Excessive production of reactive oxygen species (ROS), coupled with the depletion of antioxidants like catalase (CAT) and glutathione (GSH), contributes to DNA fragmentation and the oxidation of lipids and proteins. This oxidative imbalance activates pro-inflammatory cytokines (e.g., TNF-α, IL-1β, IL-6) and induces mitochondrial dysfunction, promoting epithelial apoptosis and tissue injury. The resulting inflammatory cascade, marked by leukocyte infiltration and cellular damage, is a key driver of vaginitis pathogenesis.[22]

3.3.2.4 Pathophysiology

The vaginal mucosa becomes inflamed, leading to discharge, itching, and pH alterations. The nature of the discharge helps distinguish between different types of vaginitis. For example, foul-smelling discharge occurs in bacterial vaginosis.[23]

3.3.2.5 Diagnosis

Accurate diagnosis requires clinical evaluation plus lab confirmation. Tools include pH testing, wet mount microscopy, KOH prep, Gram stain with Nugent score (for BV), culture (especially for *Candida* species), and molecular assays such as PCR and NAAT. Oxidative stress markers (e.g., MDA, H_2O_2), DNA fragmentation, and apoptosis biomarkers (caspase-3, Bax, cytochrome C) have been correlated with vaginitis severity, but these are primarily used in research settings and not routine clinical diagnostics. The nature of the vaginal discharge is a key diagnostic indicator.[24]

- Bacterial Vaginosis

Characterized by thin, homogeneous, foul-smelling, often fishy discharge. On microscopy, there are clue cells [vaginal epithelial cells (squamous epithelium) covered with bacteria (gram negative rods)] (Figure 3), and the vaginal pH is elevated (typically >4.5). This is linked to an overgrowth of anaerobic bacteria like *Gardnerella vaginalis* due to a reduction in *Lactobacillus*. Amsel's criteria (including pH, clue cells, discharge characteristics, and whiff test) are commonly used for diagnosis. The Nugent score, based on Gram stain, is another diagnostic method. [25]

- Vulvovaginal Candidiasis

Often presents with a thick, white, cottage cheese-like discharge. There is erythema of the vagina, and budding yeast or pseudohyphae are detected on KOH prep. Culture may be necessary to identify non-*albicans Candida* species.[26]

- Trichomoniasis

Can cause a frothy, yellow-green discharge. There is a strawberry cervix and motile flagellates seen on a wet mount.[27]

- Desquamative Inflammatory Vaginitis

Manifests as excessive purulent discharge (yellow-greenish), or mixed with blood.[28]

- Atrophic vaginitis

Clinical features of atrophic vaginitis typically include vaginal dryness, burning, discomfort during intercourse (dyspareunia), and inflammation. On examination, the vaginal mucosa may appear thin with a loss of rugal folds and, in some cases, purulent discharge. Microscopic evaluation of vaginal secretions often reveals numerous white blood cells, occasional basal and parabasal cells, a reduced presence of Lactobacillus species, and an increased number of gram-positive cocci and gram-negative rods. The vaginal pH is commonly elevated above 4.5.[29]

3.3.2.6 Differential Diagnosis

Vaginitis may mimic STIs (chlamydia, gonorrhea, herpes), UTIs, PID, dermatologic conditions (lichen sclerosus, eczema, psoriasis), vulvodynia, and allergic reactions. Foreign body-induced vaginitis, particularly in children, is another consideration.[30]

3.3.2.7 Treatment

- Bacterial Vaginosis
  - **Recommended:** Metronidazole 500 mg orally twice daily for 7 days or intravaginal metronidazole 0.75% gel once daily for 5 days or clindamycin 2% cream intravaginally at bedtime for 7 days.
  - **Alternative Regimens:** Tinidazole 2 g orally once daily for 2 days or tinidazole 1 g orally once daily for 5 days or clindamycin 300 mg orally twice daily for 7 days.
  - **Recurrent BV:** May need extended or alternative regimens. Consider suppressive therapy with twice-weekly metronidazole gel. CDC recommends using the same drugs used to treat the initial infection.[31]

> **Note**
>
> Treatment of male partners is not generally recommended.

- Vulvovaginal Candidiasis
  - Uncomplicated VVC:Fluconazole 150 mg single dose orally or topical azoles (e.g., clotrimazole, miconazole) for 1-7 days.
  - Complicated VVC (recurrent, severe, non-albicans): Fluconazole 150 mg orally every 72 hours for three doses, followed by maintenance therapy (e.g., fluconazole 150 mg weekly for six months). Topical treatments may also be used for longer durations.[32]

> **Note**
>
> Identify and manage predisposing factors such as uncontrolled diabetes or antibiotic use.

- Trichomoniasis
  - Recommended: Metronidazole 2 g orally in a single dose or tinidazole 2 g orally in a single dose.[33]

> **Note**
>
> Treat partners to prevent reinfection. HIV-positive patients may require a 7-day course of metronidazole.

- Atrophic Vaginitis
  - **First-line:** Vaginal estrogen cream (e.g., conjugated estrogens, estradiol).
  - **Non-hormonal options**: Vaginal moisturizers and lubricants for mild symptoms.
  - **Alternative:** Oral ospemifene, an estrogen agonist/antagonist.[34]

> **Note**
>
> Long-term therapy may be necessary.

While promising, antioxidant strategies require further validation through large-scale clinical studies. Vitamin C vaginal tablets have been shown to restore *Lactobacillus* dominance, reduce vaginal pH, and alleviate symptoms.[35]

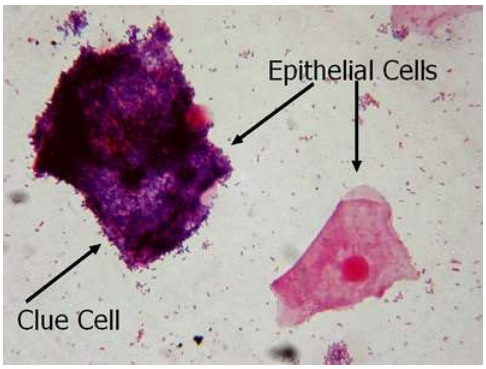


Figure 3.3.3 Two epithelial cells are seen however the one on the left is 'coated' with gram variable bacilli (*Gardnerella vaginalis*) making the cell appear purplish. On lower power scanning, these are usually seen with some frequency in a patient experiencing bacterial vaginosis.
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Image Acknowledgements

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3.3.3: Neoplastic Disroders of the Vulva and Vagina

3.3.3.1 Condylomas

- Etiology and Risk Factors

These warty lesions secondary to sexually transmitted disease comprise two main forms: Condylomata Lata (flat lesions associated with secondary syphilis and less common) and Condylomata Acuminata (CA) (papillary, elevated or flat lesions caused by low-risk HPV strains 6 and 11 and more common). These two HPV types are responsible for over 90% of CA. Several risk factors are also involved, including smoking, hormonal contraceptives, multiple sexual partners, and early coital age.[36]

- Pathogenesis

The initial site of infection is thought to be basal cells of the immature squamous epithelium that HPV reaches through defects in the epithelium. Once HPV enters the cells, two distinct biological sequences are possible. The first form is a “nonproductive or latent infection” in which HPV DNA persists in the basal cells without virus replication. Latent infections do not show morphologic alterations and can only be identified using molecular methods. The second form of HPV infection is a “productive infection.” Viral DNA replication in the intermediate and superficial cell layers of the squamous epithelium occurs independently of host chromosomal DNA synthesis. This allows large amounts of intact virions to be formed, leading to typical morphological aspects such as “koilocytic changes.”[37]

- Pathologic Features

Grossly, the lesions are exophytic and may range from discrete papillary outgrowths to extensive and coalescent “cauliflower-like” masses. Microscopically (Figure 3.3.4), CA shows a striking papillary architecture. Papillae of different sizes and shapes are lined by acanthotic squamous epithelium (i.e., increasing the number of specialized squamous epithelial cells resulting in a thick epidermis with elongated rete pegs) and have a fibrovascular stroma, often containing scattered chronic inflammatory cells. Hyperkeratosis, parakeratosis (incomplete maturation of epidermal keratinocytes, resulting in abnormal retention of nuclei in the stratum corneum), hypergranulosis, and basal cell hyperplasia are seen. Koilocytic changes (rigid perinuclear halos, binucleated nuclei, and slightly enlarged nuclei with irregular contours and coarse chromatin) are sometimes focal in the most superficial layers of the squamous epidermis. The proliferation index by immunostaining (Ki67/MIB-1) in the upper third of the epithelium is considered as a confirmatory test to the diagnosis of CA, especially in lesions without evident koilocytic changes. The presence of Ki67/MIB-1 immunostaining has been further correlated with the detection of HPV DNA by polymerase chain reaction (PCR).[38]

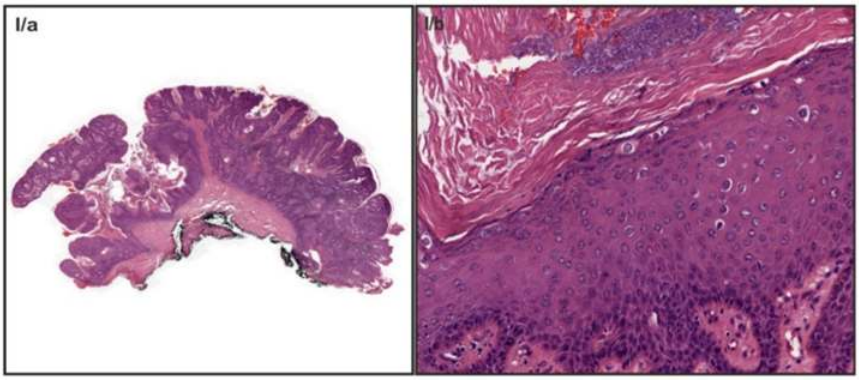


Figure 3.3.4 Histological characteristics of external genital warts. Note, the cauliflower-like architecture at the low power (I/a), Acanthosis, and parakeratosis with the presence of koilocytes in mid power image (I/b).
Image Source: Rideg, Orsolya, Angéla Oszter, Evelin Makk, Endre Kálmán, Kornélia Farkas, Tamás Tornóczky, and Krisztina Kovács. "Wide Spectrum Analysis of Human Papillomavirus Genotypes in External Anogenital Warts." Vaccines 9, no. 6 (2021). https://doi.org/10.3390/vaccines9060604. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (https://creativecommons.org/licenses/by/4.0/).

- Clinical Features

CA is prevalent in the early sexually active years, with two-thirds of the respective sexual partners complaining of warts. The median time between infection and development of lesions is about 5-6 months among women. Up to 20% of people with genital warts will present other STDs. Patients who develop CA usually present with painless bumps and, less frequently, with pruritus, discharge, or bleeding. Lesions are commonly multiple (multicentric) and multifocal, also affecting the perianal, vaginal, and cervical regions, but oral and laryngeal regions may also be involved. Latent illness may become active, particularly with pregnancy and immunosuppression. Lesions may regress spontaneously, remain stable, or progress in size and/or number.

CA are soft, raised masses with smooth, verrucous, or lobulated aspects that may appear pearly, filiform, fungating, or plaque-like eruptions. The surface commonly shows finger-like projections, generally non-pigmented. They mainly occur in the moist areas of the labia minora and vaginal opening, but all genital regions may be affected (fourchette, labia minora/majora, pubis, clitoris, urethral meatus, perineum, perianal region, anal canal, introitus, vagina, and ectocervix). Therefore, colposcopic examination, using acetic acid 2–5%, is crucial to detect potentially multiple involved sites. CA are perceived as disfiguring; they impact sexual lifestyle, causing anxiety, guilt, and loss of self-esteem and creating concerns about cancer risk.[39]

- Treatment

The most common treatments are painful and nonspecific, addressing the clinically evident lesions rather than the viral cause. Various modalities include office-based treatment (cryotherapy, electrocautery, laser, and/or surgery) or home-based treatment (chemotoxic agents or immunomodulatory therapy). First-episode patients should be STD-screened.

Management should include partner notification. Surgical treatments have the highest primary clearance rates, with initial cure rates up to 60–90%. They include electrosurgery, curettage, scissors excision, and laser therapy. Primary Prevention by Prophylactic Vaccine (Quadrivalent Gardasil) is available for the prevention of HPV-associated dysplasia and neoplasia, including cervical cancer, precancerous genital lesions, and genital warts associated with HPV types 6, 11, 16, and 18. There is now accumulating evidence that population-based quadrivalent HPV vaccination can result in dramatic declines in genital warts incidence and a reduction in HPV6/11 burden.[40]

3.3.3.2 Extramammary Paget Disease

- Definition and Etiology

Extramammary Paget's Disease is a rare intraepithelial adenocarcinoma that most commonly arises in apocrine gland-bearing areas, particularly the vulva, scrotum, perianal skin, and penis. The vulva is the most frequently affected site, accounting for approximately 65% of cases.[41]

- Epidemiology

It typically affects postmenopausal Caucasian women, with peak incidence occurring in the 6th to 7th decades of life. While it constitutes only about 1% of vulvar cancers, its clinical presentation can be deceptive, often leading to a delayed diagnosis. The disease may appear as either solitary or multifocal lesions.[42]

- Pathogenesis and Pathophysiology

The pathogenesis involves abnormal proliferation of glandular epithelial cells within the squamous epithelium. In primary extramammary Paget's disease, malignant Paget cells originate within the epidermis and may invade the dermis and subcutaneous tissue. The origin is thought to be from pluripotent basal epithelial cells or skin appendages. Secondary disease involves epidermal spread or direct invasion from adjacent malignancies, including rectal or urothelial adenocarcinoma. Some molecular modifications have been reported in primary disease may play a role in pathogenesis; these include, HER2 oncogene amplification, mutations in genes encoding the PIK3/AKT cascade, and amplification at chromosomes Xcent-q21 and 19, as well as loss at 10q24-qter.[43]

- Morphological Features

Clinically, vulvar Paget's disease may manifest as red, white, or gray eczematous plaques with crusting, ulceration, or mild elevation. Lesions are usually irregular, sharply demarcated, and frequently extend beyond visible margins, with common involvement of the labia majora and potential spread to the labia minora, clitoris, urethral meatus, inguinal folds, and perineum. Pruritus is the most frequently reported symptom. It can mimic benign dermatoses such as eczema or psoriasis, leading to delays in diagnosis.

Histologically (Figure 3.3.5), it is composed of large Paget cells with abundant pale cytoplasm and prominent nuclei, which can be arranged singly or in clusters within the epidermis. In

invasive disease, dermal invasion is evident. Immunohistochemical staining is essential: Paget cells are typically positive for CK7, EMA, CEA, PAS, and mucicarmine. Negative staining for melanocytic markers (S100, HMB-45, Melan-A) helps differentiate Paget's disease from pagetoid melanoma. Markers such as CK20 and CDX2 may suggest secondary Paget's disease. [44]

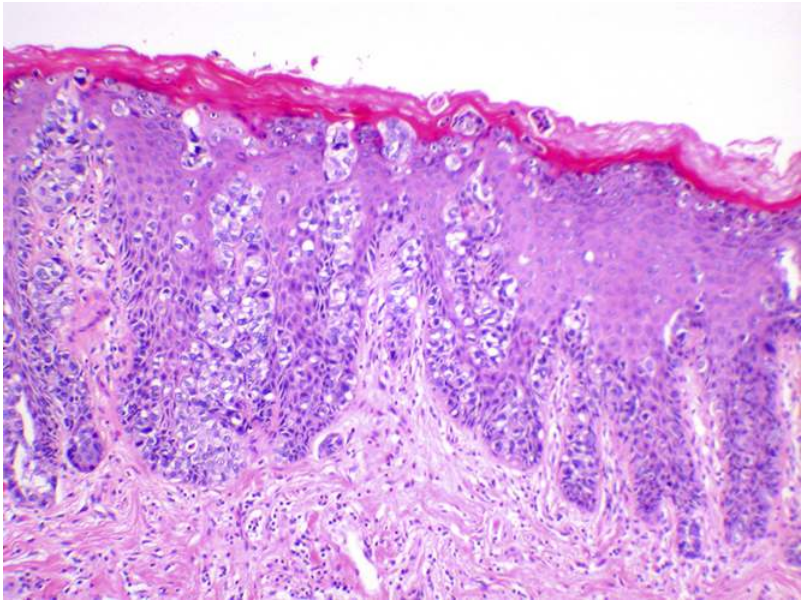


Figure 3.3.5. Vulvar Paget disease. The large cells of Paget's disease are seen predominantly in the basal epithelium, but percolate up the epithelium in what is known as 'Pagetoid spread'. Negative markers of melanoma, and positive markers of Paget, such as periodic acid Schiff stain with diastase (PAS-D), and breast markers such as Gata-3, are helpful in making this diagnosis (hematoxylin and eosin, x 10 magnification).

Image Source: Preti, Mario, Elmar Joura, Pedro Vieira-Baptista, Marc Van Beurden, Federica Bevilacqua, Maaike C.G. Bleeker, Jacob Bornstein, et al. "The European Society of Gynaecological Oncology (ESGO), the International Society for the Study of Vulvovaginal Disease (ISSVD), the European College for the Study of Vulval Disease (ECSVD) and the European Federation for Colposcopy (EFC) Consensus Statements on Pre-Invasive Vulvar Lesions." International Journal of Gynecological Cancer, 2022. https://doi.org/10.1136/ijgc-2021-003262. Copyright © 2022 The Author(s). Published by Wolters Kluwer Health, Inc. on behalf of the ASCCP. This is an open access article distributed under the Creative Commons Attribution License 4.0 (CCBY), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

- Diagnosis

Diagnosis requires histopathological confirmation through biopsy. Vulvar mapping with multiple biopsies may be necessary to assess lesion extent. Immunohistochemistry is crucial to confirm the diagnosis and rule out mimics such as melanoma or high-grade squamous intraepithelial lesions. Imaging, particularly MRI, can help assess pelvic or nodal involvement.[45][Ning et al; Preti et al]

- Differential Diagnosis

The differential diagnosis includes lichen sclerosus, candidiasis, psoriasis, dermatophytosis, seborrheic dermatitis, contact dermatitis, squamous intraepithelial lesions, pemphigus vegetans, and pagetoid melanoma. Histologic analysis with immunostaining is key for definitive distinction.[46]

- Treatment

Wide local excision remains the primary treatment modality, though recurrence rates range from 15% to 70%. Mohs micrographic surgery offers better margin control and reduced recurrence rates. Topical therapies such as 5% imiquimod, photodynamic therapy, and radiotherapy have been used for patients unfit for surgery or for recurrent disease. All patients require comprehensive evaluation to exclude synchronous malignancies, including pelvic exam, cervical cytology, transvaginal ultrasound, colonoscopy, cystoscopy, mammography, and imaging of the abdomen and pelvis.[47]

3.3.3.3 Carcinoma of the Vulva: Squamous Cell Carcinoma

- Definition and Classification

Vulvar squamous cell carcinoma (SCC) represents the most prevalent form of vulvar malignancy, accounting for about 90% of cases. The 2020 WHO classification distinguishes two main etiopathogenetic pathways: HPV-associated SCC is usually precede by precursor lesions such as high-grade squamous intraepithelial lesion (HSIL, formerly known as usual-type VIN). While HPV-independent SCC may be preceded by differentiated VIN (dVIN).[48]

- Epidemiology

Vulvar SCC is a rare cancer, comprising roughly 5% of all gynecologic malignancies, with increasing incidence among both older and younger women depending on subtype. HPV-associated SCC is more common in younger women (average age is 60 years), whereas HPV-independent SCC typically affects older women (average age is 75 years)cand often arises in a background of persistent lichen sclerosus or chronic inflammatory dermatoses.[49]

- Etiology and Pathogenesis

HPV-associated SCC is linked primarily to high-risk HPV types 16 (in more than 70% of cases), 33, and 45. Other risk factors include smoking, immunosuppression, HIV infection, history of cervical HSIL, and vulvar, perianal, and anal lesions. It arises from HSIL and demonstrates strong diffuse p16 expression and wild-type p53 staining.

HPV-independent SCC is not associated with HPV but is often linked to chronic vulvar dermatoses and differentiated vulvar intraepithelial neoplasia (dVIN). These tumors usually show TP53 mutations with p53 overexpression and absent or focal p16 staining. This subtype tends to behave more aggressively, with higher recurrence and progression rates.[50]

- Morphology and Histopathology

Early vulvar SCC and VIN frequently appear as white, plaque-like lesions (leukoplakia). Approximately 25% of these lesions may exhibit pigmentation due to melanin content. As the disease advances, these lesions can evolve into either exophytic masses or ulcerative tumors. HPV-associated SCCs typically present with basaloid or warty architecture and are often multifocal. Histologically, these tumors present as poorly differentiated SCC. In contrast, HPV-independent SCCs are usually unifocal and keratinizing. These tumors tend to be well-differentiated and have a more aggressive clinical course. dVIN-associated lesions often exhibit basal atypia, parakeratosis, and irregular rete ridges. Immunohistochemistry is crucial for distinguishing these subtypes, using markers like p16 and p53.[51]

- Imaging and Staging

MRI plays a critical role in staging, helping define lesion margins, assess tumor size (>2 cm) and depth of stromal invasion (>1 mm), and evaluate involvement of adjacent structures such as the urethra and vagina. Lesions appear as soft tissue masses with intermediate signal intensity on T2WI and restricted diffusion on DWI. Contrast enhancement may be homogeneous or heterogeneous. Lymph node status is a key prognostic indicator, and nodal enlargement (>5 mm) is used to classify advanced FIGO Stage III disease.

MRI is also useful in delineating lymph node involvement in parailiac, inguinal, and paraaortic regions using both axial and coronal planes.[52]

- Vulvar Carcinoma In Situ

Lesions include HSIL (HPV-associated) and dVIN (HPV-independent). HSIL is typically multifocal, arising in the introitus and labia minora, and shows full-thickness atypia with p16 overexpression. dVIN is usually unifocal, affecting older women, and shows basal atypia and TP53 mutation. dVIN is more likely to progress to invasive SCC (up to 50%) compared to HSIL (~10%).[53]

- Management and Treatment
  - **HSLI:** May be treated with excision, laser ablation, or topical agents (e.g., imiquimod). Biopsy is necessary to exclude invasion.
  - **dVIN:** Requires surgical excision due to high malignant potential. Management of coexisting dermatoses with topical corticosteroids is also essential.
  - **Invasive SCC**: Wide local excision or radical vulvectomy with lymph node assessment (including sentinel lymph node biopsy) is standard. MRI is valuable for surgical planning.[54]

- Surveillance and Prognosis

Prognosis is influenced by stage, nodal involvement, and subtype. HPV-associated SCCs tend to have better outcomes, while HPV-independent types carry higher risk of recurrence (12–

37%) and progression. Lifelong surveillance is recommended, particularly for dVIN-associated cases.[55]

- Carcinoma of the Vagina

Primary carcinoma of the vagina is rare and typically arises from a precursor lesion known as vaginal intraepithelial neoplasia (VaIN), which is similar to cervical intraepithelial neoplasia. It is mainly a squamous cell carcinoma linked to infection with high-risk human papillomavirus. A prior history of cervical or vulvar cancer is a significant risk factor. These tumors most frequently develop in the upper third of the vagina, especially along the posterior wall near the ectocervix, and commonly spread to regional iliac lymph nodes.[56]

Footnotes

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Image Acknowledgements

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3.4: Ovarian Pathologies

Chapter Author: Samar Hegazy, MD, PhD, MEPH

In this section:

- 3.4.1 Non-Neoplastic Lesions
- 3.4.2 Ovarian Tumors

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3.4.1: Non-Neoplastic Lesions

3.4.1.1 Follicular Cysts

Follicular cysts arise from unruptured Graafian follicles, often due to hormonal disturbances. They are typically asymptomatic, though they may occasionally lead to hormonal imbalances such as hyperestrogenism, resulting in conditions like endometrial hyperplasia.[1]

3.4.1.2 Corpus Luteum Cysts

These cysts develop from hemorrhage within a persistent corpus luteum. Clinical presentations can include menstrual irregularities, pelvic pain, and rarely, significant intraperitoneal bleeding requiring surgical intervention.[2]

3.4.1.3 Theca-Lutein Cysts

Theca-lutein cysts occur due to excessive stimulation by gonadotropins. They are usually bilateral and lined by luteinized theca cells. They are associated with gestational trophoblastic diseases such as hydatidiform moles or choriocarcinoma. They often resolve following treatment of the underlying condition.[3]

3.4.1.4 Chocolate Cysts (Endometriotic Cysts)

These cysts contain altered blood due to ovarian endometriosis. They commonly cause chronic pelvic pain, dysmenorrhea, and infertility, significantly impacting the quality of life.[4]

3.4.1.5 Polycystic Ovary Syndrome (Stein-Leventhal Syndrome)

Polycystic ovary syndrome (PCOS) is a prevalent endocrine disorder among reproductive-age women, characterized by amenorrhea, hirsutism, infertility, and obesity. The underlying pathophysiology involves insulin resistance, elevated luteinizing hormone (LH), and excess androgen production. There is marked thickening of the ovarian capsule and multiple small follicular cysts containing a granulosa cell layer and a luteinized theca interna associated with cortical stromal fibrosis with islands of focal luteinization.[5]

For more information

WHO guideline for screening and treatment of cervical pre-cancer lesions for cervical cancer prevention: Use of dual-stain cytology to triage women after a positive test for human papillomavirus (HPV) [Internet]. 2nd edition. Geneva: World Health Organization; 2024. Available from: https://www.ncbi.nlm.nih.gov/books/NBK604763/

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4. Mobeen & Aostil, 2025.

5. Mobeen & Aostil, 2025.

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3.4.2: Ovarian Tumors (WHO Classification)

3.4.2.1 Overview

Ovarian cancer is one of the gynecological cancers detected all over the world and is the fifth most common cause of death in the female population. It is associated with high mortality rates as it is usually diagnosed in advanced stages. The current screening tests are not very useful in detecting this cancer. The keys to the detection of this cancer are vaginal ultrasound and a biomarker known as CA-125; however, they couldn't prevent the high rates of deaths caused by this cancer. Histologic and molecular subtyping are critical for management of ovarian cancer. The preferred treatment for this malignancy is chemotherapy, with cisplatin as the drug of choice. Antiangiogenic bevacizumab and poly ADP-ribose polymerase inhibitors resulted in a better cure. Recurrences and relapses are not uncommon.[6]

Ovarian tumors encompass a diverse group of neoplasms classified by their cell of origin. The WHO 2020 classification divides these into four broad categories: surface epithelial tumors, germ cell tumors, sex cord–stromal tumors, and metastatic tumors. This section elaborates on the major subtypes, focusing on their definition, etiology, pathogenesis, morphology, clinical presentation, diagnosis, and treatment.[7]

3.4.2.2 Surface Epithelial Tumors

- Etiology & Epidemiology

Surface epithelial tumors originate from the ovarian surface epithelium or inclusion cysts and represent approximately 70% of all ovarian neoplasms. Risk factors include age, ovulatory cycles, endometriosis, hormone replacement therapy, and inherited mutations (e.g., BRCA1/2). These tumors are more common in peri- and postmenopausal women.[8]

- Pathogenesis

These tumors arise from mesothelial cells that undergo müllerian-type differentiation. The pathogenesis may be influenced by repeated ovulatory injury and inflammation. Malignant transformation involves specific mutations: TP53 in high-grade serous carcinoma, KRAS/BRAF in low-grade serous and mucinous tumors, and ARID1A/PIK3CA in endometrioid and clear cell carcinomas.

- Molecular Profile

Characteristic molecular alterations include mutations in TP53 and BRCA genes. Please refer to the cited publications for more details on specific molecular profiles.

- Pathophysiology

Malignant transformation leads to local invasion and potential peritoneal spread. High-grade tumors often present at an advanced stage with ascites and omental metastases.

- Clinical Picture & Diagnosis

Patients may present with abdominal distension, pelvic pain, ascites, and/or mass effect. Imaging (ultrasound, CT, MRI), tumor markers (CA-125, HE4), and histopathology are used for diagnosis.

- Treatment

Surgery is the mainstay. Adjuvant chemotherapy is used in malignant tumors, particularly high-grade serous carcinoma. Targeted therapies such as PARP inhibitors are also used.[9]

- Subtypes
  - Serous Tumors

    Serous tumors are epithelial neoplasms with serous (fallopian tube-like) differentiation. They are classified into two distinct subtypes: High-grade serous carcinoma (HGSC) and low-grade serous carcinoma (LGSC) based on morphology, molecular profile and prognosis. HGSC is the most common and deadliest subtype; low-grade serous carcinoma (LGSC) is less frequent. HGSC arises from the distal fimbrial end of the fallopian tube from a precursor lesion known as serous tubal intraepithelial carcinoma (STIC). They are associated with TP53, BRCA1/2 mutations. LGSC arise within the ovary from serous benign and borderline tumors and involves KRAS and BRAF mutations.[10]

    Serous tumors often present as bilateral cystic masses with papillary projections. HGSC shows variable features, including papillary, micropapillary, and solid growth patterns. Microscopically, two histological types have been described: classical and SET (Solid, pseudoEndometroid and Transitional) (Figure 3.4.1). In classical HGSC, the tumor cells typically exhibit marked nuclear pleomorphism with prominent nucleoli, high mitotic activity (typically > 12 mitoses per 10 high-power fields), including atypical mitoses. SET variant is characterized by solid sheets of cells simulating endometrioid and/or transitional cell carcinomas.[11]

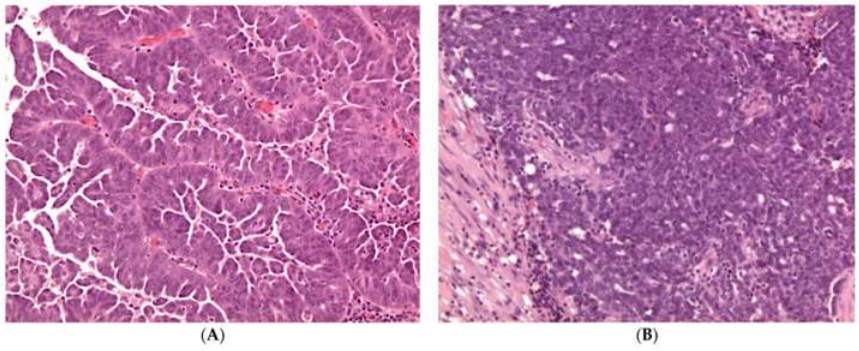


Figure 3.4.1. (A) Histologic appearance of classic high-grade serous carcinoma (HGSC) (hematoxylin and eosin, H&E, ×100); **(B)** Solid, pseudoendometrioid, transitional cell carcinoma-like (SET) variant of HGSC (hematoxylin and eosin, H&E, ×100).

Image Source: De Leo, Antonio, Donatella Santini, Claudio Ceccarelli, Giacomo Santandrea, Andrea Palicelli, Giorgia Acquaviva, Federico Chiarucci, Francesca Rosini, Gloria Ravegnini, Annalisa Pession, and et al. 2021. "What Is New on Ovarian Carcinoma: Integrated Morphologic and Molecular Analysis Following the New 2020 World Health Organization Classification of Female Genital Tumors" *Diagnostics* 11, no. 4: 697 (2021). This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). Available from: https://doi.org/10.3390/diagnostics11040697.

These tumors often show geographical necrosis and are associated with a high count of tumor-infiltrating lymphocytes. Microscopically, LGSC is composed of a homogeneous population of small cells with scant cytoplasm arranged in small papillae (Figure 2). In contrast to HGSC, tumor cells show mild to moderate nuclear atypia without pleomorphism (<3_ variation in size) and may have prominent nucleoli. Mitoses are usually less than 12 per 10 high-power fields. Psammoma bodies are frequent. LGSC is differentiated from serious borderline tumors by the presence of stromal invasion greater than microinvasion (invasive foci measuring > 5 mm or 10 mm2) (Figure 3.4.2).[12]

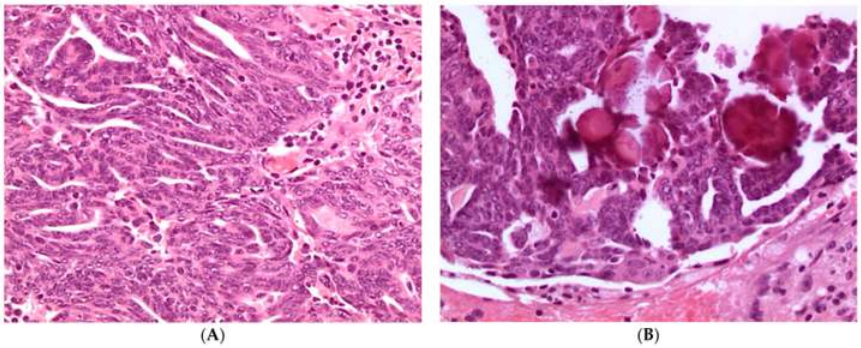


Figure 3.4.2. **(A)** Histologic appearance of low-grade serous carcinoma showing tumor cells with uniform nuclei and inconspicuous mitotic activity (hematoxylin and eosin, H&E, ×100); **(B)** Psammoma bodies are frequent in low-grade serous carcinoma (hematoxylin and eosin, H&E, ×100).

Image Source: De Leo, Antonio, Donatella Santini, Claudio Ceccarelli, Giacomo Santandrea, Andrea Palicelli, Giorgia Acquaviva, Federico Chiarucci, Francesca Rosini, Gloria Ravegnini, Annalisa Pession, and et al. 2021. "What Is New on Ovarian Carcinoma: Integrated Morphologic and Molecular Analysis Following the New 2020 World Health Organization Classification of Female Genital Tumors" Diagnostics 11, no. 4: 697 (2021). This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). Available from: https://doi.org/10.3390/diagnostics11040697.

- Mucinous Tumors

In recent years, there has been a significant shift in how ovarian mucinous tumors are classified. Many tumors previously diagnosed as primary ovarian mucinous carcinomas (MCs) are now recognized as secondary (metastatic) lesions, most commonly originating from the appendix, gastrointestinal tract, pancreas, or biliary system, especially when associated with pseudomyxoma peritonei. True primary mucinous tumors of the ovary are relatively uncommon. They account for 10–15% of all primary ovarian tumors, and the

majority—over 80%—are benign or borderline. Mucinous carcinoma, the malignant form, comprises only 3–4% of ovarian carcinomas. The exact origin of primary MCs remains unclear. While a subset may arise from ovarian teratomas, most lack any identifiable teratomatous component.[13]

Clinically and pathologically, several features help distinguish primary ovarian MCs from metastatic mucinous tumors:

- Primary MCs are typically large (>13 cm), unilateral, and lack surface involvement.
- Metastatic lesions are usually bilateral, smaller, and often associated with pseudomyxoma peritonei.

Grossly, MCs appear as large, cystic masses (8–40 cm) often with multilocular or unilocular architecture, filled with mucinous fluid. They may contain papillary or solid areas, which vary in texture from mucoid to firm.

Microscopically, MCs show a mixture of benign, borderline, and malignant components, necessitating extensive sampling. Most display gastrointestinal-type differentiation, and less commonly, endocervical-type features. Two distinct growth patterns are recognized (Figure 3.4.3):

1. Expansile: Closely packed malignant glands with little stromal invasion—associated with better prognosis.
2. Infiltrative: Evident stromal invasion, often with desmoplastic response—linked to worse outcomes.[14]

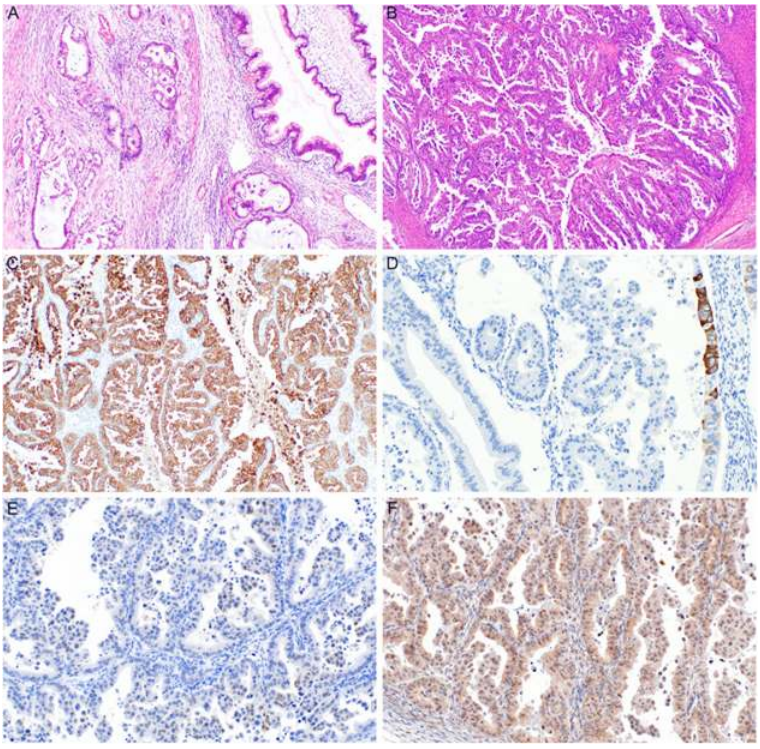


Figure 3.4.3. Mucinous carcinoma of the ovary (MC). Infiltrative type of invasion with glandular and cribriform areas **(a)** (H&E, 100x). Expansile type of invasion with areas of complex glandular proliferation **(b)** (H&E, 40x). Diffuse expression of cytokeratin 7 **(c)** (100x) and focal expression of cytokeratin 20 **(d)** (200x). Focal and weak expression of PAX8 **(e)** (200x). Tumor cells showing retained expression of DPC4 **(f)** (200x).

Image Source: Dundr, Pavel, Naveena Singh, Barbora Nožičková, Kristýna Němejcová, Michaela Bártů, and Ivana Stružinská. "Primary Mucinous Ovarian Tumors vs. Ovarian Metastases from Gastrointestinal Tract, Pancreas and Biliary Tree: A Review of Current Problematics." Diagnostic Pathology, 16, No. 20 (2021). This open access article is distributed under the terms of the Creative Commons Attribution License CC-BY 4.0. Available from: https://rdcu.be/emRz9.

- Endometrioid tumors

Ovarian endometrioid carcinoma (EC) is the second most common histologic subtype of ovarian carcinoma, accounting for 10–15% of cases. Its incidence has declined in recent years due to reclassification of many former "high-grade endometrioid carcinomas" as SET variants of high-grade serous carcinoma (HGSC). The median age at diagnosis is approximately 51 years, and most patients are diagnosed at an early stage (FIGO I or II). ECs are bilateral in 20% of cases and are synchronously associated with endometrial carcinoma in 15–20% of cases. A strong link exists between EC and endometriosis, with atypical endometriosis identified as a precursor lesion in up to 40% of cases. Molecular studies have shown shared mutations between the carcinoma and adjacent atypical endometriosis, supporting this precursor relationship.[15]

Grossly, ECs often appear as solid-cystic masses with soft tissue components and areas of hemorrhage. A residual endometriotic cyst may be found at the periphery. Microscopically, they resemble endometrial adenocarcinoma (Figure 3.4.4).

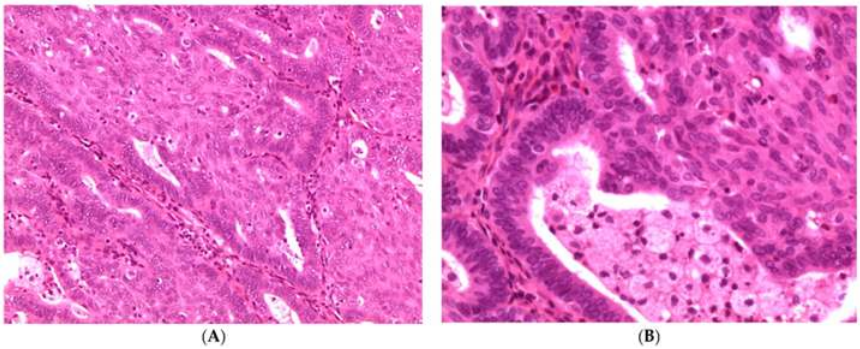


Figure 3.4.4. (A) and (B) Histologic appearance (hematoxylin and eosin, H&E) of low-grade endometrioid carcinoma with squamous differentiation (×100 and ×200, respectively).

Image Source: De Leo, Antonio, Donatella Santini, Claudio Ceccarelli, Giacomo Santandrea, Andrea Palicelli, Giorgia Acquaviva, Federico Chiarucci, Francesca Rosini, Gloria Ravegnini, Annalisa Pession, and et al. 2021. "What Is New on Ovarian Carcinoma: Integrated Morphologic and Molecular Analysis Following the New 2020 World Health Organization Classification of Female Genital Tumors" Diagnostics 11, no. 4: 697 (2021). This is an open-access article

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Low-grade ECs typically display glandular, cribriform, or villoglandular patterns, with tall columnar epithelial cells, scant eosinophilic cytoplasm, and squamous differentiation, a characteristic and helpful diagnostic feature. High-grade ECs show solid architecture, marked nuclear atypia, and high mitotic activity, requiring careful distinction from SET-type HGSC.

Three histologic clues—termed "confirmatory endometrioid features"—support the diagnosis in ambiguous cases:

1. Metaplastic changes, including squamous, mucinous, hobnail, or eosinophilic differentiation.
2. Association with endometriosis, endometrioid adenofibroma, or endometrioid borderline tumors.
3. Presence of synchronous uterine endometrioid carcinoma.

Grading follows the same system used for uterine EC:

- Grade 1: <5% solid growth
- Grade 2: 5–50% solid growth
- Grade 3: >50% solid growth

(Note: squamous areas are excluded from grading)

Two invasion patterns are recognized:

1. Expansile invasion: confluent glandular growth with minimal stromal response—associated with low-stage disease and favorable prognosis.
2. Destructive invasion: irregular infiltration into stroma with a desmoplastic reaction—linked to a more aggressive course.

Immunohistochemistry: Ovarian ECs commonly express

- PAX8
- Vimentin
- Estrogen (ER) and Progesterone (PR) receptors
- Nuclear β-catenin (in some cases)

They are generally negative or only focally positive for WT1, p53, and p16, unlike HGSC. High-grade ECs, however, may show aberrant p53 staining patterns, reflecting underlying mutations.They harbor molecular alterations such as PTEN, POLE mutations, microsatellite instability (MSI), and ARID1A mutations.[16]

- Clear Cell Carcinoma

Ovarian clear cell carcinoma (CCC) accounts for approximately 10% of ovarian carcinomas and is notable for presenting at early stages (FIGO I–II) in about 25% of such

cases. These tumors are typically unilateral and have a strong association with endometriosis, similar to the endometrioid subtype. Some CCCs also contain adenofibromatous or borderline components, which have been linked to a better prognosis—with studies showing significantly improved 5-year survival in tumors with adenofibromatous areas (≈79%) compared to those without (≈49%).

While CCC is generally considered a high-grade malignancy, early-stage disease—especially FIGO stage I, including cases with positive peritoneal cytology or capsular involvement (stage IC)—often has a favorable outcome, with 5-year survival rates between 80–90%. However, advanced-stage CCC carries a poor prognosis, often worse than that of high-grade serous carcinoma (HGSC), largely due to its limited response to platinum-based chemotherapy. Notably, mismatch repair (MMR) deficiency or association with Lynch syndrome may indicate better long-term survival, possibly due to increased tumor immunogenicity and potential for response to immunotherapy.[17]

Grossly, CCCs usually appear as large, unilateral, mixed solid and cystic masses, often with foci of endometriosis and superficial adhesions. Histologically (Figure 3.4.5), CCCs are characterized by a variety of architectural patterns, most commonly:

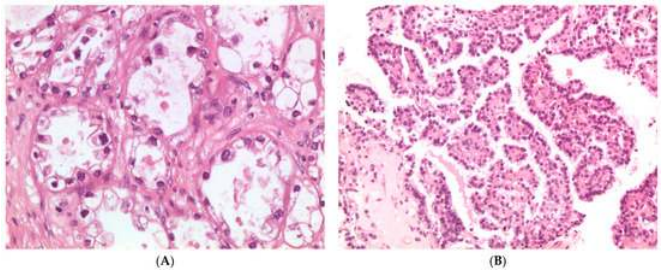
- Papillary
- Tubulocystic
- 

Figure 3.4.5. (A) Histologic appearance of clear cell carcinoma with tubulocystic pattern, tumor cells are polygonal to cuboidal and flattened with clear cytoplasm; (hematoxylin and eosin, H&E, ×200); (B) Papillary pattern shows small and regular papillae, frequently hyalinized (hematoxylin and eosin, H&E ×100).

Image Source: De Leo, Antonio, Donatella Santini, Claudio Ceccarelli, Giacomo Santandrea, Andrea Palicelli, Giorgia Acquaviva, Federico Chiarucci, Francesca Rosini, Gloria Ravegnini, Annalisa Pession, and et al. 2021. "What Is New on Ovarian Carcinoma: Integrated Morphologic and Molecular Analysis Following the New 2020 World Health Organization Classification of Female Genital Tumors" *Diagnostics* 11, no. 4: 697 (2021). This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). Available from: https://doi.org/10.3390/diagnostics11040697.

The tumor cells typically have clear, eosinophilic, or flattened cytoplasm, and large atypical nuclei with prominent nucleoli, but the cytologic atypia is relatively uniform, lacking significant pleomorphism. Mitoses are usually sparse (<5 per 10 high-power fields), which helps distinguish CCC from more proliferative ovarian carcinomas. Importantly, the

presence of clear cytoplasm alone is not diagnostic, as clear cells may be seen in other ovarian tumors (e.g., endometrioid or serous carcinoma). However, three histologic features are particularly suggestive of CCC:

1. Multiple complex papillae
2. Hyaline basement membrane or mucoid stroma in papillary cores
3. Hyaline globules (bodies)

Immunohistochemical Profile

CCC has a distinct immunophenotype:

- Positive for hepatocyte nuclear factor 1-beta (HNF-1β)
- Negative for WT1, ER, and PR
- Wild-type p53 expression

This profile aids in distinguishing CCC from other ovarian carcinoma subtypes, especially in morphologically ambiguous cases.Key molecular features include ARID1A and PIK3CA mutations.[18]

- Brenner Tumors

Brenner tumors typically present as solid, fibrous masses composed microscopically of transitional epithelium-like cells embedded within a fibrous stroma.[19]

3.4.2.3 Germ Cell Tumors

Germ cell tumors primarily affect younger women, typically under 20 years of age.[20]

- Etiology

  Arise from aberrant differentiation of primitive germ cells.

- Pathogenesis

  Stem from genetic abnormalities during germ cell differentiation.

- Molecular Profile

  Frequently involve genetic abnormalities such as isochromosome 12p (i(12p)). (Refer to "Integrated Morphologic and Molecular Analysis").

- Clinical Picture

  Common symptoms include abdominal pain, palpable masses, or hormonal symptoms related to tumor-produced substances.

- Treatment Options

  Fertility-sparing surgery combined with chemotherapy is often curative.

- Subtypes

- Dysgerminoma

Grossly, dysgerminomas are solid, lobulated masses resembling seminomas microscopically, with uniform cells and a characteristic lymphocytic infiltrate.[21]

- Endodermal Sinus (Yolk Sac) Tumor

Endodermal sinus tumors present grossly as hemorrhagic and necrotic masses. Microscopically, they exhibit Schiller-Duval bodies and secrete α-fetoprotein, aiding diagnosis and monitoring.[25]

- Teratomas

Teratomas range from benign cystic dermoid (mature) containing differentiated tissues such as hair, cartilage, and teeth to malignant immature teratomas composed of primitive neural elements (neuroectodermal tissue).[22]

- Choriocarcinoma

Choriocarcinomas are aggressive, rapidly growing tumors presenting with extensive hemorrhage and necrosis, microscopically composed of syncytiotrophoblast and cytotrophoblast, producing human chorionic gonadotropin (hCG).[23]

3.4.2.4 Sex Cord-Stroma Tumors

Sex Cord-Stroma Tumors are derived from the ovarian stroma and sex cord derivatives, including granulosa, theca, Sertoli, and Leydig cells.[24]

- Etiology & Epidemiology

  Account for ~5–8% of ovarian neoplasms. Most common in peri- and postmenopausal women (for granulosa cell tumors) or younger patients (for juvenile variants).

- Pathogenesis

  Thought to originate from primitive sex cord-stromal elements. Granulosa cell tumors commonly harbor **FOXL2** mutations (adult type). Sertoli–Leydig tumors may involve **DICER1** mutations.

- Clinical Picture & Diagnosis

  May produce estrogen (granulosa) or androgens (Sertoli–Leydig), causing abnormal bleeding or virilization. Elevated inhibin, anti-Müllerian hormone (AMH) may be present. Diagnosis confirmed via histology and immunostains (e.g., inhibin+, calretinin+).

- Treatment

  Surgical excision is curative in early-stage disease. Advanced or recurrent disease may require chemotherapy or hormonal therapy.[25]

- Subtypes

    - Fibroma

    Characterized grossly as solid, firm tumors with spindle cells in a dense collagenous stroma microscopically, occasionally associated with Meigs syndrome.

    - Thecoma

    Thecomas appear yellowish grossly due to high lipid content, microscopically showing lipid-laden thecal cells.

    - Granulosa Cell Tumor

    Granulosa cell tumors present grossly as solid-cystic lesions with hemorrhagic regions. Microscopically, they feature characteristic Call-Exner bodies and coffee bean-shaped nuclei, often harboring FOXL2 mutations.

    - Sertoli-Leydig Cell Tumor

    Grossly solid and lobulated, these tumors are composed of Sertoli and Leydig cells microscopically, often associated with androgenic symptoms and DICER1 mutations.[26]

3.4.2.5 Metastatic Tumors

Metastatic tumors are secondary ovarian tumors originating from extragenital primaries. Ovarian metastases commonly originate from gastrointestinal, breast, or endometrial cancers. Krukenberg tumors specifically refer to bilateral ovarian involvement characterized histologically by mucin-producing signet-ring cells.[27]

- Pathogenesis

    Tumor cells spread hematogenously, via lymphatics, or transcoelomically. Bilateral involvement is common.

- - Gross

    Often bilateral, solid with a nodular surface.

    - Microscopic

    Depends on primary—Krukenberg: mucin-filled signet-ring cells; colorectal metastases: dirty necrosis, glandular patterns.

- Clinical Picture & Diagnosis

    Abdominal pain or distension. CA-125 may be elevated but nonspecific. IHC critical for differentiation:

    - CK7+/CK20–: primary ovarian
    - CK7–/CK20+: GI origin
    - CDX2+, MUC2+: colorectal

- Treatment

  Depends on primary site. Oophorectomy may be performed for symptom control. Systemic therapy is based on the primary tumor.[28]

- Common Mistakes
  - Confusing primary mucinous carcinoma with metastatic colorectal cancer—look for bilaterality and IHC profile.
  - Assuming all germ cell tumors are malignant—mature teratomas are usually benign.
  - Overlooking STIC lesions in the fallopian tube during assessment for high-grade serous carcinoma.
  - Misclassifying borderline tumors as invasive carcinoma without thorough histologic sampling.

Clinical Pearls

- Psammoma bodies are commonly seen in serous tumors and can be a diagnostic clue.
- Bilateral ovarian masses should raise suspicion for metastatic disease.
- Consider struma ovarii or other monodermal teratomas when evaluating hormonally active tumors.
- Meigs syndrome (ovarian fibroma, ascites, pleural effusion) resolves with tumor resection.

Footnotes

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Image Acknowledgements

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3.6: Pathologies of Pregnancy (Forthcoming)

This section of Chapter 3 is forthcoming. For a list of common issues, please see Chatper 5.5: Disorders of Pregnancy

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3.7: Glossary

Ablation - The removal or destruction of a body part or tissue or its function. Ablation may be performed by surgery, hormones, drugs, radiofrequency, heat, or other methods [4]

Adenocarcinoma - A malignant epithelial tumor with a glandular organization. [1]

Adenomyosis - the extension of endometrial tissue (**ENDOMETRIUM**) into the **MYOMETRIUM**. It usually occurs in women in their reproductive years and may result in a diffusely enlarged uterus with ectopic and benign endometrial glands and stroma [1]

Adenosquamos (Carcinoma, Adenosquamos) - A mixed adenocarcinoma and squamous cell or epidermoid carcinoma. [1]

Adhesions - a band of scar tissue that joins two surfaces of the body that are usually separate

Adipose tissue - specialized areolar tissue rich in stored fat [3]

Adjuvant - supplement, augment, stimulate, activate, potentiate or modulate action or response of medical treatment [1]

Adnexal - of the uterine appendages (**ADNEXA UTERI**) including diseases involving the **OVARY**, the **FALLOPIAN TUBES**, and ligaments of the uterus (BROAD LIGAMENT; ROUND LIGAMENT) [1]

Amenorrhea - Absence of menstruation [4]

Androgens - Male sex hormones; for example, testosterone [4]

Angiogenesis development of new blood vessels from existing vessels [3]

Anovulation - Suspension or cessation of **OVULATION** in animals or humans with follicle-containing ovaries (**OVARIAN FOLLICLE**). Depending on the etiology, **OVULATION** may be induced with appropriate therapy. [1]

Apoptosis - programmed cell death [3]

Aromatase - An enzyme that catalyzes the desaturation (aromatization) of the ring A of C19 androgens and converts them to C18 estrogens. In this process, the 19-methyl is removed. This enzyme is membrane-bound, located in the endoplasmic reticulum of estrogen-producing cells of ovaries, placenta, testes, adipose, and brain tissues. [4]

Arterial - related to or flowing in an artery [6]

Atrophy - loss of mass and function [3]

Atypia - abnormality in cells in tissue. [7]

Autoimmune - disorders in which the immune system overreacts and begins to attack itself [4]

Basalis - the basal part of the endometrium that is not shed during menstruation

Behcet syndrome - Rare chronic inflammatory disease involving the small blood vessels. It is of unknown etiology and characterized by mucocutaneous ulceration in the mouth and genital region and uveitis with hypopyon. The neuro-ocular form may cause blindness and death. **SYNOVITIS**; **THROMBOPHLEBITIS**; gastrointestinal ulcerations; **RETINAL VASCULITIS**; and OPTIC ATROPHY may occur as well. [1]

Benign - Non-cancerous [4]

Calcification - Process by which organic tissue becomes hardened by the physiologic deposit of calcium salts. [1]

Canalization (defect) - the process of making a channel in part of the body, either naturally or using a medical procedure [6]

Carcinogenesis - the production of cancer [8]

Carcinoma - condition in which abnormal cells that look like cancer cells under a microscope are found only in the place where they first formed and haven't spread to nearby tissue [7]

Cell proliferation - All of the processes involved in increasing **CELL NUMBER** including **CELL DIVISION** [1]

Cervical os - (cervix uteri) neck portion of the **UTERUS** between the lower isthmus and the VAGINA forming the cervical canal. [1]

Chlamydia - A genus of the family **CHLAMYDIACEAE** whose species cause a variety of diseases in vertebrates including humans, mice, and swine. **Chlamydia** species are gram-negative and produce glycogen. [1]

Chromatin - substance consisting of DNA and associated proteins [3]

Coagulopathy - *(also called a bleeding disorder) is a condition in which the blood's ability to coagulate (form clots) is impaired*

Collagen (fiber) - flexible fibrous proteins that give connective tissue tensile strength [3]

Columnar - having a tall or long, narrow shape, like a column, as in columnar cells [7]

Confluent - two things, such as areas of skin or cells that join or come together without any space between them, or flow together in the same direction [7]

Cystic - relating to, formed of, or within a cyst; relating to the bladder or gall bladder [6]

Cytokines - class of protein signaling molecules; in the cardiovascular system, they stimulate the proliferation of progenitor cells and help to stimulate both nonspecific and specific resistance to disease [3]

Cytological - related to structure, function, or pathology of cells [8]

Cytoplasm - internal material between the cell membrane and nucleus of a cell, mainly consisting of a water-based fluid called cytosol, within which are all the other organelles and cellular solute and suspended materials [3]

De Novo - the first occurrence of cancer in the body [1]

Desmoplastic - characterized by the formation of fibrous tissue [8]

Diaphragm - skeletal muscle that separates the thoracic and abdominal cavities and is dome-shaped at rest [3]

Dilated - expanded, enlarged, or widened normally or abnormally in all dimensions [8]

Dysmenorrhea - Painful menstruation [4]

Dyspareunia - Genital pain before, during, or after intercourse [4]

Dysplastic - abnormal growth or development (as of organs or cells) [8]

Dysregulation - abnormality or impairment in the regulation of a metabolic, physiological, or psychological process [1]

Dysuria - Painful urination [4]

Ectocervix (Cervix uteri) - The outer part of the neck portion of the **UTERUS** between the lower isthmus and the VAGINA forming the cervical canal. [1]

Edematous - relating to or affected with edema **:** abnormally swollen with fluid [8]

Embolization - action of deliberately blocking the flow of blood in a particular blood vessel by putting material into the blood [6]

Embryogenesis - Human embryogenesis is a complicated process by which a fertilized egg develops into an embryo [3]

Endocervical - (Cervix uteri) - The inner part of the neck portion of the **UTERUS** between the lower isthmus and the **VAGINA** forming the cervical canal. [1]

Endocrine - cells, tissues, and organs that secrete hormones as a primary or secondary function and play an integral role in normal bodily processes [4]

Endometrium - inner lining of the uterus, part of which builds up during the secretory phase of the menstrual cycle and then sheds with menses [4]

Endothelium - A layer of epithelium that lines the heart, blood vessels (**ENDOTHELIUM**, **VASCULAR**), lymph vessels (**ENDOTHELIUM**, **LYMPHATIC**), and the serous cavities of the body [1]

Eosinophils - granulocytes that stain with eosin; they release antihistamines and are especially active against parasitic worms

Epithelium - sheets of cells that cover the exterior surfaces of the body, line internal cavities and passageways, and form certain glands; also known as epithelial tissue [4]

Eversion - foot movement involving the intertarsal joints of the foot in which the bottom of the foot is turned laterally, away from the midline [3]

Exogenous - describes substance made outside of the human body [3]

External os - the opening of the uterine cervix into the vagina [8]

Extrauterine - *existing, formed, or occurring outside the uterus*

Fallopian tubes - (uterine tubes or oviducts) ducts that facilitate transport of an ovulated oocyte to the uterus. [3]

Fascicular - of, related to, or consisting of fasciculi (seldner bundle of anatomical fibers, nerve fibers)

Fibroblasts - most abundant cell type in connective tissue, secretes protein fibers and matrix into the extracellular space [3]

Fibroid - benign tumor derived from smooth muscle tissue [1]

Fibrosis - A process in which muscle fibers are replaced by scar tissue [4]

Germ-line mutation - detectable and heritable alteration in the lineage of germ cells [1]

Gland - an organ of the body that secretes/produces liquid chemicals that have various purposes [6]

Gonorrhea - Acute infectious disease characterized by primary invasion of the urogenital tract. [1]

Granulomatous endometrititis - A defect of leukocyte function in which phagocytic cells ingest but fail to digest bacteria, resulting in recurring bacterial infections with granuloma formation. When chronic granulomatous disease is caused by mutations in the CYBB gene, the condition is inherited in an X-linked recessive pattern. When chronic granulomatous disease is caused by CYBA, NCF1, NCF2, or NCF4 gene mutations, the condition is inherited in an autosomal recessive pattern. [1]

Hematometra - Blood-filled UTERUS. [1]

Hemorrhage - Excessive bleeding [4]

Hemorrhagic degeneration - hemorrhagic infarction of leiomyomas that often occurs during pregnancy

Hemosiderin - A type of protein that have one or more tightly bound metal ions forming part of their structure [1]

Histocompatabilty - a state of mutual tolerance that allows some tissues to be grafted effectively to others [8]

Histology - The study of tissues [4]

Hyperandrogenic - when you have an excess amount of androgens (a group of sex hormones) in your body

Hyperechogenic - A **PRENATAL ULTRASONOGRAPHY** finding of excessively dense fetal bowel due to **MECONIUM** buildup. [1]

Hyperplasia - Abnormal growth due to the production of cells [4]

Hypertension - Blood pressure goes below the homeostatic set point when standing [4]

Hypertrophy - The enlargement of muscles [4]

Hypothalamus -major region of the diencephalon that is responsible for coordinating autonomic and endocrine control of homeostasis [4]

Hysterectomy - Surgery to remove the uterus and, sometimes, the cervix [4]

Hysteroscopy - Endoscopic examination of the uterus [4]

Iatrogenic - adverse condition in a patient occurring as the result of treatment by a physician, surgeon, or other health professional, especially infections acquired by a patient during the course of treatment [1]

Idiopathic - Something that is unknown [4]

Immunochemistry - Field of chemistry that pertains to immunological phenomena and the study of chemical reactions related to antigen stimulation of tissues. It includes physicochemical interactions between antigens and antibodies [1]

Immunocompromised - human or animal whose immunologic mechanism is deficient because of an immunodeficiency disorder or other disease or as the result of the administration of immunosuppressive drugs or radiation [1]

Infectious - transmission of **infectious** disease or pathogens. When transmission is within the same species, the mode can be horizontal or vertical (**INFECTIOUS DISEASE TRANSMISSION**, **VERTICAL**) [1]

Inflammation - basic innate immune response characterized by heat, redness, pain, and swelling [3]

Intraepithelial - Within the layer of cells that form the surface or lining of an organ. [7]

Intraepithelial neoplasia - term used to describe the presence of abnormal cells on the surface of or in the tissue that lines an organ, such as the cervix, breast, prostate, anus, vagina, vulva, penis, and mouth. [7]

Keratin pearls - *formed by local squamous epithelium accumulation which is easily recognized under a microscope [5] and is considered a marker of well-differentiated squamous cell carcinoma*

Koilocytosis - the presence of koilocytes (vacuolated pyknotic epithelial cell that has either a clear cytoplasm or a perinuclear halo and that tends to be associated with certain human papillomavirus infections) usually in the anogenital region or the uterine cervix [8]

Laparoscopy - procedure that uses a laparoscope, inserted through the abdominal wall, to examine the inside of the abdomen [4]

Laparotomy scars - scarring from surgical incision made in the wall of the abdomen [3]

Leiomyoma - A benign tumor derived from smooth muscle tissue, also known as a fibroid tumor. They rarely occur outside of the UTERUS and the GASTROINTESTINAL TRACT but can occur in the **SKIN** and **SUBCUTANEOUS TISSUE**, probably arising from the smooth muscle of small blood vessels in these tissues [1]

Lesions - areas of abnormal tissue [4]

Leukorrhea - A clear or white discharge from the **VAGINA**, consisting mainly of **MUCUS** [1]

Lichen planus - An inflammatory, pruritic disease of the skin and mucous membranes, which can be either generalized or localized. It is characterized by distinctive purplish, flat-topped papules having a predilection for the trunk and flexor surfaces. [1]

Localization - *the fact of being or becoming located or fixed in a particular place*

Lymphatics - the system of tubes that transport lymph around the body [6]

Lymphocytes - agranular leukocytes of the lymphoid stem cell line, many of which function in specific immunity [2]

Lymph-vascular - of, relating to, or containing lymphatic vessels [8]

Macroscopic - observable by the naked eye [8]

Malignancy - Cancerous [4]

Menarche - first menstruation in a pubertal female. [4]

Mesenchymal - refers to cells that develop into connective tissue, blood vessels, and lymphatic tissue [7]

Mesothelium - simple squamous epithelial portion of serous membranes, such as the superficial portion of the epicardium (the visceral pericardium) and the deepest portion of the pericardium (the parietal pericardium) [3]

Metaplasia - A condition in which there is a change of one adult cell type to another similar adult cell type. [1]

Metastasis - spread of cancer cells from a source to other parts of the body [3]

Metrorrhagia - Excessive bleeding from the uterus not related to menstruation [4]

Mitosis - type of **CELL NUCLEUS** division by means of which the two daughter nuclei normally receive identical complements of the number of **CHROMOSOMES** of the somatic cells of the species. [1]

Mitotic - of, related to, involving or occurring by cellular mitosis (cell division) [8

Monoclonal - produce by, being, composed of, or caused by cells derived from a single cell [8]

Morphology - form and structure of an organism or any of its parts [8]

Mucoid - resembling mucus [8]

Mucopurulent - containing both mucus and pus [8]

Mullerian ducts - A pair of ducts near the **WOLFFIAN DUCTS** in a developing embryo. In the male embryo, they degenerate with the appearance of testicular **ANTI-MULLERIAN HORMONE**. In the absence of anti-Mullerian hormone, Mullerian ducts give rise to the female reproductive tract, including the **OVIDUCTS**; **UTERUS**; **CERVIX**; and **VAGINA**. [1]

Multigravida - a woman who has been pregnant more than once [8]

Myomectomy - Surgical removal of a **LEIOMYOMA** of the **UTERUS**. [1]

Myometrium - smooth muscle layer of uterus that allows for uterine contractions during labor and expulsion of menstrual blood [3]

Myxoid - resembling mucus [8]

Necrosis - accidental death of cells and tissues [3]

Neoplasm - New abnormal growth of tissue. Malignant neoplasms show a greater degree of anaplasia and have the properties of invasion and metastasis, compared to benign neoplasms [1]

Neuroendocrine - of, relating to, or being a hormonal substance that influences the activity of nerves [8]

Neurogenesis - Formation of **NEURONS** which involves the differentiation and division of **STEM CELLS** in which one or both of the daughter cells become neurons. [1]

Neutrophilic - related to granulocytes that stain with a neutral dye and are the most numerous of the leukocytes; especially active against bacteria [3]

Nodule - growth or lump that may be malignant or benign [4]

Oncogene - gene that is a mutated form of a gene involved in normal cell growth and may cause the growth of cancer cells (National Cancer Institute, n.d.) [3]

Oncoprotein (Oncogene proteins) - Proteins coded by oncogenes. They include proteins resulting from the fusion of an oncogene and another gene (**ONCOGENE PROTEINS**, **FUSION**). [1]

Ontogenesis - development of course of development of an organism

Oropharynx - part of the pharynx continuous with the oral cavity that functions in respiration and digestion [3]

Ovary - female gonads that produce oocytes and sex steroid hormones (notably estrogen and progesterone)

Ovulatory dysfunction - irregular, infrequent (less than nine per year) menstrual periods or does not ovulate at all, she is said to have ovulatory dysfunction

Papillary - of, relating to, being, or resembling a papilla or nipple-shaped projection, mass or structure; marked by the presence of papillae [8]

Paracrine - Cellular signaling in which a factor secreted by a cell affects other cells in the local environment [4]

Pathogenic - causing or capable of causing disease [8]

Pedunculated - having, growing on, or being attached by a peduncle (narrow stalk by which a tumor or polyp is attached) [8]

Pelvic inflammatory disease - A spectrum of inflammation involving the female upper genital tract and the supporting tissues. It is usually caused by an ascending infection of organisms from the endocervix. Infection may be confined to the uterus (ENDOMETRITIS), the FALLOPIAN TUBES; (SALPINGITIS); the ovaries (OOPHORITIS), the supporting ligaments (PARAMETRITIS), or may involve several of the above uterine appendages. Such inflammation can lead to functional impairment and infertility. [1]

Peritoneal cavity - The space enclosed by the peritoneum. It is divided into two portions, the greater sac and the lesser sac or omental bursa, which lies behind the STOMACH. The two sacs are connected by the foramen of Winslow, or epiploic foramen. [1]

Peritonitits - Inflammation of the peritoneum [4]

Periumbilical - region of the body that immediately surrounds the umbilicus

Physiological - *relating to the way in which a living organism or bodily part functions* "slow down your body's physiological response to anger by breathing deeply"

Pituitary - bean-sized organ suspended from the hypothalamus that produces, stores, and secretes hormones in response to hypothalamic stimulation (also called hypophysis) [3]

Placental abruption - Premature separation of the normally implanted PLACENTA from the UTERUS. Signs of varying degree of severity include UTERINE BLEEDING, uterine MUSCLE HYPERTONIA, and FETAL DISTRESS or FETAL DEATH. [1]

Placenta previa - Abnormal placentation in which the PLACENTA implants in the lower segment of the UTERUS (the zone of dilation) and may cover part or all of the opening of the CERVIX. It is often associated with serious antepartum bleeding and PREMATURE LABOR. [1]

Placental retention - placenta that fails to be expelled after BIRTH of the FETUS. A PLACENTA is retained when the UTERUS fails to contract after the delivery of content, or when the placenta is abnormally attached to the MYOMETRIUM. [1]

Plasma cells - A type of B lymphocyte that produces antibodies, which bind to specific foreign or abnormal antigens in order to destroy them [4]

Pleomorphism - able to assume different forms [8]

Polypoid - organism whose genomes consist of more than two complete sets of chromosomes

Pluripotent - *capable of giving rise to several different cell types*

Polymenorrhea - Variations of MENSTRUATION which may be indicative of disease [1]

Polyp - A growth that protrudes from a mucous membrane (National Cancer Institute) [4]

Pouch of Douglas - (Douglas' Pouch) A sac or recess formed by a fold of the peritoneum. [1]

Presacral - presacral space is **t**he area between the rectum and lowest part of your the spine, which is called the sacrum. The presacral space is inside the pelvis, behind the rectum and in front of the coccyx and sacrum

Proinflammatory - promoting inflammation : capable of causing inflammation. [8]

Proliferative phase - phase of the menstrual cycle in which the endometrium proliferates [3]

Progestins - Compounds that interact with PROGESTERONE RECEPTORS in target tissues to bring about the effects similar to those of PROGESTERONE. [1]

Pyogenic - *pus-producing*

Retrograde - a backward movement or a movement that is opposite to the usual direction of flow [6]

Serous - Having to do with serum, the clear liquid part of blood. [7]

Sessile - attached permanently or established [8]

Somatic - Having to do with the body [7]

Squamocolumnar junction - the region in the uterine cervix in which the squamous lining of the vagina is replaced by the columnar epithelium typical of the body of the uterus and which is a common site of neoplastic change [8]

Squamous - of, relating to, or being a stratified epithelium that consists at least in its outer layers of small scalelike cells [8]

Stratum basalis - The deepest layers of the epidermis [4]

Stroma - the tissue that forms the structure of an organ or body part [6]

Stromal cells - Connective tissue cells of an organ found in the loose connective tissue. These are most often associated with the uterine mucosa and the ovary as well as the hematopoietic system and elsewhere. [1]

Superficial (body part) - describes a position nearer to the surface of the body

Telomerase - An essential ribonucleoprotein reverse transcriptase that adds telomeric DNA to the ends of eukaryotic CHROMOSOMES. [1]

Transabdominal - passing through or performed by passing through the abdomen of the abdominal wall [8]

Transvaginal - passing through or performed by way of the vagina [8]

Trauma - Injury or damage inflicted on the body as the direct or indirect result of an external force, with or without disruption of structural continuity [1]

Trichomonas - A genus of parasitic flagellate EUKARYOTES distinguished by the presence of four anterior flagella, an undulating membrane, and a trailing flagellum. [1]

Tuberculous salpingitis - Inflammation of the uterine salpinx, the trumpet-shaped FALLOPIAN TUBES, usually caused by ascending infections of organisms from the lower reproductive tract. Salpingitis can lead to tubal scarring, hydrosalpinx, tubal occlusion, INFERTILITY, and ectopic pregnancy (PREGNANCY, ECTOPIC) [1]

Umbilicale - pit in the center of the ABDOMINAL WALL marking the point where the **UMBILICAL** CORD entered in the FETUS.

Unicornuate uterus - a congenital irregularity where a person has only one fallopian tube and an abnormally shaped uterine cavity. It's a rare condition that causes pregnancy complications [5]

Unification defect

Upregulation - In biology, the process by which a cell increases its response to a substance or signal from outside the cell to carry out a specific function. For example, a cell may increase the number or activity of protein receptors or other molecules on its surface to make it more sensitive to a hormone or drug. [7]

Uterine ligaments - strong bands of dense connective tissue

Vacuolated - containing one or more vacuoles (small cavity or space in the tissues of an organism containing air or fluid) [8]

Vaginosis - Abnormal condition of the vagina [4]

Vascular - of, relating to, or affecting a channel for the conveyance of a body fluid (such as blood) [8]

Vascularization - process of becoming vascular (channel for the conveyance of a body fluid (such as blood) [8]

Visceral - Pertaining to internal organs [4]

Whorled - having or arranged in whorls (arrangement of similar anatomical parts in a circule aruond a point or on an axis) [8]

Xenoestrogens - foreign synthetic chemicals that mimic natural estrogens and can bind to estrogen receptors in the body

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CHAPTER OVERVIEW

4: Fertilization and Early Development of the Embryo

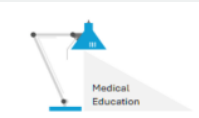
4.1: Fertilization
4.2: The Zygote
4.3: Infertility and Assisted Reproduction
4.4: Testicular Reproductive System
4.5: Glossary

Author: Judy Thorn, Ph.D.

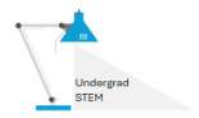
About this Chapter

In approximately nine months, a single cell—a fertilized egg—develops into a fully formed infant consisting of trillions of cells with myriad specialized functions. The dramatic changes of fertilization, embryonic development, and fetal development are followed by remarkable adaptations of the newborn to life outside the womb. An offspring's normal development depends on the appropriate synthesis of structural and functional proteins. This, in turn, is governed by the genetic material inherited from the egg and sperm, as well as environmental factors (Betts et al., Open Stax A&P second edition, 1.3.23, 28.1). This chapter addresses the biological and physiological processes associated with pregnancy, including fertilization, zygote formation, implantation, embryo formation, and maintaining pregnancy. It also covers contraception, infertility, and fetal genetic testing.

The content of this chapter is appropriate for, or easily adapted for the following audiences:







Learning Objectives

By the end of this chapter, you should be able to

- List and explain the steps involved in fertilization.
- Describe the obstacles that sperm must overcome to reach an oocyte.
- Explain capacitation and its importance in fertilization.
- Summarize the events that occur as a sperm fertilizes an oocyte.
- Sketch the stages of early development from the zygote to hatching.
- Describe cleavage and justify why cleavage is an essential step in early development.
- Correlate embryonic stage with its position in the female reproductive tract.
- Identify the cells required for the embryo to successfully implant and describe the consequences resulting from implantation in the wrong location.
- Match the extra-embryonic membranes with their function and location relative to the developing embryo.

- Describe how the placenta is formed and how it supports the developing embryo.
- Propose a treatment plan for treatment for a couple with infertility.
- List contraceptive options and explain how each works to prevent pregnancy.

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4.1: Fertilization

4.1.1 Transit of Sperm

Fertilization is a numbers game. During ejaculation, hundreds of millions of sperm (spermatozoa) are released into the vagina. Almost immediately, millions of these sperm are overcome by the vagina's acidity (approximately pH 3.8), and thick cervical mucus may block millions more from entering the uterus. Of those that do enter, thousands are destroyed by **phagocytic uterine leukocytes**. Thus, the race into the **uterine tubes**, which is the most typical site for sperm to encounter the oocyte, is reduced to a few thousand contenders. Their journey—thought to be facilitated by uterine contractions—usually takes from 30 minutes to 2 hours. If the sperm do not encounter an oocyte immediately, they can survive in the uterine tubes for another 3–5 days. Thus, fertilization can still occur if intercourse takes place a few days before ovulation. In comparison, an oocyte can survive independently for only approximately 24 hours following ovulation. Intercourse more than a day after ovulation will therefore usually not result in fertilization.[1]

For more information

More information on how sperm are produced (opens in new window) and released (opens in new window)can be found at OpenStax - Anatomy and Physiology 2E, 27.1 Anatomy and Physiology of the Testicular Reproductive System.

Additional resources for early development can be found at UNSW Embryology Online.

During the journey, fluids in the female reproductive tract prepare the sperm for fertilization through a process called capacitation or priming. Sperm must undergo the process of capacitation to have the “capacity” to fertilize an oocyte. If they reach the oocyte before capacitation is complete, they will be unable to penetrate the oocyte’s thick outer layer of cells. The fluids improve the **motility** of the spermatozoa. They also deplete cholesterol molecules embedded in the membrane of the head of the sperm, thinning the membrane in such a way that will help facilitate the release of the lysosomal (digestive) enzymes needed for the sperm to penetrate the oocyte’s exterior once contact is made.[2]

4.1.2 Contact Between Sperm and Oocyte

Upon ovulation, the oocyte released by the ovary is swept into—and along—the uterine tube. Fertilization must occur in the distal uterine tube because an unfertilized **oocyte** cannot survive the 72-hour journey to the uterus. As you will recall from your study of the **oogenesis**, this oocyte (specifically a secondary oocyte) is surrounded by two protective layers. The corona radiata is an outer layer of follicular (granulosa) cells that form around a developing oocyte in the ovary and remain with it upon ovulation. The underlying **zona pellucida** (pellucid =

"transparent") is a transparent but thick glycoprotein membrane that surrounds the cell's plasma membrane.[3]

As it is swept along the distal uterine tube, the oocyte encounters the surviving capacitated sperm, which stream toward it in response to chemical attractants released by the cells of the corona radiata. To reach the oocyte itself, the sperm must penetrate the two protective layers. The sperm first burrow through the cells of the corona radiata. Then, upon contact with the zona pellucida, the sperm bind to receptors in the zona pellucida. This initiates a process called the acrosomal reaction in which the enzyme-filled "cap" of the sperm, called the acrosome, releases its stored digestive enzymes. These enzymes clear a path through the zona pellucida that allows sperm to reach the oocyte. Finally, a single sperm makes contact with sperm-binding receptors on the oocyte's plasma membrane (Figure 4.1.1). The plasma membrane of that sperm then fuses with the oocyte's plasma membrane, and the head and mid-piece of the first sperm enter the oocyte interior.[4]

How do sperm penetrate the corona radiata? Some sperm undergo a spontaneous acrosomal reaction, which is an acrosomal reaction not triggered by contact with the zona pellucida. The digestive enzymes released by this reaction digest the extracellular matrix of the corona radiata. The first sperm to reach the oocyte is never the one to fertilize it. Rather, hundreds of sperm cells must undergo the acrosomal reaction, each helping to degrade the corona radiata and zona pellucida until a path is created to allow one sperm to contact and fuse with the plasma membrane of the oocyte.[5]

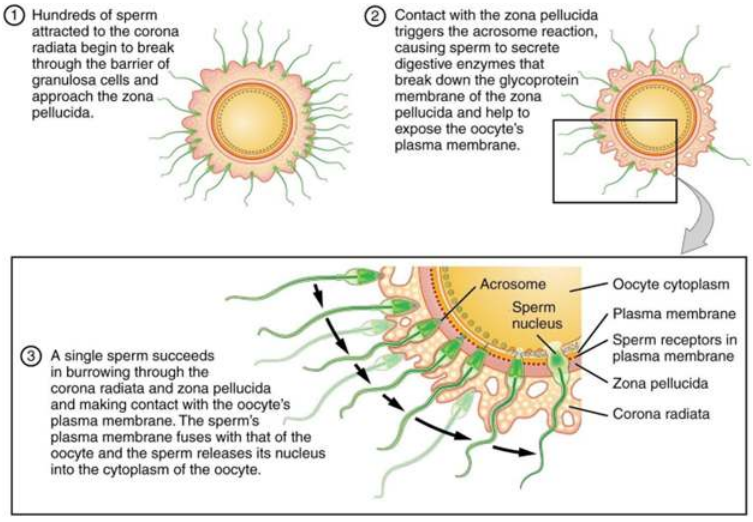


Figure 4.1.1 Sperm and the Process of Fertilization Before fertilization, hundreds of capacitated sperm must break through the surrounding corona radiata and zona pellucida so that one can contact and fuse with the oocyte plasma membrane.

Image Source: Betts, J. Gordon, Kelly A. Young, James A. Wise, Eddie Johnson, Brandon Poe, Dean H. Kruse, Oksana Korol, Jody E. Johnson, Mark Womble, Peter DeSaix. Anatomy and Physiology. (2013). Open Stax, 2013 This work is distributed under a CC BY 4.0 license. Available from Open Stax.

When the first sperm fuses with the oocyte, the oocyte deploys two mechanisms to prevent polyspermy, which is penetration by more than one sperm. This is critical because if more than one sperm were to fertilize the oocyte, the resulting zygote would be a triploid organism with three sets of chromosomes. This is incompatible with life.[6]

The first mechanism is the fast block, which involves a near-instantaneous change in sodium ion permeability upon binding of the first sperm, depolarizing the oocyte plasma membrane and preventing the fusion of additional sperm cells. The fast block sets in almost immediately and lasts for about a minute, during which time an influx of calcium ions following sperm penetration triggers the second mechanism, the slow block. In this process, referred to as the cortical reaction, cortical granules sitting immediately below the oocyte plasma membrane fuse with the membrane and release zonal inhibiting proteins and **mucopolysaccharides** into the space between the plasma membrane and the zona pellucida. Zonal inhibiting proteins cause the release of any other attached sperm and destroy the oocyte's sperm receptors, thus preventing any more sperm from binding. The mucopolysaccharides then coat the nascent zygote in an impenetrable barrier that, together with hardened zona pellucida, is called a fertilization membrane.[7]

Watch this video

Video 4.1

This movie shows *in vitro* development of a human morula to blastocyst stage occurring between day 3 and day 6 post-fertilization.

Blastocyst Day 3-6 [8]

Glossary

Motility
: The movement of cells from one location to another. It is distinct from *cytokinesis*, which is the process of dividing a cell's *cytoplasm*.

Mucopolysaccharides
: Mucopolysaccharides are long chains of sugar molecules that are found throughout the body, often in mucus and in fluid around the joints. They are more commonly called glycosaminoglycans

Oocyte
: cell that results from the division of the oogonium and undergoes meiosis I at the LH surge and meiosis II at fertilization to become a haploid ovum

Oogenesis
: process by which oogonia divide by mitosis to primary oocytes, which undergo meiosis to produce the secondary oocyte and, upon fertilization, the ovum

Phagocytic uterine leukocytes
: cells that...

Uterine tubes

(also, fallopian tubes or oviducts) ducts that facilitate transport of an ovulated oocyte to the uterus

Zona pellucida

A tough transparent membrane surrounding the OVUM. It is penetrated by the sperm during FERTILIZATION

Footnotes

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Image Acknowledgements

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4.2: The Zygote

4.2.1 Fertilization & Implantation

Fertilization occurs when a sperm and an oocyte (egg) combine and their nuclei fuse. Because each of these reproductive cells is a **haploid** cell containing half of the genetic material needed to form a human being, their combination forms a **diploid** cell. This new single cell, called a zygote, contains all the genetic material needed to form a human—half from each biological parent.

Recall that at the point of fertilization, the oocyte has not yet completed meiosis; all secondary oocytes remain arrested in the metaphase of meiosis II until fertilization. Only upon fertilization does the oocyte complete meiosis. The unneeded complement of genetic material that results is stored in a second polar body that is eventually ejected. At this moment, the oocyte has become an ovum, the female haploid gamete. The two haploid nuclei derived from the sperm and oocyte and contained within the egg are referred to as pronuclei. They decondense, expand, and replicate their DNA in preparation for mitosis. The **pronuclei** then migrate toward each other, their nuclear envelopes disintegrate, and the male- and female-derived genetic material intermingles. This step completes the fertilization process and results in a single-celled diploid zygote with all the genetic instructions it needs to develop into a human.[9]

Throughout this text, we will express embryonic and fetal ages in terms of weeks from fertilization, commonly called conception. The period required for full development of a fetus **in utero** is referred to as gestation (gestare = “to carry” or “to bear”). It can be subdivided into distinct gestational periods. The first 2 weeks of **prenatal** development are referred to as the pre-embryonic stage. A developing human is referred to as an embryo during weeks 3–8, and a fetus from the ninth week of gestation until birth. In this section, we’ll cover the pre-embryonic and embryonic stages of development, which are characterized by cell division, migration, and differentiation. By the end of the embryonic period, all of the organ systems are structured in rudimentary form, although the organs themselves are either nonfunctional or only semi-functional.[10]

Following fertilization, the zygote and its associated membranes, together referred to as the conceptus, continue to be projected toward the uterus by **peristalsis** and beating cilia of the epithelial cells of the Fallopian tube. During its journey to the uterus, the zygote undergoes five or six rapid mitotic cell divisions. Although each cleavage results in more cells, it does not increase the total volume of the conceptus. (Figure 4.2.1) Each daughter cell produced by cleavage is called a blastomere (blastos = “germ,” in the sense of a seed or sprout).[11]

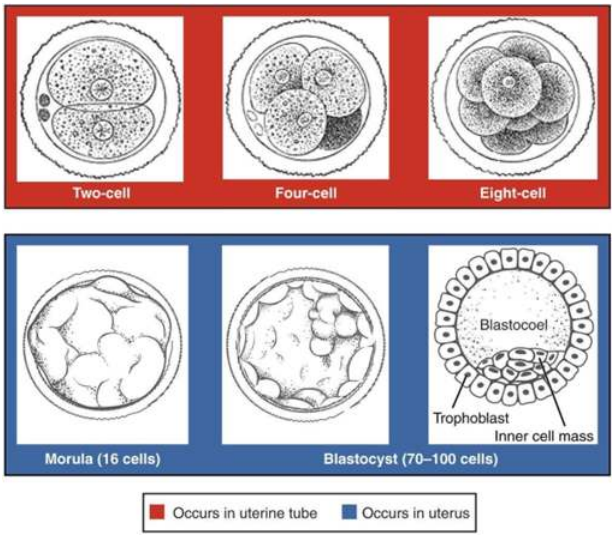


Figure 4.2.1 Pre-Embryonic Cleavages - Pre-embryonic cleavages make use of the abundant cytoplasm of the conceptus as the cells rapidly divide without changing the total volume.
Image Source: Betts, J. Gordon, Kelly A. Young, James A. Wise, Eddie Johnson, Brandon Poe, Dean H. Kruse, Oksana Korol, Jody E. Johnson, Mark Womble, Peter DeSaix. Anatomy and Physiology. (2013). Open Stax, 2013 This work is distributed under a CC BY 4.0 license. Available from Open Stax.

Approximately 3 days after fertilization, a 16-cell conceptus reaches the uterus. The cells that had been loosely grouped are now compacted and look more like a solid mass. The name given to this structure is the morula (morula = “little mulberry”). Once inside the uterus, the conceptus floats freely for several more days. It continues to divide, creating a ball of approximately 100 cells and consuming nutritive endometrial secretions called uterine milk while the uterine lining thickens. The ball of now tightly bound cells starts to secrete fluid and organize themselves around a fluid-filled cavity, the blastocoel. At this developmental stage, the conceptus is referred to as a blastocyst. Within this structure, a group of cells forms into an inner cell mass, which is fated to become the embryo. The cells that form the outer shell are called **trophoblasts** (trophe = “to feed” or “to nourish”). These cells will develop into the **chorionic sac** and the fetal portion of the placenta (the organ of nutrient, waste, and gas exchange between a pregnant person and the developing offspring).[12]

The inner mass of embryonic cells is totipotent during this stage, meaning that each cell has the potential to differentiate into any cell type in the human body. Totipotency lasts for only a few days before the cells’ fates are set as being the precursors to a specific lineage of cells.[13]

As the blastocyst forms, the trophoblast excretes enzymes that begin to degrade the zona pellucida. In a process called “hatching,” the conceptus breaks free of the zona pellucida in preparation for implantation.[14]

Watch

Video 4.2

Cell Division

Source: MedlinePlus [Internet]. National Library of Medicine. (2020). Available from: Available from: https://medlineplus.gov/.

Video 4.3

Fertilization

Source: Hill, Mark A. "Embryology" Main Page. (2025) https://embryology.med.unsw.edu.au/e....php/Main_Page

For more information

More information about fertilization and early development before implantation can be found online in StatPearls Embryology.

Source: Khan YS and KM Ackerman. "Embryology, Week 1". In: StatPearls [Internet]. (April 17, 2023). Available from: https://www.ncbi.nlm.nih.gov/books/NBK554562/

At the end of the first week, the blastocyst comes in contact with the uterine wall and adheres to it, embedding itself in the uterine lining via the trophoblast cells. Thus begins the process of implantation, which signals the end of the pre-embryonic stage of development. (Figure 4.2.2)

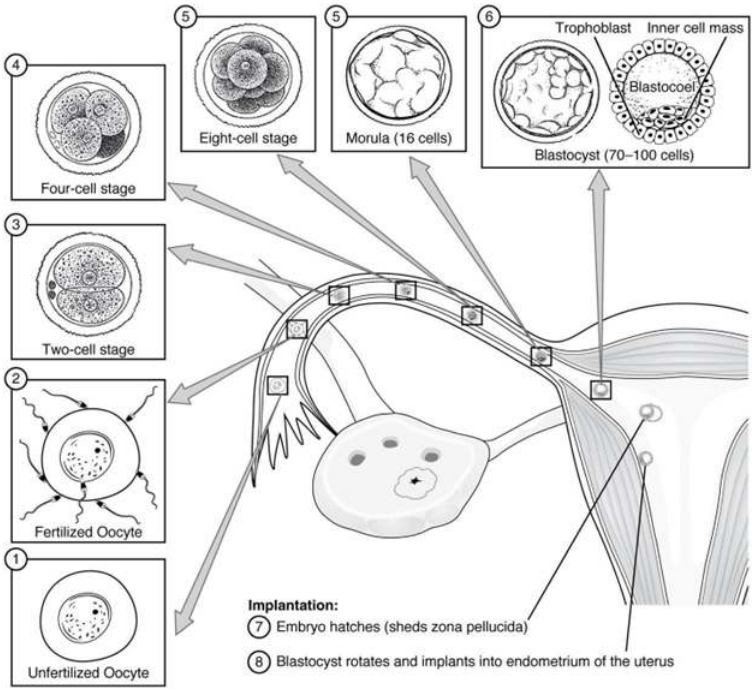


Figure 4.2.2 Pre-Embryonic Development - Ovulation, fertilization, pre-embryonic development, and implantation occur at specific locations within the female reproductive system in a time span of approximately 1 week.

Image Source: Betts, J. Gordon, Kelly A. Young, James A. Wise, Eddie Johnson, Brandon Poe, Dean H. Kruse, Oksana Korol, Jody E. Johnson, Mark Womble, Peter DeSaix. Anatomy and Physiology. (2013). Open Stax, 2013 This work is distributed under a CC BY 4.0 license. Available from Open Stax.

Implantation can be accompanied by minor bleeding. The blastocyst typically implants in the fundus of the uterus or on the posterior wall. However, if the **endometrium** is not fully developed and ready to receive the blastocyst, the blastocyst will detach and find a better spot. A significant percentage (50–75 percent) of blastocysts fail to implant; when this occurs, the blastocyst is shed with the endometrium during **menses**. The high rate of implantation failure is one reason why pregnancy typically requires several ovulation cycles to achieve.[15]

When implantation succeeds and the blastocyst adheres to the endometrium, the superficial cells of the trophoblast fuse, forming the **syncytiotrophoblast**, a multinucleated body that digests endometrial cells to firmly secure the blastocyst to the uterine wall. In response, the uterine mucosa rebuilds itself and envelops the blastocyst (Figure 4.2.3).

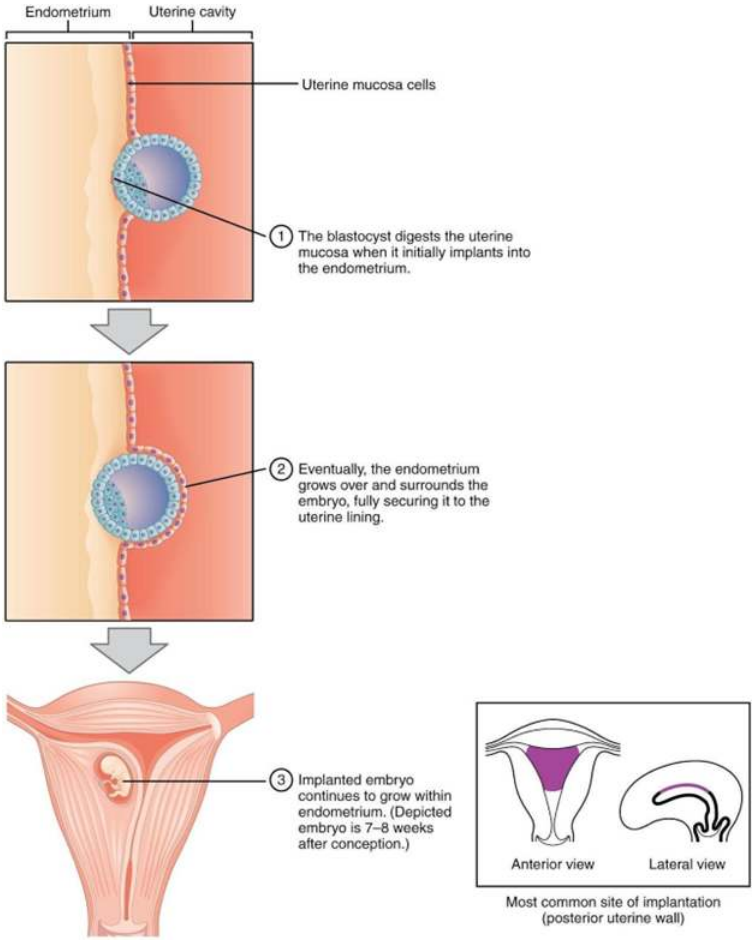


Figure 4.2.3 Implantation - During implantation, the trophoblast cells of the blastocyst adhere to the endometrium and digest endometrial cells until the blastocyst is attached securely.
Image Source: Betts, J. Gordon, Kelly A. Young, James A. Wise, Eddie Johnson, Brandon Poe, Dean H. Kruse, Oksana Korol, Jody E. Johnson, Mark Womble, Peter DeSaix. *Anatomy and Physiology*. (2013). Open Stax, 2013 This work is distributed under a CC BY 4.0 license. Available from Open Stax.

The trophoblast secretes human chorionic gonadotropin (hCG), a hormone that directs the corpus luteum to survive, enlarge, and continue producing **progesterone** and estrogen to suppress menses. These functions of hCG are necessary for creating an environment suitable

for the developing embryo. As a result of this increased production, hCG accumulates in the maternal bloodstream and is excreted in the urine. **Implantation** is complete by the middle of the second week. Just a few days after implantation, the trophoblast has secreted enough hCG for an at-home urine pregnancy test to give a positive result.[16]

Most of the time, an embryo implants within the body of the uterus in a location that can support growth and development. However, in one to two percent of cases, the embryo implants either outside the uterus (an ectopic pregnancy) or in a region of the uterus that can create complications for the pregnancy. If the embryo implants in the inferior portion of the uterus, the placenta may grow over the opening of the cervix, a condition called placenta previa.[17]

For more information

More information about fertilization and early development before implantation can be found online in StatPearls Embryology.

Source: Khan Yusuf S. and KKristin M. Ackerman. "Embryology, Week 1". In: StatPearls [Internet]. (April 17, 2023). Available from: https://www.ncbi.nlm.nih.gov/books/NBK554562/

4.2.2 Disorders of Embryo Development and **Implantation**

In the vast majority of **ectopic pregnancies**, the embryo does not complete its journey to the uterus and implants in the uterine tube, referred to as a tubal pregnancy. However, there are also ovarian ectopic pregnancies (in which the egg never left the ovary) and abdominal ectopic pregnancies (in which an egg was “lost” to the abdominal cavity during the transfer from ovary to uterine tube or in which an embryo from a tubal pregnancy re-implanted in the abdomen). Once in the abdominal cavity, an embryo can implant into any well-vascularized structure—the rectouterine cavity (Douglas’ pouch), the mesentery of the intestines, and the greater omentum are some common sites.[18]

Tubal pregnancies can be caused by scar tissue within the tube following a sexually transmitted bacterial infection. The scar tissue impedes the progress of the embryo into the uterus—in some cases “snagging” the embryo and, in other cases, blocking the tube completely. Approximately one half of tubal pregnancies resolve spontaneously. Implantation in a uterine tube causes bleeding, which appears to stimulate smooth muscle contractions and expulsion of the embryo. In the remaining cases, medical or surgical intervention is necessary. If an ectopic pregnancy is detected early, the embryo’s development can be arrested by the administration of the cytotoxic drug **methotrexate**, which inhibits the metabolism of folic acid. If diagnosis is late and the uterine tube is already ruptured, surgical repair is essential.[19] Ectopic pregnancy is responsible for 5–10% of all pregnancy-related deaths.[20]

Even if the embryo has successfully found its way to the uterus, it does not always implant in an optimal location (the fundus or the posterior wall of the uterus). Placenta previa can result if

an embryo implants close to the internal os of the uterus (the internal opening of the cervix). As the fetus grows, the placenta can partially or completely cover the opening of the cervix (Figure 4.2.4). Although it occurs in only 0.5 percent of pregnancies, placenta previa is the leading cause of antepartum hemorrhage (profuse vaginal bleeding after week 24 of pregnancy but prior to childbirth).[21]

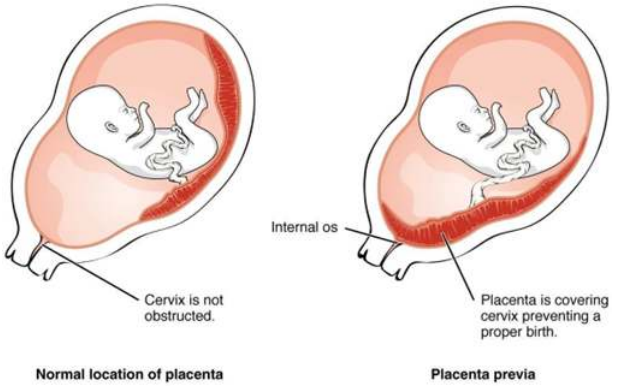


Figure 4.2.4 Placenta Previa - An embryo that implants too close to the opening of the cervix can lead to placenta previa, a condition in which the placenta partially or completely covers the cervix.
Image Source: Betts, J. Gordon, Kelly A. Young, James A. Wise, Eddie Johnson, Brandon Poe, Dean H. Kruse, Oksana Korol, Jody E. Johnson, Mark Womble, Peter DeSaix. Anatomy and Physiology. (2013). Open Stax, 2013. This work is distributed under a CC BY 4.0 license. Available from Open Stax.

In some cases a tumor develops inside the uterus from tissue that forms after conception. This tissue is made of **trophoblast cells**. Sometimes there is a problem with the fertilized egg and trophoblast cells. Instead of a healthy fetus developing, a tumor forms. Until there are signs or symptoms of the tumor, the pregnancy will seem like a normal pregnancy. Most GTD is benign (not cancer) and does not spread, but some types become malignant and spread to nearby tissues or distant parts of the body. Gestational trophoblastic disease (GTD) is a general term that includes different types of disease including hydatidiform moles (complete and partial) and gestational trophoblastic **neoplasia** (GTN). **Hydatidiform moles**, the most common type of GTD, are slow-growing tumors that look like sacs of fluid. A hydatidiform mole is also called a molar pregnancy. The cause of hydatidiform moles is not known. Hydatidiform moles may be complete or partial. A complete hydatidiform moles forms when sperm fertilizes an egg that does not contain the mother's DNA. The egg has DNA from the father and the cells that were meant to become the placenta are abnormal. A partial hydatidiform moles form when sperm fertilizes a normal egg and there are two sets of DNA from the sperm in the fertilized egg. Only part of the fetus forms and the cells that were meant to become the placenta are abnormal. Most hydatidiform moles are benign, but they sometimes become cancerous.

Gestational trophoblastic neoplasia (GTN) is a type of gestational trophoblastic disease (GTD) that is almost always malignant, and includes invasive moles, **choriocarcinomas,** placental-site **trophoblastic tumors** and epithelioid trophoblastic tumors. These conditions are treated with surgery, chemotherapy and radiation therapy.

For more information

More information regarding ectopic pregnancy and ultrasounds for ectopic pregnancy can be found online in "Ectopic Pregnancy," *StatPearls.*

Source: Baker, Mark and Jonathan dela Cruz. "Ectopic Pregnancy, Ultrasound." In *StatPearls* [Internet]. (January 16, 2023). Available from: https://www.ncbi.nlm.nih.gov/books/NBK482192/

More information about placenta abnormalities, placenta accreta, and placenta previa can be found online in "Placenta Abnormalities," *StatPearls.*

Source: Rathburn, Kimberly M. and Jason P. Hildebrand. "Placenta Abnormalities". In *StatPearls.* [Internet] (October 17, 2022). Available from: https://www.ncbi.nlm.nih.gov/books/NBK459355/

Additional resources for gestational trophoblastic disease and treatment can be found online in "Gestational Trophoblastic Diesease Treatment," (PDQ) - Health Professional Version, National Cancer Institute.

4.2.3 Creation and Organization of the Embryonic Membranes

During the second week of development, with the embryo implanted in the uterus, cells within the blastocyst start to organize into layers. Some grow to form the extraembryonic membranes needed to support and protect the growing embryo: the amnion, the yolk sac, the allantois, and the chorion.[22]

At the beginning of the second week, the cells of the inner cell mass form into a two-layered disc of embryonic cells, and a space—the amniotic cavity—opens up between it and the trophoblast (Figure 4.2.5).

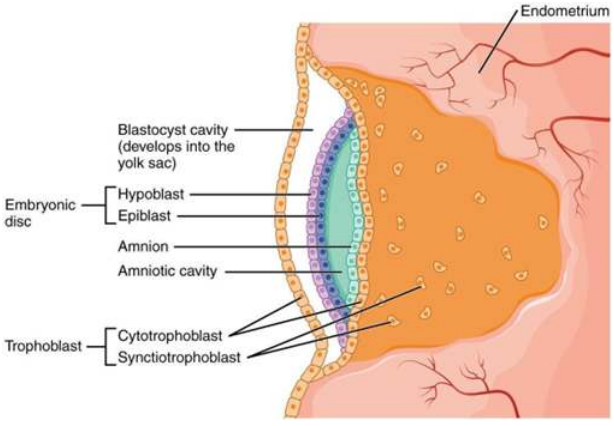


Figure 4.2.5 Development of the Embryonic Disc Formation of the embryonic disc leaves spaces on either side that develop into the amniotic cavity and the yolk sac.

Image Source: Betts, J. Gordon, Kelly A. Young, James A. Wise, Eddie Johnson, Brandon Poe, Dean H. Kruse, Oksana Korol, Jody E. Johnson, Mark Womble, Peter DeSaix. *Anatomy and Physiology*. (2013). Open Stax, 2013. This work is distributed under a CC BY 4.0 license. Available from Open Stax.

Cells from the upper layer of the disc (the epiblast) extend around the amniotic cavity, creating a membranous sac that forms into the amnion by the end of the second week. The **amnion** fills with amniotic fluid and eventually grows to surround the embryo. Early in development, amniotic fluid consists almost entirely of a filtrate of maternal plasma, but as the kidneys of the fetus begin to function at approximately the eighth week, they add urine to the volume of amniotic fluid. Floating within the amniotic fluid, the embryo—and later, the fetus—is protected from trauma and rapid temperature changes. It can move freely within the fluid and can prepare for swallowing and breathing out of the uterus.[23]

On the ventral side of the embryonic disc, opposite the amnion, cells in the lower layer of the embryonic disk (the hypoblast) extend into the blastocyst cavity and form a **yolk sac**. The yolk sac supplies some nutrients absorbed from the trophoblast and also provides primitive blood circulation to the developing embryo for the second and third week of development. When the placenta takes over nourishing the embryo at approximately week 4, the yolk sac has been greatly reduced in size and its main function is to serve as the source of blood cells and germ cells (cells that will give rise to gametes). During week 3, a finger-like outpocketing of the yolk sac develops into the allantois, a primitive excretory duct of the embryo that will become part of the urinary bladder. Together, the stalks of the yolk sac and **allantois** establish the outer structure of the umbilical cord.[24]

The last of the extraembryonic membranes is the chorion, which is the one membrane that surrounds all others. The development of the chorion will be discussed in more detail shortly, as it relates to the growth and development of the placenta.

For more information

More information about amniotic fluid can be found online in "Placenta Previa," *StatPearls.*

More information about the yolk sac can be found online in "Embryology, Yolk Sac," *StatPearls.*

A review of the beginning of pregnancy can be found online at "The surprising science of how pregnancy begins," *Shots Health News from NPR.*

4.2.4 The Placenta

4.2.4.1 Development of the Placenta

During the first several weeks of development, the cells of the endometrium—referred to as decidual cells—nourish the nascent embryo. During prenatal weeks 4–12, the developing placenta gradually takes over the role of feeding the embryo, and the decidual cells are no longer needed. The mature placenta is composed of tissues derived from the embryo, as well as maternal tissues of the endometrium. The placenta connects to the conceptus via the umbilical cord, which carries deoxygenated blood and wastes from the fetus through two umbilical arteries; nutrients and oxygen are carried from the pregnant person to the fetus

through the single umbilical vein. The umbilical cord is surrounded by the amnion, and the spaces within the cord around the blood vessels are filled with Wharton's jelly, a mucous connective tissue.

The placenta develops throughout the embryonic period and during the first several weeks of the fetal period; placentation is complete by weeks 14–16. As a fully developed organ, the placenta provides nutrition and excretion, respiration, and endocrine function. (Figure 4.2.6).

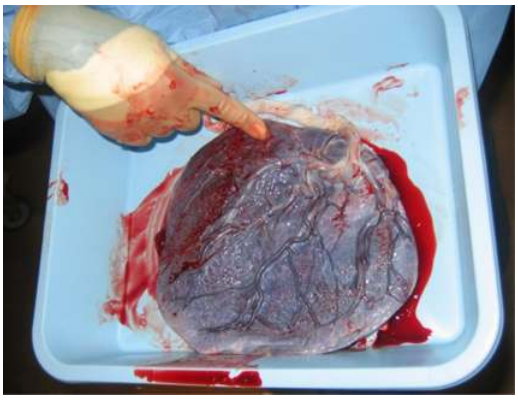


Figure 4.2.6 Placenta - This post-expulsion placenta and umbilical cord (white) are viewed from the fetal side.

Image Source: Betts, J. Gordon, Kelly A. Young, James A. Wise, Eddie Johnson, Brandon Poe, Dean H. Kruse, Oksana Korol, Jody E. Johnson, Mark Womble, Peter DeSaix. Anatomy and Physiology. (2013). Open Stax, 2013 This work is distributed under a CC BY 4.0 license. Available from Open Stax.

It receives blood from the fetus through the umbilical arteries. Capillaries in the chorionic villi filter fetal wastes out of the blood and return clean, oxygenated blood to the fetus through the umbilical vein. Nutrients and oxygen are transferred from maternal blood surrounding the villi through the capillaries and into the fetal bloodstream. Some substances move across the placenta by simple diffusion. Oxygen, carbon dioxide, and any other **lipid-soluble** substances take this route. Other substances move across by **facilitated diffusion**. This includes water-soluble glucose. The fetus has a high demand for amino acids and iron, and those substances are moved across the placenta by active transport.

The maternal portion of the placenta develops from the deepest layer of the endometrium, the decidua basalis. To form the embryonic portion of the placenta, the syncytiotrophoblast and the underlying cells of the trophoblast (cytotrophoblast cells) begin to proliferate along with a layer of extraembryonic mesoderm cells. These form the chorionic membrane, which envelops the entire conceptus as the chorion. The chorionic membrane forms finger-like structures called chorionic villi that burrow into the endometrium like tree roots, making up the fetal portion of the placenta. The **cytotrophoblast** cells perforate the chorionic villi, burrow farther into the endometrium, and remodel maternal blood vessels to augment maternal blood flow surrounding the villi. Meanwhile, fetal mesenchymal cells derived from the mesoderm fill the villi

and differentiate into blood vessels, including the three umbilical blood vessels that connect the embryo to the developing placenta (Figure 4.2.7).

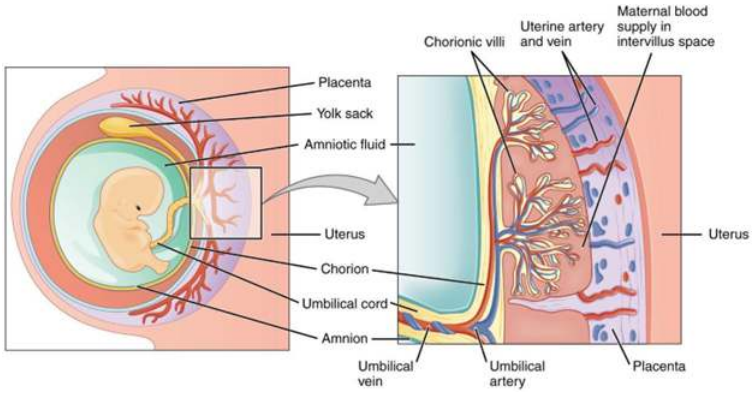


Figure 4.2.7 Cross-Section of the Placenta - In the placenta, maternal and fetal blood components are conducted through the surface of the chorionic villi, but maternal and fetal bloodstreams never mix directly.
Image Source: Betts, J. Gordon, Kelly A. Young, James A. Wise, Eddie Johnson, Brandon Poe, Dean H. Kruse, Oksana Korol, Jody E. Johnson, Mark Womble, Peter DeSaix. Anatomy and Physiology. (2013). Open Stax, 2013 This work is distributed under a CC BY 4.0 license. Available from Open Stax.

Maternal and fetal blood does not commingle because blood cells cannot move across the placenta. This separation prevents the pregnant person's cytotoxic T cells from reaching and subsequently destroying the fetus, which bears “non-self” antigens. Further, it ensures the fetal red blood cells do not enter the pregnant person's circulation and trigger antibody development (if they carry “non-self” antigens)—at least until the final stages of pregnancy or birth. This is the reason that, even in the absence of preventive treatment, an Rh− person doesn’t develop antibodies that could cause **hemolytic disease** in their first Rh+ fetus.

Although blood cells are not exchanged, the **chorionic villi** provide ample surface area for the two-way exchange of substances between maternal and fetal blood. The rate of exchange increases throughout gestation as the villi become thinner and increasingly branched. The placenta is permeable to lipid-soluble fetotoxic substances: alcohol, nicotine, **barbiturates**, antibiotics, certain pathogens, and many other substances that can be dangerous or fatal to the developing embryo or fetus. For these reasons, pregnant people should avoid fetotoxic substances. Alcohol consumption by pregnant people, for example, can result in a range of abnormalities referred to as fetal alcohol spectrum disorders (FASD). These include organ and facial malformations, as well as cognitive and behavioral disorders.

4.2.4.2 Functions of the Placenta

- Nutrition and Digestion
  - Mediates diffusion of maternal glucose, amino acids, fatty acids, vitamins, and minerals
  - Stores nutrients during early pregnancy to accommodate increased fetal demand later in pregnancy
  - Excretes and filters fetal nitrogenous wastes into maternal blood

- Respiration
  - Mediates maternal-to-fetal oxygen transport and fetal-to-maternal carbon dioxide transport
- Endocrine Function
  - Secretes several hormones, including hCG, estrogens, and progesterone, to maintain the pregnancy and stimulate maternal and fetal development
  - Mediates the transmission of maternal hormones into fetal blood and vice versa

For more information

More information about the role of the placenta, how the placenta forms, and ongoing research about the importance of the placenta in human development can be found online in "Embryology, Placenta," *StatPearls.*

4.2.5 Development of Twins

Most of the time, a person releases a single egg during an ovulation cycle. However, in approximately 1 percent of ovulation cycles, two eggs are released and both are fertilized. Two zygotes form, implant, and develop, resulting in the birth of dizygotic (or fraternal) twins. Because dizygotic twins develop from two eggs fertilized by two sperm, they are no more identical than siblings born at different times.

Much less commonly, a zygote can divide into two separate offspring during early development. This results in the birth of monozygotic (or identical) twins. Although the zygote can split as early as the two-cell stage, splitting occurs most commonly during the early blastocyst stage, with roughly 70–100 cells present. These two scenarios are distinct from each other, in that the twin embryos that separated at the two-cell stage will have individual placentas, whereas twin embryos that form from separation at the blastocyst stage will share a placenta and a **chorionic cavity.**[25]

For more information

More information about twin births can be found online in "Twin Births (Archived)," *StatPearls*

Glossary Terms

Allantois

An extraembryonic membranous sac derived from the YOLK SAC of REPTILES; BIRDS; and MAMMALS. It lies between two other extraembryonic membranes, the AMNION and the CHORION. The allantois serves to store urinary wastes and mediate exchange of gas and nutrients for the developing embryo.

Amnion

The innermost membranous sac that surrounds and protects the developing embryo which is bathed in the AMNIOTIC FLUID. Amnion cells are secretory EPITHELIAL CELLS and contribute to the

amniotic fluid.

Barbituates

A class of chemicals derived from barbituric acid or thiobarbituric acid. Many of these are GABA MODULATORS used as HYPNOTICS AND SEDATIVES, as ANESTHETICS, or as ANTICONVULSANTS.

Choriocarcinoma

A malignant metastatic form of trophoblastic tumors. Unlike the HYDATIDIFORM MOLE, **choriocarcinoma** contains no CHORIONIC VILLI but rather sheets of undifferentiated cytotrophoblasts and syncytiotrophoblasts (TROPHOBLASTS). It is characterized by the large amounts of CHORIONIC GONADOTROPIN produced. DNA analyses can determine tissue origins: placental (fetal) origin or non-placental origin.

Chorionic sac

The fetal part of the placenta.

Chorionic villi

Projections of the chorionic membrane that burrow into the endometrium and develop into the placenta.

Cytotophoblast

Cells lining the outside of the BLASTOCYST. After binding to the ENDOMETRIUM, trophoblasts develop into two distinct layers, an inner layer of mononuclear cytotrophoblasts and an outer layer of continuous multinuclear cytoplasm, the syncytiotrophoblasts, which form the early fetal-maternal interface.

Diploid

A cell containing two matched sets of chromosomes.

Ectopic pregnancy

The implantation of an embryo outside of the uterus.

Endometrium

The inner lining of the uterus, part of which builds up during the secretory phase of the menstrual cycle and then sheds with menses.

Facilitated diffusion

Diffusion of a substance with the aid of a membrane protein.

Gestational trophoblastic neoplasia

A group of diseases arising from pregnancy that are commonly associated with hyperplasia of trophoblasts (TROPHOBLAST) and markedly elevated human CHORIONIC GONADOTROPIN. They include HYDATIDIFORM MOLE, invasive mole (HYDATIDIFORM MOLE, INVASIVE), placental-site trophoblastic tumor (TROPHOBLASTIC TUMOR, PLACENTAL SITE), and CHORIOCARCINOMA. These neoplasms have varying propensities for invasion and spread

Haploid

the presence of a single set of chromosomes in an organism's cells. Sexually reproducing organisms are diploid (having two sets of chromosomes, one from each parent). In humans, only the egg and sperm cells are haploid

Hemolytic disease

Hemolytic disease of the newborn (HDN) is a blood disorder in a fetus or newborn infant. In some infants, it can be fatal.

Hydatidiform mole

Trophoblastic hyperplasia associated with normal gestation, or molar pregnancy. It is characterized by the swelling of the CHORIONIC VILLI and elevated human CHORIONIC GONADOTROPIN. Hydatidiform moles or molar pregnancy may be categorized as complete or partial based on their gross morphology, histopathology, and karyotype.

Implantation

The process by which a blastocyst embeds itself in the uterine endometrium.

In utero

In the uterus, before birth.

Lipid-soluble

A drug's solubility in fatty or oily solutions.

Menses

The shedding of the inner portion of the endometrium out though the vagina; also referred to as menstruation.

Methotrexate

An antineoplastic antimetabolite with immunosuppressant properties. It is an inhibitor of TETRAHYDROFOLATE DEHYDROGENASE and prevents the formation of tetrahydrofolate, necessary for synthesis of thymidylate, an essential component of DNA.

Neoplasia

New abnormal growth of tissue. Malignant neoplasms show a greater degree of anaplasia and have the properties of invasion and metastasis, compared to benign neoplasms.

Persistalsis

A movement, caused by sequential muscle contraction, that pushes the contents of the intestines or other tubular organs in one direction.

Prenatal

Having to do with the time a female is pregnant, before birth occurs; also called antenatal.

Progesterone

A sex hormone important in regulating the reproductive cycle in those with ovaries and the maintenance of pregnancy.

Syncytiotrophoblast

Superficial cells of the trophoblast that fuse to form a multinucleated body that digests endometrial cells to firmly secure the blastocyst to the uterine wall.

Trophoblast

The fluid-filled shell of squamous cells destined to become the chorionic villi, placenta, and associated fetal membranes.

Trophobalstic tumor

Trophoblastic growth, which may be gestational or nongestational in origin. Trophoblastic neoplasia resulting from pregnancy is often described as gestational trophoblastic disease to distinguish it from germ cell tumors which frequently show trophoblastic elements, and from the trophoblastic differentiation which sometimes occurs in a wide variety of epithelial cancers. Gestational trophoblastic growth has several forms, including HYDATIDIFORM MOLE and CHORIOCARCINOMA.

Yolk sac

The membrane associated with primitive circulation to the developing embryo; source of the first blood cells and germ cells and contributes to the umbilical cord structure.

Footnotes

9. Betts, J. Gordon, Kelly A. Young, James A. Wise, Eddie Johnson, Brandon Poe, Dean H. Kruse, Oksana Korol, Jody E. Johnson, Mark Womble, Peter DeSaix. *Anatomy and Physiology*. (2013). Open Stax, 2013 This work is distributed under a CC BY 4.0 license. Available from Open Stax.
10. Betts et al., 2013
11. Betts et al., 2013
12. Betts et al., 2013
13. Betts et al., 2013
14. Betts et al., 2013
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17. Betts et al., 2013
18. Betts et al., 2013
19. Betts et al., 2013
20. Houser M, Kandalaft N, Khati NJ. Ectopic pregnancy: a resident's guide to imaging findings and diagnostic pitfalls. *Emerg Radiol* 2022; 29(1): 161–172
21. Betts et al., 2013
22. Betts et al., 2013
23. Betts et al., 2013
24. Betts et al., 2013
25. Betts et al., 2013

Image Acknolwedgements

Betts, J. Gordon, Kelly A. Young, James A. Wise, Eddie Johnson, Brandon Poe, Dean H. Kruse, Oksana Korol, Jody E. Johnson, Mark Womble, Peter DeSaix. *Anatomy and Physiology*. (2013). Open Stax, 2013 This work is distributed under a CC BY 4.0 license. Available from Open Stax.

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4.3: Infertility and Assisted Reproduction

4.3.1 Overview

Infertility is a term used to describe the inability of a couple to get pregnant or the inability of a woman to carry a pregnancy to term. Infertility is defined clinically as not being able to achieve pregnancy after 1 year of having regular, unprotected intercourse, or after 6 months if the woman is older than 35 years of age.

Many different medical conditions and other factors can contribute to fertility problems, and an individual case may have a single cause, several causes, or—in some cases—no identifiable cause.

About 9% of men and about 11% of women of reproductive age in the United States have experienced fertility problems.[28]

- In one-third of infertile couples, the problem is with the man.
- In one-third of infertile couples, the problem can't be identified or is with both the man and woman.
- In one-third of infertile couples, the problem is with the woman.

Infertility means not being able to become pregnant after a year of trying. If a woman can get pregnant but keeps having miscarriages or stillbirths, that's also called infertility. Infertility is fairly common. After one year of having unprotected sex, about 15% of couples are unable to get pregnant. About a third of the time, infertility can be traced to the woman. In another third of cases, it is because of the man. The rest of the time, infertility is due to both partners, or no cause can be found.[29]

Fertility declines with age in both men and women, but the effects of age are much greater in women. In their 30s, women's chances of conception decrease from 25%–30% in their 20s or early 30s to about 20% in their 40s. In their early 30s, women are about half as fertile as they are in their early 20s, and their chance of conception declines significantly after age 35.[30] Male fertility also declines with age, but more gradually.

4.3.2 Treatments for Infertility

Before treatment, a fertility evaluation is used to confirm that all essential processes are functioning by confirming ovulation, ovarian reserve, the structure of the uterus and fallopian tubes, and semen analysis. Based on the results of testing the three major fertility treatments, also referred to as Assisted Reproductive Technologies (ART) can be used separately or in combination: ovulation, induction, **intrauterine insemination** (IUI) and in vitro fertilization (IVF).[31]

4.3.2.1 In Vitro Fertilization

IVF, which stands for **in vitro fertilization**, is an assisted reproductive technology. In vitro, which in Latin translates to “in glass,” refers to a procedure that takes place outside of the body. There are many different indications for IVF. The procedure is used frequently in supporting LGBTQ people, people using surrogates/gestational carriers, and people who have difficulties reproducing. For example, a person may produce healthy eggs, but the eggs cannot reach the uterus because the uterine tubes are blocked or otherwise compromised. A person may have a low sperm count, low sperm motility, sperm with an unusually high percentage of morphological abnormalities, or sperm that are incapable of penetrating the zona pellucida of an egg.[32]

A typical IVF procedure begins with egg collection. A normal ovulation cycle produces only one oocyte, but the number can be boosted significantly (to 10–20 oocytes) by administering a short course of **gonadotropins**. The course begins with follicle-stimulating hormone (FSH) analogs, which support the development of multiple follicles, and ends with a **luteinizing hormone** (LH) analog that triggers ovulation. Right before the ova would be released from the ovary, they are harvested using ultrasound-guided oocyte

retrieval. In this procedure, ultrasound allows a physician to visualize mature follicles. The ova are aspirated (sucked out) using a syringe.[33]

In parallel, sperm are obtained from the male partner or from a sperm bank. The sperm are prepared by washing to remove seminal fluid because seminal fluid contains a peptide, FPP (or, fertilization promoting peptide), that—in high concentrations—prevents capacitation of the sperm. The sperm sample is also concentrated, to increase the sperm count per milliliter.[34] If there are severe problems with the sperm—for example, the count is exceedingly low, or the sperm are completely nonmotile, or incapable of binding to or penetrating the zona pellucida—a sperm can be injected into an egg. This is called intracytoplasmic sperm injection (ICSI).[34]

The embryos are then incubated until they either reach the eight-cell stage or the blastocyst stage. In the United States, fertilized eggs are typically cultured to the blastocyst stage because this results in a higher pregnancy rate. Finally, the embryos are transferred to a woman's uterus using a plastic catheter (tube). Figure 4.3.1 illustrates the steps involved in IVF.[35]

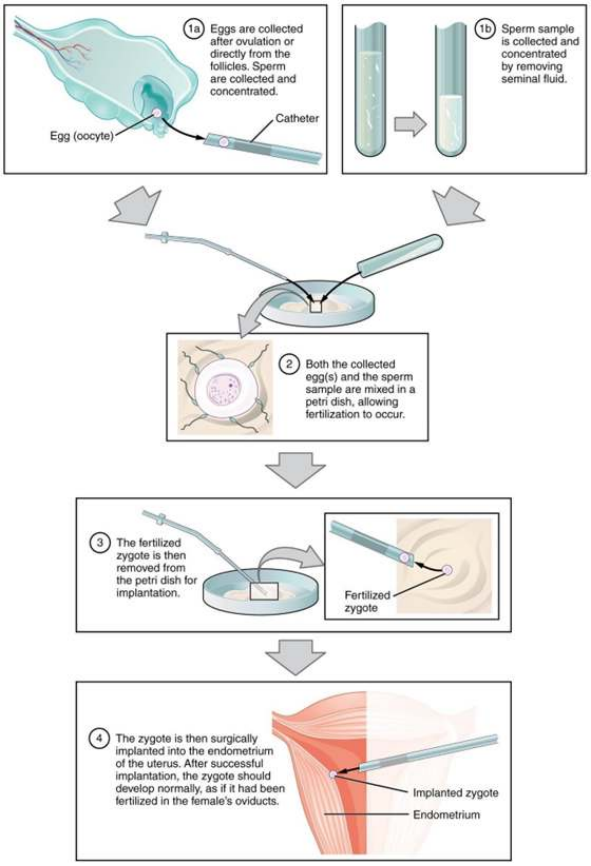
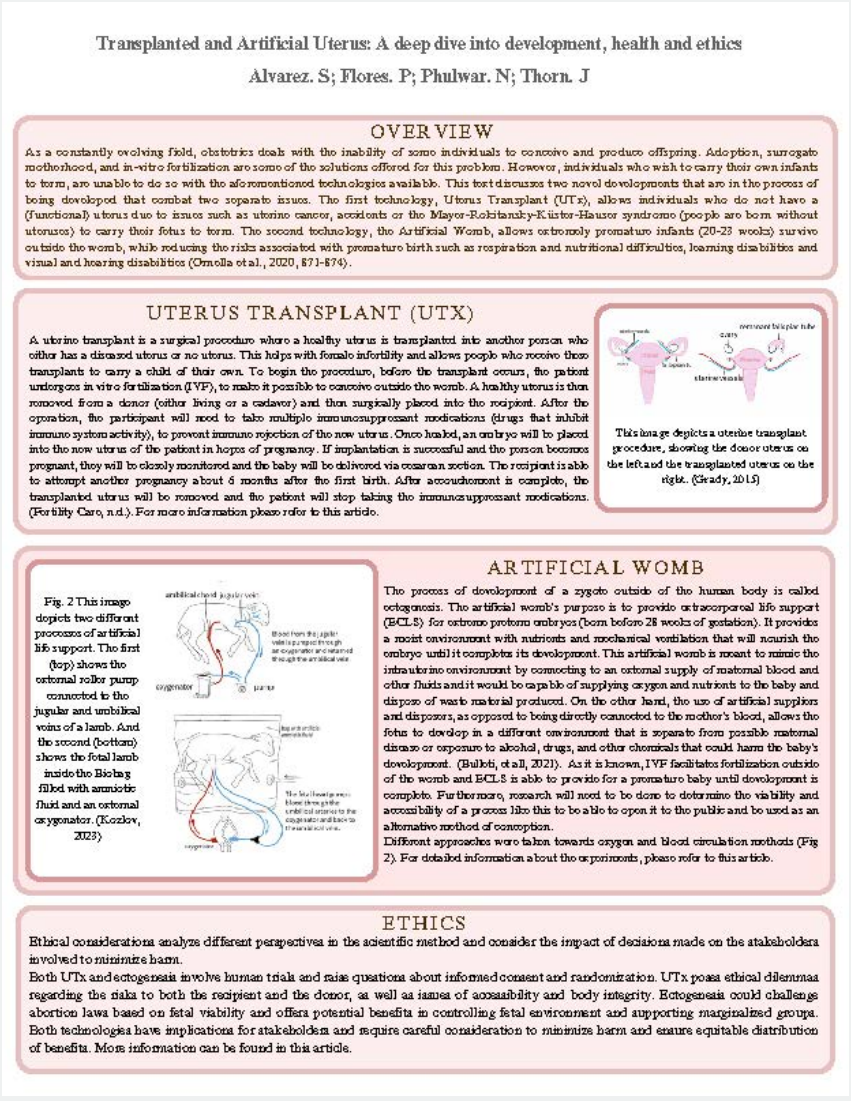


Figure 4.3.1 IVF - In vitro fertilization involves egg collection from the ovaries, fertilization in a petri dish, and the transfer of embryos into the uterus.
Image Source: Betts, J. Gordon, Kelly A. Young, James A. Wise, Eddie Johnson, Brandon Poe, Dean H. Kruse, Oksana Korol, Jody E. Johnson, Mark Womble, Peter DeSaix. *Anatomy and Physiology*. (2013). Open Stax, 2013 This work is distributed under a CC BY 4.0 license. Available from Open Stax.

IVF is a relatively new and still-evolving technology, and until recently it was necessary to transfer multiple embryos to achieve a good chance of a pregnancy. Today, however, transferred embryos are much more likely to implant successfully, so countries that regulate the IVF industry cap the number of embryos that can be transferred per cycle at two. This reduces the risk of multiple-birth pregnancies.The rate of success for

IVF is correlated with the age of the gestational carrier (which may be the child's mother or a surrogate). More than 40% of females under 35 succeed in giving birth following IVF, but the rate drops to a little over 10%t in females over 40.[36]

Student Contribution



Transplanted and Artificial Uterus: A deep dive into development, health and ethics

Alvarez. S; Flores. P; Phulwar. N; Thorn. J

OVERVIEW

As a constantly evolving field, obstetrics deals with the inability of some individuals to conceive and produce offspring. Adoption, surrogate motherhood, and in-vitro fertilization are some of the solutions offered for this problem. However, individuals who wish to carry their own infants to term, are unable to do so with the aforementioned technologies available. This text discusses two novel developments that are in the process of being developed that combat two separate issues. The first technology, Uterus Transplant (UTx), allows individuals who do not have a (functional) uterus due to issues such as uterine cancer, accidents or the Mayer-Rokitansky-Küster-Hauser syndrome (people are born without uteruses) to carry their fetus to term. The second technology, the Artificial Womb, allows extremely premature infants (20-23 weeks) survive outside the womb, while reducing the risks associated with premature birth such as respiration and nutritional difficulties, learning disabilities and visual and hearing disabilities (Ornella et al., 2020, 871-874).

UTERUS TRANSPLANT (UTX)

A uterine transplant is a surgical procedure where a healthy uterus is transplanted into another person who either has a diseased uterus or no uterus. This helps with female infertility and allows people who receive these transplants to carry a child of their own. To begin the procedure, before the transplant occurs, the patient undergoes in vitro fertilization (IVF), to make it possible to conceive outside the womb. A healthy uterus is then removed from a donor (either living or a cadaver) and then surgically placed into the recipient. After the operation, the participant will need to take multiple immunosuppressant medications (drugs that inhibit immune system activity), to prevent immune rejection of the new uterus. Once healed, an embryo will be placed into the new uterus of the patient in hopes of pregnancy. If implantation is successful and the person becomes pregnant, they will be closely monitored and the baby will be delivered via cesarean section. The recipient is able to attempt another pregnancy about 6 months after the first birth. After accouchement is complete, the transplanted uterus will be removed and the patient will stop taking the immunosuppressant medications. (Fertility Care, n.d.). For more information please refer to this article.

This image depicts a uterine transplant procedure, showing the donor uterus on the left and the transplanted uterus on the right. (Grady, 2015)

Fig. 2 This image depicts two different processes of artificial life support. The first (top) shows the external roller pump connected to the jugular and umbilical veins of a lamb. And the second (bottom) shows the fetal lamb inside the Biobag filled with amniotic fluid and an external oxygenator. (Kozlov, 2023)

ARTIFICIAL WOMB

The process of development of a zygote outside of the human body is called ectogenesis. The artificial womb's purpose is to provide extracorporeal life support (ECLS) for extreme preterm embryos (born before 28 weeks of gestation). It provides a moist environment with nutrients and mechanical ventilation that will nourish the embryo until it completes its development. This artificial womb is meant to mimic the intrauterine environment by connecting to an external supply of maternal blood and other fluids and it would be capable of supplying oxygen and nutrients to the baby and dispose of waste material produced. On the other hand, the use of artificial suppliers and disposers, as opposed to being directly connected to the mother's blood, allows the fetus to develop in a different environment that is separate from possible maternal disease or exposure to alcohol, drugs, and other chemicals that could harm the baby's development. (Bulleti, et all, 2021). As it is known, IVF facilitates fertilization outside of the womb and ECLS is able to provide for a premature baby until development is complete. Furthermore, research will need to be done to determine the viability and accessibility of a process like this to be able to open it to the public and be used as an alternative method of conception.

Different approaches were taken towards oxygen and blood circulation methods (Fig 2). For detailed information about the experiments, please refer to this article.

ETHICS

Ethical considerations analyze different perspectives in the scientific method and consider the impact of decisions made on the stakeholders involved to minimize harm.

Both UTx and ectogenesis involve human trials and raise questions about informed consent and randomization. UTx poses ethical dilemmas regarding the risks to both the recipient and the donor, as well as issues of accessibility and body integrity. Ectogenesis could challenge abortion laws based on fetal viability and offers potential benefits in controlling fetal environment and supporting marginalized groups. Both technologies have implications for stakeholders and require careful consideration to minimize harm and ensure equitable distribution of benefits. More information can be found in this article.

PDF of above summary

Full text of article *Transplanted and Artifical Uterus: A deep dive into development, health and ethics* can be found in *Chapter 11.4: Student Contributions.*

4.3.3 Genetic Testing

Fetal or prenatal genetic testing provides parents the opportunity to know the genetic makeup of an embryo or fetus in utero. Typically, this type of genetic testing is used to identify genetic disorders. With this knowledge and the help of genetic counselors, parents can prepare in advance for treatment of the child after birth or in some cases choose to seek an abortion.

Fetal genetic testing became possible once the number of chromosomes in a human cell was identified (46 chromosomes)[37], and after a means to safely collect fetal cells prenatally, **amniocentesis**, was

developed.[38]. Initially, fetal genetic testing focused on the determination of chromosome number and structure including the chromosomal the abnormality **Trisomy 21/Down syndrome**.

4.3.3.1 Down Syndrome Example

The following is courtesy of the Eunice Kennedy Shriver National Institute of Child Health and Human Development

Down syndrome (Trisomy 21) is a set of cognitive and physical symptoms that result from having an extra chromosome 21 or an extra piece of that chromosome. It is the most common chromosomal cause of mild to moderate intellectual disabilities. People with Down syndrome also have some distinct physical features, such as a flat-looking face, and they are at risk for a number of other health conditions such as Alzheimer's disease/dementia, autism, **cataracts**, **celiac disease**, congenital heart disease, and diabetes.

Health care providers can check for Down syndrome during pregnancy or after a child is born. There are two types of tests for Down syndrome during pregnancy, one is a prenatal screening test. This test can show an increased likelihood that a fetus has Down syndrome, but it cannot determine Down syndrome is definitely present. If a screening test shows an increased likelihood, a diagnostic test can be ordered. A prenatal diagnostic test can determine with certainty that Down syndrome is present. Diagnostic tests carry a slightly greater risk to the fetus than do screening tests. The American Congress of Obstetricians and Gynecologists (ACOG) recommends that all pregnant individuals be offered a Down syndrome screening test.[39]

There are several options for Down syndrome prenatal screening. These include:

- A blood test and an ultrasound test during the first trimester of pregnancy. This is the most accepted approach for screening during the first trimester. A blood test enables a health care provider to check for "markers," such as certain proteins, in the pregnant parent's blood that suggest an increased likelihood of Down syndrome.[40] Then the health care provider does an ultrasound test, which uses high-frequency sound waves to create images. An ultrasound can detect fluid at the back of a fetus's neck, which sometimes indicates Down syndrome. The ultrasound test is called measurement of **nuchal translucency**. During the first trimester, this combined method results in more effective or comparable detection rates than methods used during the second trimester.[41]
- A blood test during the second trimester of pregnancy. As in the first trimester, a blood test enables a health care provider to check for markers in the mother's blood. A triple screen looks for levels of three different markers; a quadruple screen looks for levels of four different markers.[42]
- A combined test (sometimes called an integrated test). This approach uses both a blood test and an ultrasound during the first trimester as well as a second-trimester blood test. Health care providers then combine all these results to produce one Down syndrome risk rating.[43]
- If an individual is pregnant with twins or triplets, a blood test will not be as reliable because the substances from a Down syndrome fetus may be harder to detect.[44]

If a screening test suggests the likelihood of Down syndrome, a diagnostic test can be performed. ACOG recommends that pregnant individuals of all ages be given the option of skipping the screening test and getting a diagnostic test first. Until recently, only women over age 35 and other at-risk women were offered this option because diagnostic tests carry a slight risk of miscarriage.[45] Before having diagnostic testing, a pregnant individual and their family may want to meet with a genetic counselor to discuss their family history and the risks and benefits of testing in their specific situation.

Diagnostic testing for Down syndrome involves removing a sample of genetic material. After it is removed, the sample is checked for extra material from chromosome 21, which may indicate that a fetus has Down syndrome. Parents usually get the results of the test a week or two later. The following procedures are used to extract samples.

- Chorionic villus sampling (CVS). A health care provider takes a sample of cells from a part of the placenta and then tests the sample for the extra chromosome. This test is done between weeks 9 and 11 of pregnancy.
- Amniocentesis. A health care provider takes a sample of amniotic fluid, which is then tested for the extra chromosome. This test cannot be done until week 14 to 18 of the pregnancy.
- Percutaneous umbilical blood sampling (PUBS). A health care provider takes a sample of fetal blood in the umbilical cord through the uterus. The blood is then tested for the extra chromosome. PUBS is the most accurate diagnostic method and can confirm the results of CVS or amniocentesis. However, PUBS cannot be performed until later in the pregnancy, during weeks 18 to 22.[46]

Prenatal diagnostic testing does involve some risk to the mother and fetus, including a slight risk of miscarriage.[47]

A pregnant individual who is at risk for having an infant with Down syndrome also can have a chromosomal test using their blood. A pregnant individual's blood carries DNA from the fetus, which may show extra chromosome 21 material.[48] A more invasive test then would usually confirm the blood test.

Watch this video

Video 4.4 - Understanding your fetal ultrasound
Source: YouTube

Another approach to diagnosis is used in conjunction with in vitro fertilization. Preimplantation genetic diagnosis (PGD) allows clinicians to detect chromosome imbalances or other genetic conditions in a fertilized egg before it is implanted into the uterus. This technique is useful mostly for couples who are at risk of passing on a variety of genetic conditions, including X-linked disorders, as well as couples who have suffered repeated spontaneous pregnancy losses, sub-fertile couples, or those at risk for single-gene disorders.

Those interested in PGD should have genetic counseling and should consider close monitoring and additional testing during their pregnancies, given some increased risk of chromosomal abnormalities arising secondary to the **in vitro fertilization** process.[49]

A diagnosis of Down syndrome after birth is often based initially on physical signs of the syndrome. But because individuals with Down syndrome may not have these symptoms, and because many of these symptoms are common in the general population, the health care provider will take a sample of the baby's blood to confirm the diagnosis. The blood sample is analyzed to determine the number of the baby's chromosomes.[50]

For more information

More information about prenatal genetic screening can be found online in *StatPearls - Prenatal Genetic Screening.*

Develop a Treatment Plan 4.3.1

In the last hundred years, there have been multiple advancements in technology to treat infertility, including the ability to freeze sperm (1953), IVF (1978), the use of donor eggs (1983), the ability to freeze embryos (1984), preimplantation genetic testing (1990), **intracytoplasmic sperm injection** (1992), and the ability to freeze (vitrify) eggs (1999).

Describe how these technologies could be used to help otherwise infertile couples have a child. Specifically consider (1) an older man and an older woman who are infertile, (2) individuals with uterine or other health issues (hint: gestational surrogacy), (3) same sex females &/or pre-transition trans men and (4) same sex males.

Birth Control Choices

Your Birth Control Choices

Method	How to Use	Impact on Bleeding	Things to Know	How well does it work?*
External Condom 	• Use a new condom each time you have sex • Use a polyurethane condom if allergic to latex	None	• Can buy at many stores • Can put on as part of sex play/foreplay • Can help prevent early ejaculation • Can be used for oral, vaginal, and anal sex • Protects against HIV and other STIs • Can decrease penile sensation • Can cause loss of erection • Can break or slip off • Does not need a prescription	87%
Internal Condom 	• Use a new condom each time you have sex • Use extra lubrication as needed	None	• Can put in as part of sex play/foreplay • Can be used for anal and vaginal sex • May increase vaginal/anal pleasure • Good for people with latex allergy • Protects against HIV and other STIs • Can decrease penile sensation • May be noisy • May be hard to insert • May slip out of place during sex • May require a prescription from your health care provider	79%
Diaphragm Caya® and Milex® 	• Put in vagina each time you have sex • Use with spermicide every time	None	• Can last several years • Costs very little to use • May protect against some infections, but not HIV • Using spermicide may raise the risk of getting HIV • Should not be used with vaginal bleeding or infection • Raises risk of bladder infection	83%
Emergency Contraception Pills Progestin EC (Plan B® One-Step and others) and ulipristal acetate (ella®) 	• Works best the sooner you take it after unprotected sex • You can take EC up to 5 days after unprotected sex • If pack contains 2 pills, take both at once	• Your next monthly bleeding may come early or late • May cause spotting	• Available at pharmacies, health centers, or health care providers: call ahead to see if they have it • People of any age can get progestin EC without a prescription • May cause stomach upset or nausea • Progestin EC does not interact with testosterone, but we don't know whether Ulipristal acetate EC does or not • Ulipristal acetate EC requires a prescription • May cost a lot • Ulipristal acetate EC works better than progestin EC if your body mass index (BMI) is over 26. • Ulipristal acetate EC works better than progestin EC 3-5 days after sex	58 - 94%

*Typical Use

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Method	How to Use	Impact on Bleeding	Things to Know	How well does it work?*
Fertility Awareness Natural Family Planning 	• Predict fertile days by: taking temperature daily, checking vaginal mucus for changes, and/or keeping a record of your monthly bleeding • It works best if you use more than one of these methods • Avoid sex or use condoms/spermicide on fertile days	• Does not work well if your monthly bleeding is irregular	• Costs little • Can help with avoiding or trying to become pregnant • Use a different method on fertile days • This method requires a lot of effort • Does not require a prescription	85%
The Implant Nexplanon® 	• A clinician places it under the skin of the upper arm • It must be removed by a clinician	• Can cause irregular bleeding and spotting • After 1 year, you may have no monthly bleeding at all • Cramps often improve	• Long lasting (up to 5 years) • You can become pregnant right after it is removed • It may lower the risk of uterine lining cancer, ovarian cancer, and polycystic ovary syndrome (PCOS) • May cause mood changes	> 99%
IUD: Copper ParaGard® 	• Must be placed in uterus by a clinican • Usually removed by a clinician	• May cause cramps and heavy monthly bleeding • May cause spotting between monthly bleeding (if you take testosterone, this may not be an issue)	• May be left in place for up to 12 years • You can become pregnant right after removal • It may lower the risk of uterine lining cancer, ovarian cancer, and polycystic ovary syndrome (PCOS) • Rarely, uterus is injured during placement	> 99%
IUD: Hormonal Liletta®, Mirena®, Skyla® and others 	• Must be placed in uterus by a clinician • Usually removed by a clinician	• May improve cramps • May cause lighter monthly bleeding, spotting, or no monthly bleeding at all	• Uses levonorgestrel, a progestin • May be left in place 3 to 8 years, depending on which IUD you choose • You can become pregnant right after removal • It may lower the risk of uterine lining cancer, ovarian cancer, and polycystic ovary syndrome (PCOS) • Rarely, uterus is injured during placement	> 99%

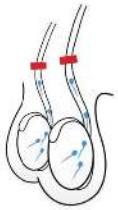
*Typical Use

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Method	How to Use	Impact on Bleeding	Things to Know	How well does it work?*
The Patch Ortho Evra® 	• Apply a new patch once a week for three weeks • No patch in week 4	• Can make monthly bleeding more regular and less painful • May cause spotting the first few months	• You can become pregnant right after stopping patch • Can irritate skin under the patch • This method contains estrogen - it is unclear if estrogen interacts with testosterone	93%
The Pill 	• Take the pill daily	• Often causes spotting, which may last for many months	• Can improve PMS symptoms • Can improve acne • Helps prevent cancer of the ovaries • This method contains estrogen - it is unclear if estrogen interacts with testosterone • You can become pregnant right after stopping the pills • May cause nausea, weight gain, headaches, change in sex drive - some of these can be relieved by changing to a new brand	93%
Progestin-Only Pills 	• Take the pill daily	• Can make monthly bleeding more regular and less painful • May cause spotting the first few months	• You can become pregnant right after stopping the pills • It may lower the risk of uterine lining cancer, ovarian cancer, and polycystic ovary syndrome (PCOS) • May cause depression, hair or skin changes, change in sex drive	93%
The Ring ANNOVERA® Nuvaring® 	• Insert a small ring into the vagina • Monthly Ring: Change ring each month • Yearly Ring: Change ring each year	• Can make monthly bleeding more regular and less painful • May cause spotting the first few months • Can increase vaginal discharge	• There are two types: a monthly ring and a yearly ring. • One size fits all • Private • You can become pregnant right after stopping the ring • This method contains estrogen - it is unclear if estrogen interacts with testosterone	93%
The Shot Depo-Provera® 	• Get a shot every 3 months (13 weeks) • Give yourself the shot or get it in a medical office	• Often decreases monthly bleeding • May cause spotting or no monthly bleeding	• Each shot works for up to 15 weeks • Private for user • Helps prevent cancer of the uterus • May cause weight gain, depression, hair or skin changes, change in sex drive • It may lower the risk of uterine lining cancer, ovarian cancer, and polycystic ovary syndrome (PCOS) • Side effects may last up to 6 months after you stop the shots	96%

*Typical Use

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Method	How to Use	Impact on Bleeding	Things to Know	How well does it work?*
Sterilization: Tubal Methods 	• These methods block or cut the Fallopian tubes • A clinician reaches the tubes through your belly	None	• These methods are permanent and highly effective • Reversal is difficult • The risks include infection, bleeding, pain, and reactions to anesthesia	> 98%
Sterilization: Vasectomy 	• A clinician blocks or cuts the tubes that carry sperm from your testicles	None	• This method is permanent and highly effective • It is more effective, safer, and cheaper than tubal procedures • Can be done in the clinician's office • No general anesthesia needed • Reversal is difficult • Risks include infection, pain, and bleeding • It takes up to 3 months to work	> 99%
Vaginal Acidifying Gel Phexxi® 	• Insert gel each time you have sex	None	• Can be put in as part of sex play/foreplay • Does not have any hormones • Requires a prescription • May irritate vagina, penis • Should not be used with urinary tract infection	86%
Vaginal Spermicide Cream, gel, sponge, foam, inserts, film 	• Insert spermicide each time you have sex.	None	• Can buy at many stores • Can be put in as part of sex play/foreplay • Comes in many forms: cream, gel, sponge, foam, inserts, film • May raise the risk of getting HIV • May irritate vagina, penis • Cream, gel, and foam can be messy • Does not require a prescription	79%
Withdrawal Pull-out	• Pull penis out of vagina before ejaculations (that is, before coming)	None	• Costs nothing • Less pleasure for some • Does not work if penis is not pulled out in time • Must interrupt sex	80%

*Typical Use

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Image Source: Reproductive Health Access Project. "Your Birth Control Choices". ND. This work is distributed under a CC BY 4.0 license. Available from Reproductive Health Access Project.

Glossary Terms

Amniocentesis

A procedure for obtaining amniotic fluid.

Cataract

Partial or complete opacity on or in the lens or capsule of one or both eyes, impairing vision or causing blindness. The many kinds of cataracts are classified by their morphology (size, shape, location) or etiology.

Celiac disease

A malabsorption syndrome that is precipitated by the ingestion of foods containing GLUTEN, such as wheat, rye, and barley. It is characterized by INFLAMMATION of the SMALL INTESTINE, loss of MICROVILLI structure, failed INTESTINAL ABSORPTION, and MALNUTRITION.

In vitro fertilization

A process where the ova is fertilized outside the body and then implanted into the uterus.

Intracytoplasmic sperm injection

An assisted fertilization technique consisting of the microinjection of a single viable sperm into an extracted ovum. It is used principally to overcome low sperm count, low sperm motility, inability of sperm to penetrate the egg, or other conditions related to male infertility.

Intrauterine insemination

infertility treatment that is sometimes referred to as "artificial insemination." During this procedure, specially prepared sperm are inserted into the woman's uterus. This treatment may be recommended for couples in which the male has close to normal sperm count and motility (movement) and the ability to produce a semen sample in the office (or, under some circumstances, at home) and the woman has open, functioning fallopian tubes.

Nuchal translucency measurement

A prenatal ultrasonography measurement of the soft tissue behind the fetal neck. Either the translucent area below the skin in the back of the fetal neck (nuchal translucency) or the distance between occipital bone to the outer skin line (nuchal fold) is measured.

Trisomy 21/Down Syndrome

A chromosome disorder associated either with an extra CHROMOSOME 21 or an effective TRISOMY for chromosome 21. Clinical manifestations include HYPOTONIA, short stature, BRACHYCEPHALY, upslanting palpebral fissures, epicanthus, Brushfield spots on the iris, protruding tongue, small ears, short, broad hands, fifth finger clinodactyly, single transverse palmar crease, and moderate to severe INTELLECTUAL DISABILITY.

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4.4: Testicular Reproductive System

Learning Objectives

- Describe the structure and function of the organs of the testicular reproductive system
- Describe the structure and function of the sperm cell
- Explain the events during spermatogenesis that produce haploid sperm from diploid cells
- Identify the importance of testosterone in reproductive function

4.4.1 Overview

People often use the words "female" and "male" to describe two different concepts: our sense of gender identity, and our biological sex as determined by our X/Y chromosomes, hormones, sex organs, and other physical characteristics. For some people, gender identity is different from biological sex or their sex assigned at birth. In this chapter and the next chapter, "female" and "male" refer to sex only, and the typical reproductive anatomy of XX and XY individuals is discussed.

Unique for its role in reproduction, a **gamete** is a specialized sex cell, which in humans carries 23 chromosomes—one half the number in body cells. In almost all sexually reproducing species, these two haploid cells differ in size; the smaller gamete is called the male gamete and the larger one is called the female gamete. At fertilization, the chromosomes in one male gamete, called a **sperm** (or spermatozoon), combine with the chromosomes in one female gamete, called an **ovum**. The function of the male, or testicular, reproductive system (Figure 4.4.1) is to produce sperm and transfer them to the female reproductive tract. The paired **testes** are a crucial component in this process, as they produce both sperm and **androgens**, the hormones that support male reproductive physiology. In male humans, the most important androgen is **testosterone**. For people with a penis, several accessory organs and ducts aid the process of sperm maturation and transport the sperm and other seminal components to the penis, which may deliver sperm to the female reproductive tract. In this section, we examine each of these different structures and discuss the process of sperm production and transport.[51]

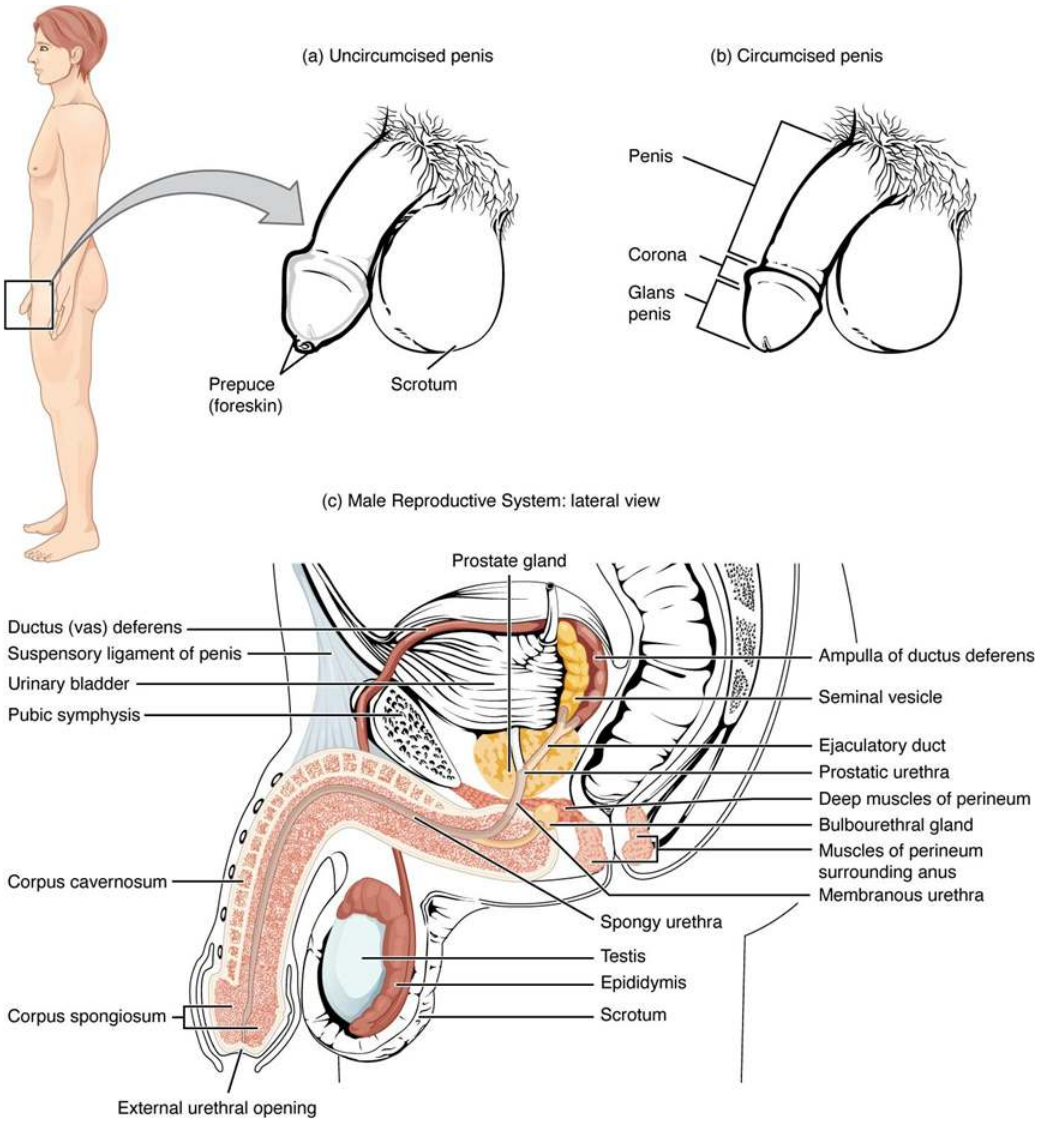


Figure 4.4.1 Testicular Reproductive System - The structures of the testicular reproductive system include the testes, the epididymides, the penis, and the ducts and glands that produce and carry semen. Sperm exit the scrotum through the ductus deferens, which is bundled in the spermatic cord. The seminal vesicles and prostate gland add fluids to the sperm to create semen.

Image Source: Betts, J. Gordon, Kelly A. Young, James A. Wise, Eddie Johnson, Brandon Poe, Dean H. Kruse, Oksana Korol, Jody E. Johnson, Mark Womble, Peter DeSaix. *Anatomy and Physiology*. (2013). Open Stax, 2013 This work is distributed under a CC BY 4.0 license. Available from Open Stax

4.4.2 Scrotum

The testes are located in a skin-covered, highly pigmented, muscular sack called the **scrotum** that extends from the body behind the penis (Figure 4.10). This location is important in sperm production, which occurs within the testes and proceeds more efficiently when the testes are kept 2 to 4°C below core body temperature.

The **dartos muscle** makes up the subcutaneous muscle layer of the scrotum (Figure 4.4.2). It continues internally to make up the scrotal septum, a wall that divides the scrotum into two

compartments, each housing one testis. Descending from the internal oblique muscle of the abdominal wall are the two **cremaster muscles**, which cover each testis like a muscular net. By contracting simultaneously, the dartos and cremaster muscles can elevate the testes in cold weather (or water), moving the testes closer to the body and decreasing the surface area of the scrotum to retain heat. Alternatively, as the environmental temperature increases, the scrotum relaxes, moving the testes farther from the body core and increasing scrotal surface area, which promotes heat loss. Externally, the scrotum has a raised medial thickening on the surface called the **raphae**.[52]

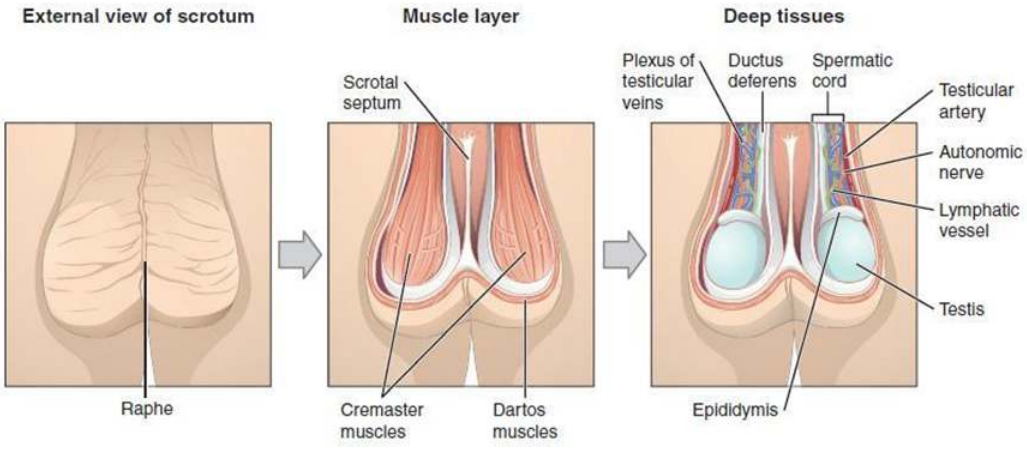


Figure 4.4.2 - This anterior view shows the structures of the scrotum and testes.
Image Source: Betts, J. Gordon, Kelly A. Young, James A. Wise, Eddie Johnson, Brandon Poe, Dean H. Kruse, Oksana Korol, Jody E. Johnson, Mark Womble, Peter DeSaix. *Anatomy and Physiology*. (2013). Open Stax, 2013 This work is distributed under a CC BY 4.0 license. Available from Open Stax.

4.4.3 Testes

The testes (singular = testis) are the male gonads—that is, the male reproductive organs. They produce both sperm and androgens, such as testosterone, and are active throughout the reproductive lifespan.

Paired ovals, adult testes are each approximately 4 to 5 cm in length and are housed within the scrotum (Figure 4.4.3). They are surrounded by two distinct layers of protective connective tissue (Figure 4.12). The outer **tunica vaginalis** is a serous membrane that has both a parietal and a thin visceral layer. Beneath the tunica vaginalis is the **tunica albuginea**, a tough, white, dense connective tissue layer covering the testis itself. Not only does the tunica albuginea cover the outside of the testis, it also invaginates to form septa that divide the testis into 300 to 400 structures called **lobules.** Within the lobules, sperm develop in structures called seminiferous tubules. During the seventh month of the developmental period of a male fetus, each testis moves through the abdominal musculature to descend into the scrotal cavity. This is called the “descent of the testis.” Cryptorchidism is the clinical term used when one or both of the testes fail to descend into the scrotum before birth.[53]

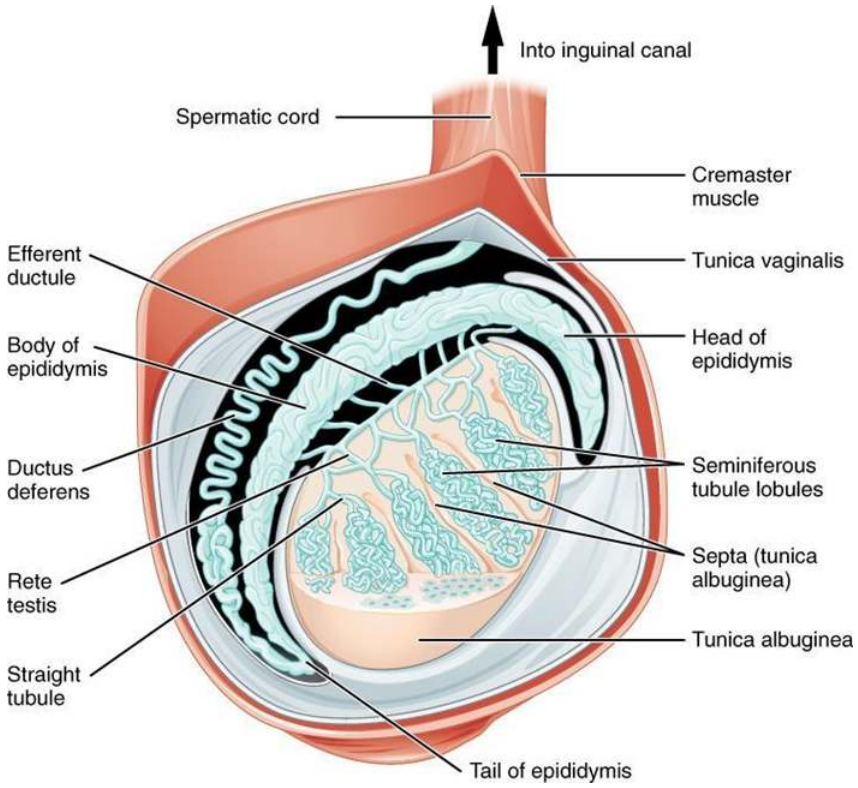


Figure 4.4.3 Anatomy of the Testis - This sagittal view shows the seminiferous tubules, the site of sperm production. Formed sperm are transferred to the epididymis, where they mature. They leave the epididymis during an ejaculation via the ductus deferens.

Image Source: Betts, J. Gordon, Kelly A. Young, James A. Wise, Eddie Johnson, Brandon Poe, Dean H. Kruse, Oksana Korol, Jody E. Johnson, Mark Womble, Peter DeSaix. *Anatomy and Physiology*. (2013). Open Stax, 2013. This work is distributed under a CC BY 4.0 license. Available from Open Stax

The tightly coiled seminiferous tubules form the bulk of each testis. They are composed of developing sperm cells surrounding a **lumen**, the hollow center of the tubule, where formed sperm are released into the duct system of the testis. Specifically, from the lumens of the seminiferous tubules, sperm move into the straight tubules (or tubuli recti), and from there into a fine meshwork of tubules called the rete testes. Sperm leave the rete testes, and the testis itself, through the 15 to 20 efferent ductules that cross the tunica albuginea.[54]

Inside the seminiferous tubules are six different cell types. These include supporting cells called sustentacular cells, as well as five types of developing sperm cells called germ cells. Germ cell development progresses from the basement membrane—at the perimeter of the tubule—toward the lumen. Let's look more closely at these cell types.

4.4.3.1 Sertoli Cells

Surrounding all stages of the developing sperm cells are elongate, branching Sertoli cells. Sertoli cells are a type of supporting cell called a sustentacular cell, or sustentocyte, typically found in epithelial tissue. Sertoli cells secrete signaling molecules that promote sperm production and can control whether germ cells live or die. They extend physically around the

germ cells from the peripheral basement membrane of the seminiferous tubules to the lumen. Tight junctions between these sustentacular cells create the blood–testis barrier, which keeps blood-borne substances from reaching the germ cells and, at the same time, keeps surface antigens on developing germ cells from escaping into the bloodstream and prompting an autoimmune response.

4.4.3.2 Germ Cells

The least mature cells, the spermatogonia (singular = spermatogonium), line the basement membrane inside the tubule. Spermatogonia are the stem cells of the testis, which means that they are still able to differentiate into a variety of different cell types throughout adulthood. Spermatogonia divide to produce primary and secondary spermatocytes, then spermatids, which finally produce formed sperm. The process that begins with spermatogonia and concludes with sperm production is called spermatogenesis.

4.4.3.3 Spermatogenesis

As just noted, spermatogenesis occurs in the seminiferous tubules that form the bulk of each testis (Figure 4.4.3). The process begins at puberty, after which time sperm are produced constantly throughout a male's life. One production cycle, from spermatogonia through formed sperm, takes approximately 64 days. A new cycle starts approximately every 16 days, although this timing is not synchronous across the seminiferous tubules. Sperm counts—the total number of sperm a person produces—slowly decline after age 35, and some studies suggest that smoking can lower sperm counts irrespective of age.[55]

The process of spermatogenesis begins with mitosis of the diploid spermatogonia (Figure 4.4.4). Because these cells are diploid (2*n*), they each have a complete copy of the person's genetic material, or 46 chromosomes. However, mature gametes are haploid (1*n*), containing 23 chromosomes—meaning that daughter cells of spermatogonia must undergo a second cellular division through the process of meiosis.

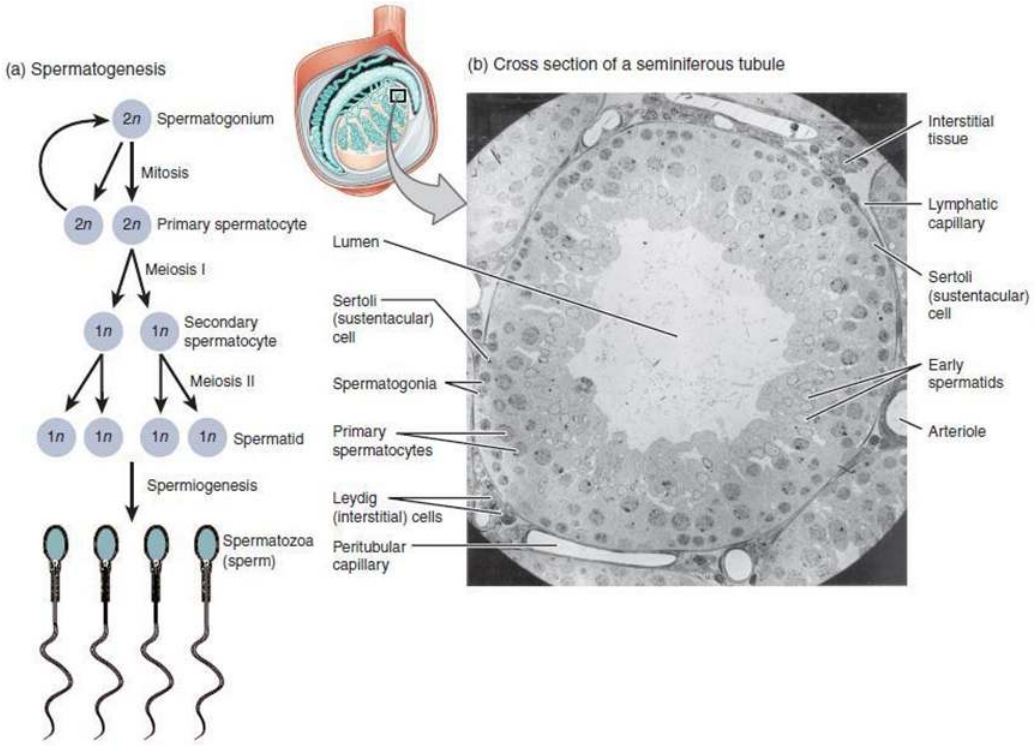


Figure 4.4.4 Spermatogenesis - (a) Mitosis of a spermatogonial stem cell involves a single cell division that results in two identical, diploid daughter cells (spermatogonia to primary spermatocyte). Meiosis has two rounds of cell division: primary spermatocyte to secondary spermatocyte, and then secondary spermatocyte to spermatid. This produces four haploid daughter cells (spermatids). (b) In this electron micrograph of a cross-section of a seminiferous tubule from a rat, the lumen is the light-shaded area in the center of the image. The location of the primary spermatocytes is near the basement membrane, and the early spermatids are approaching the lumen (tissue source: rat). EM × 900. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)

Image Source: Betts, J. Gordon, Kelly A. Young, James A. Wise, Eddie Johnson, Brandon Poe, Dean H. Kruse, Oksana Korol, Jody E. Johnson, Mark Womble, Peter DeSaix. *Anatomy and Physiology*. (2013). Open Stax, 2013 This work is distributed under a CC BY 4.0 license. Available from Open Stax.

Two identical diploid cells result from spermatogonia mitosis. One of these cells remains a spermatogonium, and the other becomes a primary spermatocyte, the next stage in the process of spermatogenesis. As in mitosis, DNA is replicated in a primary spermatocyte, before it undergoes a cell division called meiosis I. During meiosis I, each of the 23 pairs of chromosomes separates. This results in two cells, called secondary spermatocytes, each with only half the number of chromosomes. Now, a second round of cell division (meiosis II) occurs in both secondary spermatocytes. During meiosis II each of the 23 replicated chromosomes divides, similar to what happens during mitosis. Thus, meiosis results in separating the chromosome pairs. This second meiotic division results in a total of four cells with only half of the number of chromosomes. Each of these new cells is a spermatid. Although haploid, early spermatids look very similar to cells in the earlier stages of spermatogenesis, with a round shape, central nucleus, and large amount of cytoplasm. A process called spermiogenesis

transforms these early spermatids, reducing the cytoplasm, and beginning the formation of the parts of a true sperm. The fifth stage of germ cell formation—spermatozoa, or formed sperm—is the end result of this process, which occurs in the portion of the tubule nearest the lumen. Eventually, the sperm are released into the lumen and are moved along a series of ducts in the testis toward a structure called the epididymis for the next step of sperm maturation.

4.4.4 Structure of Formed Sperm

Sperm are smaller than most cells in the body; in fact, the volume of a sperm cell is 85,000 times less than that of the female gamete. Approximately 100 to 300 million sperm are produced each day, whereas females typically ovulate only one **oocyte** per month. As is true for most cells in the body, the structure of sperm cells speaks to their function. Sperm have a distinctive head, mid-piece, and tail region (Figure 4.4.5). The head of the sperm contains the extremely compact haploid nucleus with very little **cytoplasm.** These qualities contribute to the overall small size of the sperm (the head is only 5 μm long). A structure called the acrosome covers most of the head of the sperm cell as a “cap” filled with lysosomal enzymes important for preparing sperm to participate in fertilization. Tightly packed **mitochondria** fill the mid-piece of the sperm. ATP produced by these mitochondria will power the **flagellum**, which extends from the neck and the mid-piece through the tail of the sperm, enabling it to move the entire sperm cell. The central strand of the flagellum, the axial filament, is formed from one centriole inside the maturing sperm cell during the final stages of spermatogenesis.[56]

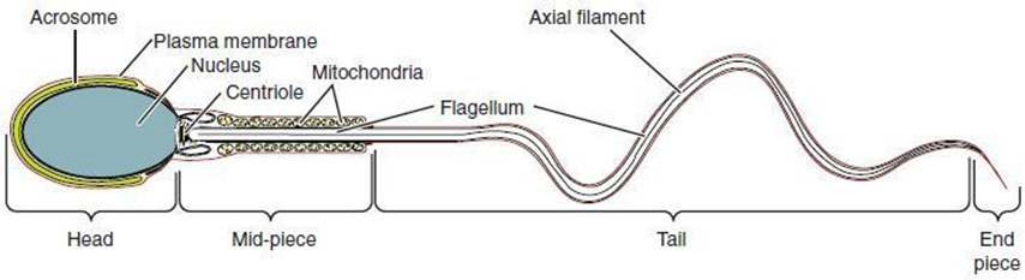


Figure 4.4.5 Structure of Sperm - Sperm cells are divided into a head, containing DNA; a mid-piece, containing mitochondria; and a tail, providing motility. The acrosome is oval and somewhat flattened.
Image Source: Betts, J. Gordon, Kelly A. Young, James A. Wise, Eddie Johnson, Brandon Poe, Dean H. Kruse, Oksana Korol, Jody E. Johnson, Mark Womble, Peter DeSaix. *Anatomy and Physiology*. (2013). Open Stax, 2013 This work is distributed under a CC BY 4.0 license. Available from Open Stax

4.4.5 Sperm Transport

To fertilize an egg without medical intervention, sperm must be moved from the seminiferous tubules in the testes, through the epididymis, and—later during **ejaculation**—along the length of the penis and out into the female reproductive tract.

4.4.5.1 Role of the Epididymis

From the lumen of the seminiferous tubules, the immotile sperm are surrounded by testicular fluid and moved to the epididymis (plural = epididymides), a coiled tube attached to the testis

where newly formed sperm continue to mature (Figure 4.4.4). Though the epididymis does not take up much room in its tightly coiled state, it would be approximately 6 m (20 feet) long if straightened. It takes an average of 12 days for sperm to move through the coils of the epididymis, with the shortest recorded transit time in humans being one day. Sperm enter the head of the epididymis and are moved along predominantly by the contraction of smooth muscles lining the epididymal tubes. As they are moved along the length of the epididymis, the sperm further mature and acquire the ability to move under their own power. Once inside the female reproductive tract, they will use this ability to move independently toward the unfertilized egg. The more mature sperm are then stored in the tail of the epididymis (the final section) until ejaculation occurs.[57]

4.4.5.2 Duct System

During ejaculation, sperm exit the tail of the epididymis and are pushed by smooth muscle contraction to the ductus deferens (also called the **vas deferens**). The ductus deferens is a thick, muscular tube bundled together inside the scrotum with connective tissue, blood vessels, and nerves into a structure called the spermatic cord (Figure 4.4.2 & 4.4.3). Because the ductus deferens is physically accessible within the scrotum, surgical sterilization to interrupt sperm delivery can be performed by cutting and sealing a small section of the ductus (vas) deferens. This procedure is called a vasectomy, and it is an effective form of birth control. Although it may be possible to reverse a vasectomy, clinicians consider the procedure permanent, and advise people to undergo it only if they are certain they no longer wish to have children.

From each epididymis, each ductus deferens extends superiorly into the abdominal cavity through the inguinal canal in the abdominal wall. From here, the ductus deferens continues posteriorly to the pelvic cavity, ending posterior to the bladder where it dilates in a region called the ampulla (meaning “flask”).

Sperm make up only 5 percent of the final volume of semen, the thick, milky fluid that is ejaculated. The bulk of semen is produced by three critical accessory glands of the male reproductive system: the seminal vesicles, the prostate, and the bulbourethral glands.

4.4.5.3 Seminal Vesicles

As sperm pass through the ampulla of the ductus deferens at ejaculation, they mix with fluid from the associated seminal vesicle (Figure 4.4.2). The paired seminal vesicles are glands that contribute approximately 60 percent of the semen volume. Seminal vesicle fluid contains large amounts of fructose, which is used by the sperm mitochondria to generate ATP to allow movement through the female reproductive tract.

The fluid, now containing both sperm and seminal vesicle secretions, next moves into the associated ejaculatory duct, a short structure formed from the ampulla of the ductus deferens and the duct of the seminal vesicle. The paired ejaculatory ducts transport the seminal fluid into the next structure, the prostate gland.[58]

4.4.5.4 Prostate Gland

The centrally located prostate gland sits anterior to the rectum at the base of the bladder surrounding the prostatic urethra (the portion of the urethra that runs within the prostate, (Figure 4.4.6).

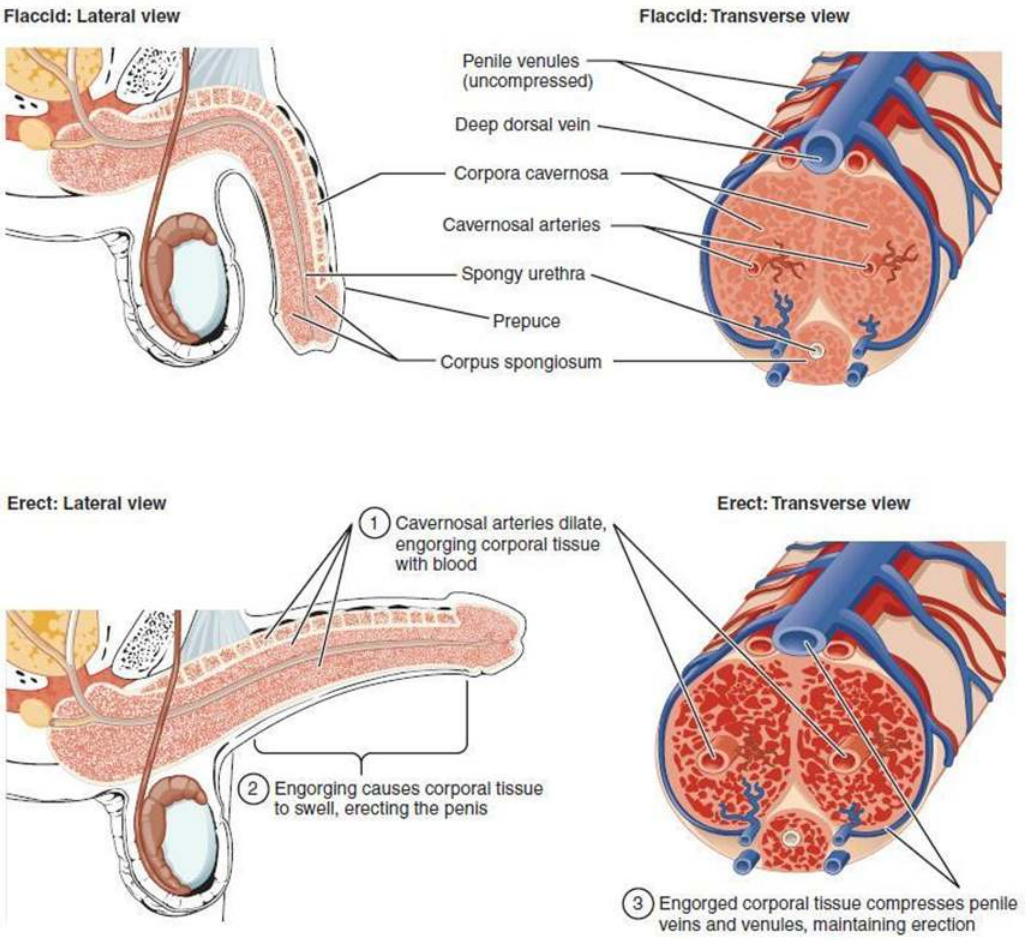


Figure 4.4.6 Cross-Sectional Anatomy of the Penis - Three columns of erectile tissue make up most of the volume of the penis.

Image Source: Betts, J. Gordon, Kelly A. Young, James A. Wise, Eddie Johnson, Brandon Poe, Dean H. Kruse, Oksana Korol, Jody E. Johnson, Mark Womble, Peter DeSaix. *Anatomy and Physiology*. (2013). Open Stax, 2013 This work is distributed under a CC BY 4.0 license. Available from Open Stax

About the size of a walnut, the prostate is formed of both muscular and glandular tissues. It excretes an alkaline, milky fluid to the passing seminal fluid—now called semen—that is critical to first coagulate and then decoagulate the semen following ejaculation. The temporary thickening of semen helps retain it within the female reproductive tract, providing time for sperm to utilize the fructose provided by seminal vesicle secretions. When the semen regains its fluid state, sperm can then pass farther into the female reproductive tract. The prostate normally doubles in size during puberty. At approximately age 25, it gradually begins to enlarge again.

4.4.5.5 Bulbourethral Glands

The final addition to semen is made by two bulbourethral glands (or Cowper's glands) that release a thick, salty fluid that lubricates the end of the urethra and the vagina and helps to clean urine residues from the penile urethra. The fluid from these accessory glands is released after the male becomes sexually aroused, and shortly before the release of the semen. It is, therefore, sometimes called pre-ejaculate. It is important to note that, in addition to the lubricating proteins, it is possible for bulbourethral fluid to pick up sperm already present in the urethra, and therefore it may be able to cause pregnancy.

4.4.6 The Penis

The penis is the male organ of copulation (sexual intercourse). It is flaccid for non-sexual actions, such as urination, and turgid and rod-like with sexual arousal. When erect, the stiffness of the organ allows it to penetrate into the vagina and deposit semen into the female reproductive tract.[59]

The shaft of the penis surrounds the urethra (Figure 4.4.6). The shaft is composed of three column-like chambers of erectile tissue that span the length of the shaft. Each of the two larger lateral chambers is called a corpus cavernosum (plural = corpora cavernosa). Together, these make up the bulk of the penis. The corpus spongiosum, which can be felt as a raised ridge on the erect penis, is a smaller chamber that surrounds the spongy, or penile, urethra. The end of the penis, called the glans penis, has a high concentration of nerve endings, resulting in very sensitive skin that influences the likelihood of ejaculation (Figure 4.4.3). The skin from the shaft extends down over the glans and forms a collar called the prepuce (or foreskin). The foreskin also contains a dense concentration of nerve endings, and both lubricate and protect the sensitive skin of the glans penis. A surgical procedure called circumcision, often performed for religious or social reasons, removes the prepuce, typically within days of birth.

Both sexual arousal and REM sleep (during which dreaming occurs) can induce an erection. Penile erections are the result of vasocongestion, or engorgement of the tissues because of more arterial blood flowing into the penis than is leaving in the veins. During sexual arousal, nitric oxide (NO) is released from nerve endings near blood vessels within the corpora cavernosa and spongiosum. Release of NO activates a signaling pathway that results in relaxation of the smooth muscles that surround the penile arteries, causing them to dilate. This dilation increases the amount of blood that can enter the penis and induces the endothelial cells in the penile arterial walls to also secrete NO and perpetuate the vasodilation. The rapid increase in blood volume fills the erectile chambers, and the increased pressure of the filled chambers compresses the thin-walled penile venules, preventing venous drainage of the penis. The result of this increased blood flow to the penis and reduced blood return from the penis is erection. Depending on the flaccid dimensions of a penis, it can increase in size slightly or greatly during erection, with the average length of an erect penis measuring approximately 15 cm.[60]

4.4.7 Testosterone

Testosterone, an androgen, is a steroid hormone produced by Leydig cells. The alternate term for Leydig cells, interstitial cells, reflects their location between the seminiferous tubules in the testes. In male embryos, testosterone is secreted by Leydig cells by the seventh week of development, with peak concentrations reached in the second trimester. This early release of testosterone results in the anatomical differentiation of the male sexual organs. In childhood, testosterone concentrations are low. They increase during puberty, activating characteristic physical changes and initiating spermatogenesis.

4.4.7.1 Functions of Testosterone

The continued presence of testosterone is necessary to keep the male reproductive system working properly, and Leydig cells produce approximately 6 to 7 mg of testosterone per day. Testicular steroidogenesis (the manufacture of androgens, including testosterone) results in testosterone concentrations that are 100 times higher in the testes than in the circulation. Maintaining these normal concentrations of testosterone promotes spermatogenesis, whereas low levels of testosterone can lead to infertility. In addition to intratesticular secretion, testosterone is also released into the systemic circulation and plays an important role in muscle development, bone growth, the development of secondary sex characteristics, and maintaining libido (sex drive) in both males and females. In females, the ovaries secrete small amounts of testosterone, although most is converted to estradiol. A small amount of testosterone is also secreted by the adrenal glands in both sexes.

The regulation of testosterone concentrations throughout the body is critical for male reproductive function (Figure 4.4.7).[61]

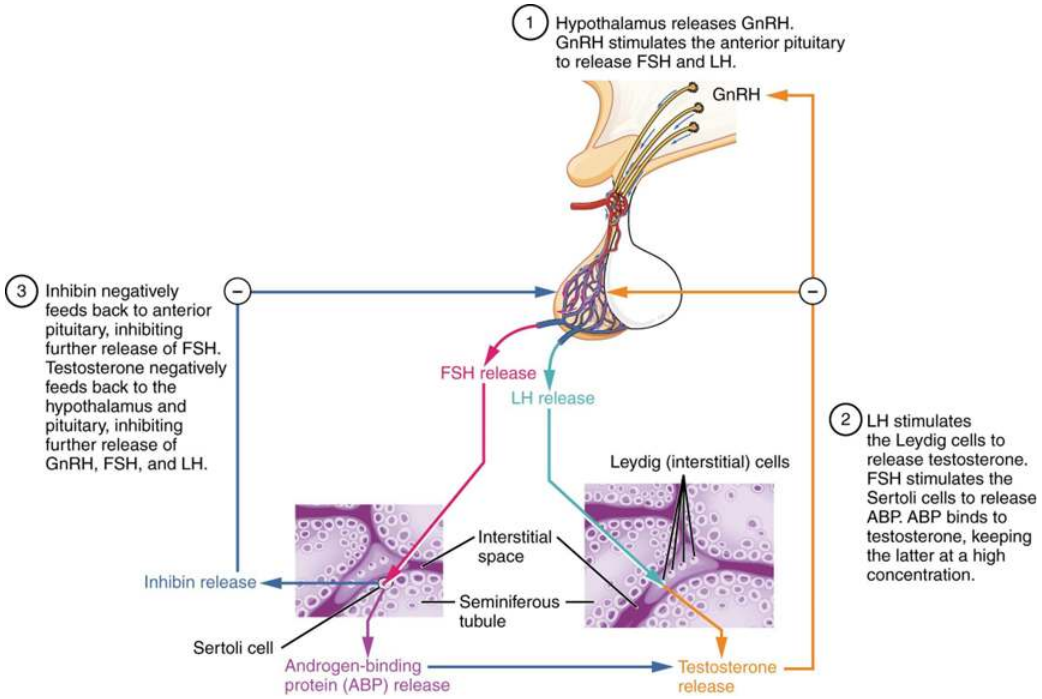


Figure 4.4.7 Regulation of Testosterone Production - The hypothalamus and pituitary gland regulate the production of testosterone and the cells that assist in spermatogenesis. GnRH activates the anterior pituitary to produce LH and FSH, which in turn stimulate Leydig cells and Sertoli cells, respectively. The system is a negative feedback loop because the end products of the pathway, testosterone and inhibin, interact with the activity of GnRH to inhibit their own production.

Image Source: Betts, J. Gordon, Kelly A. Young, James A. Wise, Eddie Johnson, Brandon Poe, Dean H. Kruse, Oksana Korol, Jody E. Johnson, Mark Womble, Peter DeSaix. *Anatomy and Physiology*. (2013). Open Stax, 2013 This work is distributed under a CC BY 4.0 license. Available from Open Stax

The regulation of Leydig cell production of testosterone begins outside of the testes. The hypothalamus and the pituitary gland in the brain integrate external and internal signals to control testosterone synthesis and secretion. The regulation begins in the hypothalamus. Pulsatile release of a hormone called gonadotropin-releasing hormone (GnRH) from the hypothalamus stimulates the endocrine release of hormones from the pituitary gland. Binding of GnRH to its receptors on the anterior pituitary gland stimulates release of the two gonadotropins: luteinizing hormone (LH) and follicle-stimulating hormone (FSH). These two hormones are critical for reproductive function in all humans. In the testes, FSH binds predominantly to the Sertoli cells within the seminiferous tubules to promote spermatogenesis. FSH also stimulates the Sertoli cells to produce hormones called inhibins, which function to inhibit FSH release from the pituitary, thus reducing testosterone secretion. These polypeptide hormones correlate directly with Sertoli cell function and sperm number; inhibin B can be used as a marker of spermatogenic activity. LH binds to receptors on Leydig cells in the testes and upregulates the production of testosterone.[62]

A negative feedback loop predominantly controls the synthesis and secretion of both FSH and LH. Low blood concentrations of testosterone stimulate the hypothalamic release of GnRH. GnRH then stimulates the anterior pituitary to secrete LH into the bloodstream. In the testis, LH binds to LH receptors on Leydig cells and stimulates the release of testosterone. When concentrations of testosterone in the blood reach a critical threshold, testosterone itself will bind to androgen receptors on both the hypothalamus and the anterior pituitary, inhibiting the synthesis and secretion of GnRH and LH, respectively. When the blood concentrations of testosterone once again decline, testosterone no longer interacts with the receptors to the same degree and GnRH and LH are once again secreted, stimulating more testosterone production. This same process occurs with FSH and inhibin to control spermatogenesis.

Student Contribution

Summary for **Male Birth Control Summary**

Amira, Isabel, and Caroline

Male vs. Female

The responsibility of contraception has largely fallen on female partners. Compared to the multitude of female hormonal birth control options, there is currently no hormonal male birth control on the market. This widening disparity in gender equality, equitable views, and double standard in biomedical research on male birth control could be hindering its advancement (ChoGlueck 2022, Jacobstein et al. 2023, Nguyen and Jacobsohn, 2023).

Vasalgel

A non-hormonal male long acting reversible contraction (LARC) in development is Vasalgel. The product is injected into the vas deferens and precipitates to block flow of sperm (Khourdaji et al, 2018). Clinical trials on rabbits and monkeys showed that Vasalgel was effective in preventing pregnancy for up to 2 years, and once it is flushed out of the vas deferens with sodium bicarbonate, sperm can flow again (Colagross-Schouten et al, 2018; Waller et al, 2017). However, further testing and sperm analysis must be done for Vasalgel to be available as a male LARC for the general population.

Testosterone

There are also hormonal methods in development. In clinical trials, administration of testosterone and progestin has shown to effectively suppress spermatogenesis. While most studies are on testosterone injections, research is underway for a self-administered transdermal gel option (Amory et al, 2023). While these hormonal methods have proven to be effective, they are not widely available due to uncomfortable side effects such as acne, mood changes, headaches, and night sweats (Ilani et al, 2011).

Anti-fertility Vaccines

A variety of anti-fertility vaccines have been under development, targeting specific hormones that play a role in gamete production. Talwar and Raghupathy (1989) discussed the developments of a single injection procedure for sterilization or castration of male animals. The injection consists of Bacillus Calmette-Guerin, a vaccine widely used for tuberculosis disease, as it can degenerate the blood-testis barrier and induce the production of anti-sperm antibodies. This leads either to reversible blockage of spermatogenesis or permanent destruction of Leydig cells depending on whether it is injected in uniform concentrations or a single high-concentrated shot, respectively. Success rate of the procedure is promising, showing signs of full effectiveness on
mammals with temporary inflammation at the site of injection being the only side effect (Talwar & Raghupathy 1989). They have also been testing vaccines inducing antibodies against human chorionic gonadotropin, causing degeneration of the tubules as well as Lumen cells. The procedure resulted in decline of testosterone leves, size of testicles and an overall hindrance to spermatogenesis. (Talwar & Raghupathy 1989). Bao et al.(2019) suggests a procedure where four reagents are injected simultaneously and, depending on the ratio of each, could induce “physical clogging of the vas deferens and chemical inhibition of the sperm motility.” The method also promises a short and simple approach to reverse the effects in a procedure that wouldn’t need a clinical setting. This
serum is still undergoing trials, as the study examines further research to be done including “verifying the safety of materials” through more animal experiments and analysis of long term side effects.

Heat-Based Methods

Another effective method being tested is the use of temperature regulation to “reverse” spermatogenesis through germ cell apostasis(Liu, 2010). Since
spermatogenesis is known to take place in specific temperature conditions, where the scortum is lower than the core body temperature, trials showed that increasing testicular temperature or heat exposure would cause germinal epitherlium damage, suppressing the gamete production process as well as the amount of sperm output(Liu, 2010). As mentioned by Kandeel and Swerdloff (1988), depending on the amount of heat, a small amount would damage mainly primary spermatocytes and a larger exposure would destroy spermatids. A side effect recorded was “raising the temperature in the testis to
values above the minimal effective exposure (42 to 43°C in most species) may carry a risk of a permanent testicular injury” (Kandeel & Swerdloff, 1988).

Male Willingness

Surveys taken in the 1970s vs the 1990s show an increase in male willingness to take hormonal contraception (Balswik 1972, Martin et al. 2000). Women’s views similarly reflect this interest in a male birth control pill, with a 2020 survey showing 69.7% in favor of male contraception (Richard et al. 2022). This general support of male birth control suggests further development of a male birth control pill is necessary.

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Full text of this article can be found in Chapter 11.4, Student Contributions.

Glossary Terms

Androgens

Compounds that interact with ANDROGEN RECEPTORS in target tissues to bring about the effects similar to those of TESTOSTERONE. Depending on the target tissues, androgenic effects can be on SEX DIFFERENTIATION; male reproductive organs, SPERMATOGENESIS; secondary male SEX CHARACTERISTICS; LIBIDO; development of muscle mass, strength, and power.

Cremaster muscles

Muscles forming the ABDOMINAL WALL including RECTUS ABDOMINIS; ABDOMINAL OBLIQUE MUSCLES, transversus abdominis, pyramidalis muscles and quadratus abdominis

Cytoplasm

The part of a cell that contains the CYTOSOL and small structures excluding the CELL NUCLEUS; MITOCHONDRIA; and large VACUOLES

Dartos muslce

the scrotal part of the dartos fascia, composed by smooth cells

Ejaculation

The emission of SEMEN to the exterior, resulting from the contraction of muscles surrounding the male internal urogenital ducts

Flagella

A whiplike motility appendage present on the surface cells. Prokaryote flagella are composed of a protein called FLAGELLIN. Bacteria can have a single flagellum, a tuft at one pole, or multiple flagella covering the entire surface. In eukaryotes, flagella are threadlike protoplasmic extensions used to propel flagellates and sperm. Flagella have the same basic structure as CILIA but are longer in proportion to the cell bearing them and present in much smaller numbers

Gamete

haploid reproductive cell that contributes genetic material to form an offspring

Luman

term that describes the cavity within the tubular structure. It usually refers to the space inside digestive, respiratory, and urogenital organs or vessels of the body

Mitochondria

cellular organelles bound by a double lipid bilayer that function primarily in the production of cellular energy (ATP)

Oocyte

A cell that results from the division of the oogonium and undergoes meiosis I at the LH surge and meiosis II at fertilization to become a haploid ovum.

Ovum

A haploid female gamete resulting from completion of meiosis II at fertilization.

Scrotum

The external pouch of skin and muscle that houses the testes.

Sperm

(also, spermatozoon) The male gamete.

Testes

The testes (singular = testis) are the male gonads—that is, the male reproductive organs. They produce both sperm and androgens, such as testosterone, and are active throughout the reproductive lifespan.

Testosterone

A potent androgenic steroid and major product secreted by the LEYDIG CELLS of the TESTIS. Its production is stimulated by LUTEINIZING HORMONE from the PITUITARY GLAND. In turn, testosterone exerts feedback control of the pituitary LH and FSH secretion. Depending on the tissues, testosterone can be further converted to DIHYDROTESTOSTERONE or ESTRADIOL

Tunica albuginea

The fibrous envelope that extends the length of the corpus cavernosum penis and corpus spongiosum penis. It is a bi-layered

Tunica vaginalis

A closed peritoneal sac surrounding the front and sides of the testis and extends upwards over the spermatic cord

Vas deferens

The excretory duct of the testes that carries SPERMATOZOA. It rises from the SCROTUM and joins the SEMINAL VESICLES to form the ejaculatory duct.

Footnotes

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4.5: Glossary

> *To review common anatomical and directional terms, please see* Chapter 1. Anatomy of the Female Reproductive System.

Allantois - An extra-embryonic membranous sac derived from the YOLK SAC of REPTILES; BIRDS; and MAMMALS. It lies between two other extra-embryonic membranes, the AMNION and the CHORION. The allantois serves to store urinary wastes and mediate exchange of gas and nutrients for the developing embryo. [2]

Amniocentesis - A procedure for obtaining amniotic fluid. [6]

Amnion - The innermost membranous sac that surrounds and protects the developing embryo which is bathed in the AMNIOTIC FLUID. Amnion cells are secretory EPITHELIAL CELLS and contribute to the amniotic fluid. [2]

Androgens - Male sex hormones; for example, testosterone. [6]

Barbiturates - A class of chemicals derived from barbituric acid or thiobarbituric acid. Many of these are GABA MODULATORS used as HYPNOTICS AND SEDATIVES, as ANESTHETICS, or as ANTICONVULSANTS. [2]

Cataract - Partial or complete opacity on or in the lens or capsule of one or both eyes, impairing vision or causing blindness. The many kinds of cataract are classified by their morphology (size, shape, location) or etiology. [2]

Celiac Disease - A malabsorption syndrome that is precipitated by the ingestion of foods containing GLUTEN, such as wheat, rye, and barley. It is characterized by INFLAMMATION of the SMALL INTESTINE, loss of MICROVILLI structure, failed INTESTINAL ABSORPTION, and MALNUTRITION. [2]

Choriocarcinoma - A malignant metastatic form of trophoblastic tumors. Unlike the HYDATIDIFORM MOLE, **choriocarcinoma** contains no CHORIONIC VILLI but rather sheets of undifferentiated cytotrophoblasts and syncytiotrophoblasts (TROPHOBLASTS). It is characterized by the large amounts of CHORIONIC GONADOTROPIN produced. DNA analyses can determine tissue origins: placental (fetal) origin or non-placental origin. [2]

Chorionic cavity

Chorionic sac

Chorionic villi - Projections of the chorionic membrane that burrow into the endometrium and develop into the placenta. [3]

Cremaster muscles - Muscles forming the ABDOMINAL WALL including RECTUS ABDOMINIS; ABDOMINAL OBLIQUE MUSCLES, transversus abdominis, pyramidalis muscles and quadratus abdominis. [2]

Cytoplasm - The part of a cell that contains the CYTOSOL and small structures excluding the CELL NUCLEUS; MITOCHONDRIA; and large VACUOLES. [2]

Cytotrophoblast - Cells lining the outside of the BLASTOCYST. After binding to the ENDOMETRIUM, trophoblasts develop into two distinct layers, an inner layer of mononuclear cytotrophoblasts and an outer layer of continuous multinuclear cytoplasm, the syncytiotrophoblasts, which form the early fetal-maternal interface (PLACENTA). [2]

Dartos muscle

Diffusion - The movement of a substance from an area of higher concentration to one of lower concentration [1]

Diploid - A cell containing two matched sets of chromosomes [6]

Ectopic Pregnancy - Implantation of an embryo outside of the uterus. [3]

Ejaculation - The emission of SEMEN to the exterior, resulting from the contraction of muscles surrounding the male internal urogenital ducts. [2]

Endometrium - inner lining of the uterus, part of which builds up during the secretory phase of the menstrual cycle and then sheds with menses. [1]

Facilitated diffusion - diffusion of a substance with the aid of a membrane protein [1]

Flagella - A whiplike motility appendage present on the surface cells. Prokaryote flagella are composed of a protein called FLAGELLIN. Bacteria can have a single flagellum, a tuft at one pole, or multiple flagella covering the entire surface. In eukaryotes, flagella are threadlike protoplasmic extensions used to propel flagellates and sperm. Flagella have the same basic structure as CILIA but are longer in proportion to the cell bearing them and present in much smaller numbers. [2]

Gamete - haploid reproductive cell that contributes genetic material to form an offspring. [5]

Gestational trophoblastic neoplasia - A group of diseases arising from pregnancy that are commonly associated with hyperplasia of trophoblasts (TROPHOBLAST) and markedly elevated human CHORIONIC GONADOTROPIN. They include HYDATIDIFORM MOLE, invasive mole (HYDATIDIFORM MOLE, INVASIVE), placental-site trophoblastic tumor (TROPHOBLASTIC TUMOR, PLACENTAL SITE), and CHORIOCARCINOMA. These neoplasms have varying propensities for invasion and spread. [2]

Glans penis - bulbous end of the penis that contains a large number of nerve endings. [5]

Haploid - the presence of a single set of chromosomes in an organism's cells. Sexually reproducing organisms are diploid (having two sets of chromosomes, one from each parent). In humans, only the egg and sperm cells are haploid. [7]

Hemolytic disease - Hemolytic disease of the newborn (HDN) is a blood disorder in a fetus or newborn infant. In some infants, it can be fatal. [4]

Hydatidiform mole - Trophoblastic hyperplasia associated with normal gestation, or molar pregnancy. It is characterized by the swelling of the CHORIONIC VILLI and elevated human

CHORIONIC GONADOTROPIN. Hydatidiform moles or molar pregnancy may be categorized as complete or partial based on their gross morphology, histopathology, and karyotype. [2]

Implantation - process by which a blastocyst embeds itself in the uterine endometrium. [3]

In utero

In vitro fertilization - A process where the ova is fertilized outside the body and then implanted into the uterus. [6]

Intracytoplasmic sperm injection - An assisted fertilization technique consisting of the microinjection of a single viable sperm into an extracted ovum. It is used principally to overcome low sperm count, low sperm motility, inability of sperm to penetrate the egg, or other conditions related to male infertility. [2]

Intrauterine insemination - infertility treatment that is sometimes referred to as "artificial insemination." During this procedure, specially prepared sperm are inserted into the woman's uterus. This treatment may be recommended for couples in which the male has close to normal sperm count and motility (movement) and the ability to produce a semen sample in the office (or, under some circumstances, at home) and the woman has open, functioning fallopian tubes. [8]

Lobules

Lipid-soluble

Lumen -

Menses - shedding of the inner portion of the endometrium out though the vagina; also referred to as menstruation. [1]

Methotrexate - An antineoplastic antimetabolite with immunosuppressant properties. It is an inhibitor of TETRAHYDROFOLATE DEHYDROGENASE and prevents the formation of tetrahydrofolate, necessary for synthesis of thymidylate, an essential component of DNA. [2]

Mitochondria - cellular organelles bound by a double lipid bilayer that function primarily in the production of cellular energy (ATP). [1]

Motility - The movement of cells from one location to another. Distinguish from CYTOKINESIS which is the process of dividing the CYTOPLASM of a cell. [2]

Mucopolysaccharides - Mucopolysaccharides are long chains of sugar molecules that are found throughout the body, often in mucus and in fluid around the joints. They are more commonly called glycosaminoglycans. [4]

Neoplasia - New abnormal growth of tissue. Malignant **neoplasms** show a greater degree of anaplasia and have the properties of invasion and metastasis, compared to benign **neoplasms**. [2]

Nuchal Translucency Measurement - A prenatal ultrasonography measurement of the soft tissue behind the fetal neck. Either the translucent area below the skin in the back of the fetal neck (nuchal translucency) or the distance between occipital bone to the outer skin line (nuchal fold) is measured. [2]

Oocyte - A cell that results from the division of the oogonium and undergoes meiosis I at the LH surge and meiosis II at fertilization to become a haploid ovum. [1]

Oogenesis -The process by which oogonia divide by mitosis to primary oocytes, which undergo meiosis to produce the secondary oocyte and, upon fertilization, the ovum. [1]

Ovum - A haploid female gamete resulting from completion of meiosis II at fertilization. [1]

paired testes

Persistalsis - A movement, caused by sequential muscle contraction, that pushes the contents of the intestines or other tubular organs in one direction. [2]

Phagocytic uterine leukocytes

Chandra, A., & Copen, C. E. (2013, August 14). *Infertility and impaired fecundity in the United States, 1982–2010 ...* cdc.gov. Retrieved February 7, 2018, from https://www.cdc.gov/nchs/data/nhsr/nhsr067.pdf

Prenatal -having to do with the time a female is pregnant, before birth occurs; also called antenatal [6]

Progesterone - sex hormone important in regulating the reproductive cycle in those with ovaries and the maintenance of pregnancy. [1]

Pronuclei

Raphae

Scrotum - external pouch of skin and muscle that houses the testes. [5]

Scrotal septum

Secrete

Sperm - (also, spermatozoon) male gamete. [5]

Spermatozoa - (singular = spermatogonium) diploid precursor cells that become sperm **[1]**

Syncytiotrophoblast - superficial cells of the trophoblast that fuse to form a multinucleated body that digests endometrial cells to firmly secure the blastocyst to the uterine wall. [3]

Testes - The testes (singular = testis) are the male gonads—that is, the male reproductive organs. They produce both sperm and androgens, such as testosterone, and are active throughout the reproductive lifespan. [5]

Testosterone - A potent androgenic steroid and major product secreted by the LEYDIG CELLS of the TESTIS. Its production is stimulated by LUTEINIZING HORMONE from the PITUITARY GLAND. In turn, testosterone exerts feedback control of the pituitary LH and FSH secretion.

Depending on the tissues, testosterone can be further converted to DIHYDROTESTOSTERONE or ESTRADIOL. [2]

Trisomy 21/Down Syndrome - A chromosome disorder associated either with an extra CHROMOSOME 21 or an effective TRISOMY for chromosome 21. Clinical manifestations include HYPOTONIA, short stature, BRACHYCEPHALY, upslanting palpebral fissures, epicanthus, Brushfield spots on the iris, protruding tongue, small ears, short, broad hands, fifth finger clinodactyly, single transverse palmar crease, and moderate to severe INTELLECTUAL DISABILITY. [2]

Trophoblast - fluid-filled shell of squamous cells destined to become the chorionic villi, placenta, and associated fetal membranes. [3]

Trophobalstic tumor - Trophoblastic growth, which may be gestational or nongestational in origin. Trophoblastic neoplasia resulting from pregnancy is often described as gestational trophoblastic disease to distinguish it from germ cell tumors which frequently show trophoblastic elements, and from the trophoblastic differentiation which sometimes occurs in a wide variety of epithelial cancers. Gestational trophoblastic growth has several forms, including HYDATIDIFORM MOLE and CHORIOCARCINOMA. [2]

Tunica albuginea

Tunica vaginalis

Uterine tubes - (also, fallopian tubes or oviducts) ducts that facilitate transport of an ovulated oocyte to the uterus. [1]

Vas deferens - The excretory duct of the testes that carries SPERMATOZOA. It rises from the SCROTUM and joins the SEMINAL VESICLES to form the ejaculatory duct. [2]

Yolk sac - membrane associated with primitive circulation to the developing embryo; source of the first blood cells and germ cells and contributes to the umbilical cord structure. [3]

Zona pellucida - A tough transparent membrane surrounding the OVUM. It is penetrated by the sperm during FERTILIZATION. [2]

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CHAPTER OVERVIEW

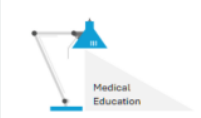
5: Pregnancy and Birth

5.1: Fetal Development of the Heart
5.2: Pregnancy and Labor
5.3: Changes in the Neonate
5.4: Lactation
5.5: Disorders of Pregnancy
5.6: Pregnancy that does not result in a Child
5.7: Glossary

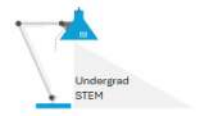
Author: Judy Thorn, Ph.D.

About this Chapter

The content of this chapter is appropriate for, or easily adapted for the following audiences:







Learning Objectives

By the end of this chapter, learners will be able to

- Differentiate between the embryonic period and the fetal period
- Describe the fetal circulatory system and explain the role of the shunts
- Trace the development of a fetus from the end of the embryonic period to birth
- Explain how estrogen, progesterone, and hCG are involved in maintaining pregnancy
- List the contributors to weight gain during pregnancy
- Describe the major changes to the maternal digestive, circulatory, and integumentary systems during pregnancy
- Summarize the events leading to labor
- Identify and describe each of the three stages of childbirth
- Discuss the importance of an infant's first breath
- Explain the closing of the cardiac shunts
- Describe thermoregulation in the newborn
- Summarize the importance of intestinal flora in the newborn
- Describe the structure of the lactating breast
- Summarize the process of lactation
- Explain how the composition of breast milk changes during the first days of lactation and in the course of a single feeding
- Identify emergencies associated with miscarriages

- Outline typical history, physical, and laboratory evaluation of miscarriages
- Summarize the management options available for miscarriages
- Describe interprofessional team strategies for improving care coordination and communication to patients undergoing miscarriage

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5.1: Fetal Development of the Heart

Learning Objectives

By the end of this section, learners will be able to

- Differentiate between the embryonic period and the fetal period
- Describe the fetal circulatory system and explain the role of the shunts
- Trace the development of a fetus from the end of the embryonic period to birth

A developing human is called a fetus from the ninth week of **gestation** until birth. This 30-week period of development is marked by continued cell growth and differentiation, which fully develop the structures and functions of the immature organ systems formed during the embryonic period. The completion of fetal development results in a newborn who, although still immature in many ways, is capable of survival outside the uterus.[1]

5.1.1 The Fetal Circulatory System

When the heart first forms in the embryo, it exists as two parallel tubes derived from **mesoderm** and lined with **endothelium**, which then fuse together. As the embryo develops into a fetus, the tube-shaped heart folds and further differentiates into the four chambers present in a mature heart. Unlike a mature cardiovascular system, however, the fetal cardiovascular system also includes circulatory shortcuts, or shunts. A **shunt** is an anatomical (or sometimes surgical) diversion that allows blood flow to bypass immature organs such as the lungs and liver until childbirth.[2]

The **placenta** provides the fetus with necessary oxygen and nutrients via the umbilical vein. (Remember that veins carry blood toward the heart. In this case, the blood flowing to the fetal heart is oxygenated because it comes from the placenta. The respiratory system is immature and cannot yet oxygenate blood on its own.) From the umbilical vein, the oxygenated blood flows toward the inferior **vena cava**, all but bypassing the immature liver, via the **ductus venosus** shunt (Figure 5.1.1). The liver receives just a trickle of blood, which is all that it needs in its immature, semifunctional state. Blood flows from the inferior vena cava to the right atrium, mixing with fetal venous blood along the way.[3]

Although the fetal liver is semifunctional, the fetal lungs are nonfunctional. The fetal circulation, therefore, bypasses the lungs by shifting some of the blood through the **foramen ovale**, a shunt that directly connects the right and left atria and avoids the **pulmonary trunk** altogether. Most of the rest of the blood is pumped to the right ventricle and, from there, into the pulmonary trunk, which splits into pulmonary arteries. However, a shunt within the pulmonary artery, the **ductus arteriosus**, diverts a portion of this blood into the aorta. This ensures that only a small volume of oxygenated blood passes through the immature pulmonary circuit, which has only

minor metabolic requirements. Blood vessels of uninflated lungs have high resistance to flow, a condition that encourages blood to flow to the aorta, which presents much lower resistance. The oxygenated blood moves through the foramen ovale into the left atrium, where it mixes with the now deoxygenated blood returning from the pulmonary circuit. This blood then moves into the left ventricle, where it is pumped into the aorta. Some of this blood moves through the coronary arteries into the myocardium, and some moves through the **carotid arteries** to the brain.[4]

The descending aorta carries partially oxygenated and partially deoxygenated blood into the lower regions of the body. It eventually passes into the umbilical arteries through branches of the internal **iliac arteries**. The deoxygenated blood collects waste as it circulates through the fetal body and returns to the umbilical cord. Thus, the two umbilical arteries carry blood low in oxygen and high in carbon dioxide and fetal wastes. This blood is filtered through the placenta, where wastes diffuse into the maternal circulation. Oxygen and nutrients from the pregnant person diffuse into the placenta and from there into the fetal blood, and the process repeats.

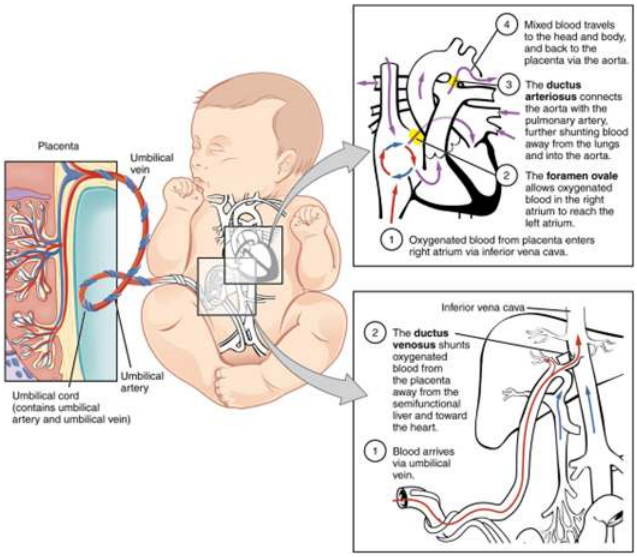


Figure 5.1.1 Fetal Circulatory System - The fetal circulatory system includes three shunts to divert blood from undeveloped and partially functioning organs, as well as blood supply to and from the placenta.
Image Source: Betts, J. Gordon, Kelly A. Young, James A. Wise, Eddie Johnson, Brandon Poe, Dean H. Kruse, Oksana Korol, Jody E. Johnson, Mark Womble, Peter DeSaix. "Fetal Development", Chapter 28.3 in *Anatomy and Physiology.* (2013). Chapter 28.3, "Fetal Development". Open Stax, 2013 This work is distributed under a CC BY 4.0 license. Available from Open Stax

5.1.2 Other Fetal Organs

During weeks 9–12 of fetal development, the brain continues to expand, the body elongates, and ossification continues. Fetal movements are frequent during this period but are jerky and not well-controlled. The bone marrow begins to take over the process of **erythrocyte** production—a task that the liver performed during the embryonic period. The liver now secretes **bile**. The fetus circulates amniotic fluid by swallowing it and producing urine. The eyes are well-

developed by this stage, but the eyelids are fused shut. The fingers and toes begin to develop nails. By the end of week 12, the fetus measures approximately 9 cm (3.5 in) from crown to rump.[5]

Weeks 13–16 are marked by sensory organ development. The eyes move closer together; blinking motions begin, although the eyes remain sealed shut. The lips exhibit sucking motions. The ears move upward and lie flatter against the head. The scalp begins to grow hair. The excretory system is also developing: the kidneys are well-formed, and **meconium**, or fetal feces, begins to accumulate in the intestines. Meconium consists of ingested amniotic fluid, cellular debris, mucus, and bile.[6]

During approximately weeks 16–20, as the fetus grows and limb movements become more powerful, the pregnant person may begin to feel **quickening**, or fetal movements. However, space restrictions limit these movements and typically force the growing fetus into the "fetal position," with the arms crossed and the legs bent at the knees. Sebaceous glands coat the skin with a waxy, protective substance called **vernix caseosa** that protects and moisturizes the skin and may provide lubrication during childbirth. A silky hair called **lanugo** also covers the skin during weeks 17–20, but it is shed as the fetus continues to grow. Extremely premature infants sometimes exhibit residual lanugo.[7]

Developmental weeks 21–30 are characterized by rapid weight gain, which is important for maintaining a stable body temperature after birth. The bone marrow completely takes over erythrocyte synthesis, and the axons of the spinal cord begin to be myelinated, or coated in the electrically insulating glial cell sheaths that are necessary for efficient nervous system functioning. (The process of myelination is not completed until adolescence.) During this period, the fetus grows eyelashes. The eyelids are no longer fused and can be opened and closed. The lungs begin producing surfactant, a substance that reduces surface tension in the lungs and assists in proper lung expansion after birth. Inadequate surfactant production in premature newborns may result in respiratory distress syndrome, and as a result, the newborn may require surfactant replacement therapy, supplemental oxygen, or maintenance in a continuous positive airway pressure (CPAP) chamber during their first days or weeks of life. In male fetuses, the testes descend into the scrotum near the end of this period. The fetus at 30 weeks measures 28 cm (11 in) from crown to rump and exhibits the approximate body proportions of a full-term newborn, but still is much leaner.[8]

The fetus continues to lay down subcutaneous fat from week 31 until birth. The added fat fills out the hypodermis, and the skin transitions from red and wrinkled to soft and pink. Lanugo is shed, and the nails grow to the tips of the fingers and toes. Immediately before birth, the average crown-to-rump length is 35.5–40.5 cm (14–16 in), and the fetus weighs approximately 2.5–4 kg (5.5–8.8 lbs). Once born, the newborn is no longer confined to the fetal position, so subsequent measurements are made from head to toe instead of from crown to rump. At birth, the average length is approximately 51 cm (20 in).[9]

For more information

A summary of the stages of pregnancy, as experienced by the pregnant person, and an overview of the stages of development of the fetus can be found online from the Office on Women's Health (OASH.gov).

Exercise 5.1.1

At what point in fetal development can a regular heartbeat be detected?

Answer

8 weeks

Glossary

Bile
A fluid that is made and released by the liver and stored in the gallbladder. Bile helps with digestion. It breaks down fats into fatty acids, which can be taken into the body by the digestive tract.

Carotid arteries
Two principal arteries on both sides of the neck that supply blood to the head and neck; each divides into two branches, the internal carotid artery and the external carotid artery.

Ductus artiosus
A shunt in the fetal pulmonary trunk that diverts oxygenated blood back to the aorta.

Ductus venosus
A shunt that allows oxygenated blood in the umbilical vein to bypass the liver and is essential for normal fetal circulation.

Endothelium
A layer of epithelium that lines the heart, blood vessels, lymph vessels, and the serous cavities of the body.

Erythrocyte
Red blood cell. Mature erythrocytes are non-nucleated, biconcave disks containing HEMOGLOBIN whose function is to transport OXYGEN.

Foramen
An opening, hole, or passage, especially in a bone.

Gestation
The process or period of developing inside the womb between conception and birth.

Iliac arteris
Either of two large arteries originating from the abdominal aorta; they supply blood to the pelvis, abdominal wall, and legs.

Lanugo
Soft, fine hair covering a fetus while inside the uterus.

Meconium
Fetal wastes consisting of ingested amniotic fluid, cellular debris, mucus, and bile.

Mesoderm
The middle germ layer of an embryo, derived from three paired mesenchymal aggregates along the neural tube.

Placenta
A highly vascularized mammalian fetal–maternal organ and major site of transport of oxygen, nutrients, and fetal waste products. It includes a fetal portion (CHORIONIC VILLI) derived from TROPHOBLASTS and a maternal portion

(DECIDUA) derived from the uterine ENDOMETRIUM. The placenta produces an array of steroid, protein and peptide hormones (PLACENTAL HORMONES)

Pulmonary trunk

large arterial vessel that carries blood ejected from the right ventricle; divides into the left and right pulmonary arteries

Quickening

fetal movements that are strong enough to be felt by the mother

Shunt

A circulatory shortcut that diverts the flow of blood from one region to another.

Vena cava

The inferior (venous trunk which receives blood from the lower extremities and from the pelvic and abdominal organs) and superior (venous trunk which returns blood from the head, neck, upper extremities and chest) venae cavae.

Vernix caseosa

Waxy, cheese-like substance that protects the delicate fetal skin until birth.

Footnotes

1. Betts, J. Gordon, Kelly A. Young, James A. Wise, Eddie Johnson, Brandon Poe, Dean H. Kruse, Oksana Korol, Jody E. Johnson, Mark Womble, Peter DeSaix. "Fetal Development", Chapter 28.3 in *Anatomy and Physiology.* (2013). Chapter 28.3, "Fetal Development". Open Stax, 2013 This work is distributed under a CC BY 4.0 license. Available from Open Stax
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5.2: Pregnancy and Labor

Learning Objectives

By the end of this section, learners will be able to

- Explain how estrogen, progesterone, and hCG are involved in maintaining pregnancy
- List the contributors to weight gain during pregnancy
- Describe the major changes to the maternal digestive, circulatory, and integumentary systems during pregnancy
- Summarize the events leading to labor
- Identify and describe each of the three stages of childbirth

5.2.1 Pregnancy

A full-term pregnancy lasts approximately 270 days (approximately 38.5 weeks) from conception to birth. Because it is easier to remember the first day of the last menstrual period (LMP) than to estimate the date of conception, obstetricians set the due date as 284 days (approximately 40.5 weeks) from the LMP. This assumes that conception occurred on day 14 of the menstrual cycle, which is usually a good approximation. The 40 weeks of an average pregnancy are usually discussed in terms of three **trimesters**, each approximately 13 weeks. During the second and third trimesters, the pre-pregnancy uterus—about the size of a fist—grows dramatically to contain the fetus, causing a number of anatomical changes in the pregnant person (Figure 5.2.1).[10]

For more information

For additional information on these anatomical changes, please see "Stages of Pregnancy" from the Office on Women's Health.

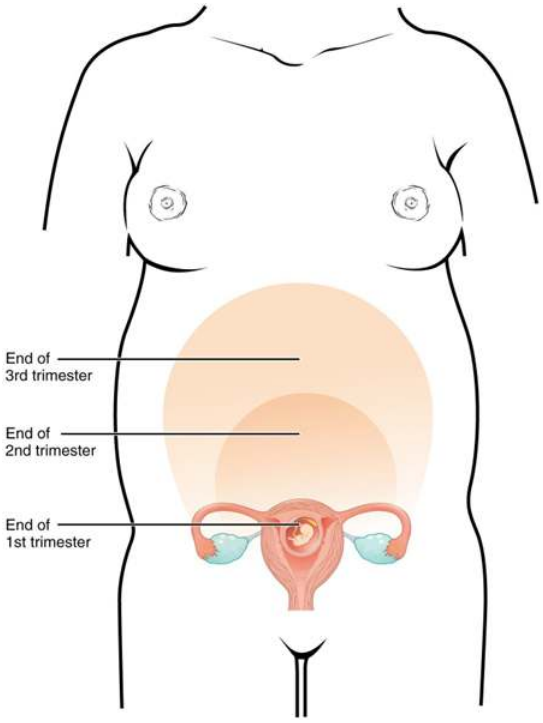


Figure 5.2.1 Size of Uterus throughout Pregnancy **-** The uterus grows throughout pregnancy to accommodate the fetus.

Image Source: Betts, J. Gordon, Kelly A. Young, James A. Wise, Eddie Johnson, Brandon Poe, Dean H. Kruse, Oksana Korol, Jody E. Johnson, Mark Womble, Peter DeSaix. "Changes During Pregnancy, Labor, and Birth." Chapter 28.4 in *Anatomy and Physiology.* (2013). Open Stax, 2013. This work is distributed under a CC BY 4.0 license. Available from Open Stax

5.2.1.1 Effects of Hormones

Virtually all of the effects of pregnancy can be attributed in some way to the influence of hormones—particularly estrogens, progesterone, and hCG. During weeks 7–12 from the LMP, the pregnancy hormones are primarily generated by the **corpus luteum**. **Progesterone** secreted by the corpus luteum stimulates the production of **decidual cells** of the **endometrium** that nourish the **blastocyst** before placentation. As the placenta develops and the corpus luteum degenerates during weeks 12–17, the **placenta** gradually takes over as the **endocrine** organ of pregnancy.[11]

The placenta converts weak **androgens** secreted by the maternal and fetal **adrenal glands** to estrogens, which are necessary for pregnancy to progress. Estrogen levels climb throughout the pregnancy, increasing 30-fold by childbirth. Estrogens have the following actions:

- They suppress FSH and LH production, effectively preventing ovulation. (This function is the biological basis of hormonal birth control pills.)
- They induce the growth of fetal tissues and are necessary for the maturation of the fetal lungs and liver.
- They promote fetal viability by regulating progesterone production and triggering fetal synthesis of cortisol, which helps with the maturation of the lungs, liver, and endocrine

organs such as the thyroid and adrenal glands.
- They stimulate maternal tissue growth, leading to uterine enlargement and **mammary duct** expansion and branching.

Relaxin, another hormone secreted by the **corpus luteum** and then by the placenta, helps prepare the body for childbirth. It increases the elasticity of the symphysis pubis joint and pelvic ligaments, making room for the growing fetus and allowing expansion of the pelvic outlet for childbirth. Relaxin also helps dilate the cervix during labor.[12]

The placenta takes over the synthesis and secretion of progesterone throughout pregnancy as the corpus luteum degenerates. Like estrogen, progesterone suppresses FSH and LH. It also inhibits uterine contractions, protecting the fetus from preterm birth. This hormone decreases in late gestation, allowing uterine contractions to intensify and eventually progress to true labor. The placenta also produces hCG. In addition to promoting survival of the corpus luteum, hCG stimulates the male fetal gonads to secrete testosterone, which is essential for the development of the male reproductive system.[13]

The anterior pituitary enlarges and ramps up its hormone production during pregnancy, raising the levels of **thyrotropin**, **prolactin**, and **adrenocorticotropic** hormone (ACTH). Thyrotropin, in conjunction with placental hormones, increases the production of thyroid hormone, which raises the maternal metabolic rate. This can markedly augment a pregnant person's appetite and cause hot flashes. Prolactin stimulates enlargement of the mammary glands in preparation for milk production. ACTH stimulates maternal cortisol secretion, which contributes to fetal protein synthesis. In addition to the pituitary hormones, increased parathyroid levels mobilize calcium from maternal bones for fetal use.[14]

5.2.1.2 Weight Gain

The second and third trimesters of pregnancy are associated with dramatic changes in maternal anatomy and physiology. The most obvious anatomical sign of pregnancy is the dramatic enlargement of the abdominal region, coupled with weight gain. This weight results from the growing fetus as well as the enlarged uterus, amniotic fluid, and placenta. Additional breast tissue and dramatically increased blood volume also contribute to weight gain (Table 5.1). Surprisingly, fat storage accounts for only approximately 2.3 kg (5 lbs) in a normal pregnancy and serves as a reserve for the increased metabolic demand of breastfeeding.

During the first trimester, a pregnant person does not need to consume additional calories to maintain a healthy pregnancy. However, a weight gain of approximately 0.45 kg (1 lb) per month is common. During the second and third trimesters, the appetite increases, but it is only necessary to consume an additional 300 calories per day to support the growing fetus. Most pregnant people gain approximately 0.45 kg (1 lb) per week.

Table 5.1 Contributors to Weight Gain During Pregnancy

Table Source: Betts, J. Gordon, Kelly A. Young, James A. Wise, Eddie Johnson, Brandon Poe, Dean H. Kruse, Oksana Korol, Jody E. Johnson, Mark Womble, Peter DeSaix.

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Component	Weight (kg)	Weight (lb)
Fetus	3.2–3.6	7–8
Placenta and fetal membranes	0.9–1.8	2–4
Amniotic fluid	0.9–1.4	2–3
Breast tissue	0.9–1.4	2–3
Blood	1.4	4
Fat	0.9–4.1	3–9
Uterus	0.9–2.3	2–5
Total	10–16.3	22–36

5.2.1.3 Changes in Organ Systems During Pregnancy

As the body adapts to pregnancy, characteristic physiologic changes occur. These changes can sometimes prompt symptoms that are often referred to collectively as the common discomforts of pregnancy.

- Digestive and Urinary System Changes

Nausea and vomiting, sometimes triggered by an increased sensitivity to odors, are common during the first few weeks to months of pregnancy. This phenomenon is often referred to as “morning sickness,” although the nausea may persist all day. The source of pregnancy nausea is thought to be the increased circulation of pregnancy-related hormones, specifically circulating estrogen, progesterone, and **hCG**. Decreased intestinal peristalsis may also contribute to nausea. By about week 12 of pregnancy, nausea typically subsides.[15]

A common gastrointestinal complaint during the later stages of pregnancy is gastric reflux, or heartburn, which results from the upward, constrictive pressure of the growing uterus on the stomach. The same decreased **peristalsis** that may contribute to nausea in early pregnancy is also thought to be responsible for pregnancy-related constipation as pregnancy progresses.[16]

The downward pressure of the uterus also compresses the urinary bladder, leading to frequent urination. The problem is exacerbated by increased urine production. In addition, the maternal urinary system processes both maternal and fetal wastes, further increasing the total volume of urine.[17]

- Circulatory System Changes

Blood volume increases substantially during pregnancy so that by childbirth, it exceeds its preconception volume by 30% or approximately 1–2 liters. The greater blood volume helps to manage the demands of fetal nourishment and fetal waste removal. In conjunction with increased blood volume, the pulse and blood pressure also rise moderately during pregnancy. As the fetus grows, the uterus compresses underlying pelvic blood vessels, hampering venous

return from the legs and pelvic region. As a result, many pregnant people develop varicose veins or hemorrhoids.[18]

- Respiratory System Changes

During the second half of pregnancy, the respiratory minute volume (volume of gas inhaled or exhaled by the lungs per minute) increases by 50% to compensate for the oxygen demands of the fetus and the increased maternal metabolic rate. The growing uterus exerts upward pressure on the diaphragm, decreasing the volume of each and potentially causing shortness of breath, or **dyspnea**. During the last several weeks of pregnancy, the pelvis becomes more elastic, and the fetus descends lower in a process called **lightening**. This typically ameliorates dyspnea.[19]

The respiratory mucosa swell in response to increased blood flow during pregnancy, leading to nasal congestion and nose bleeds, particularly when the weather is cold and dry. Humidifier use and increased fluid intake are often recommended to counteract congestion.[20]

- Integumentary System Changes

The dermis stretches extensively to accommodate the growing uterus, breast tissue, and fat deposits on the thighs and hips. The torn connective tissue beneath the dermis can cause **striae** (stretch marks) on the abdomen, which appear as red or purple marks during pregnancy that fade to a silvery-white color in the months after childbirth.

An increase in **melanocyte-stimulating** hormone, in conjunction with estrogens, darkens the areolae and creates a line of pigment from the umbilicus to the pubis called the linea nigra (Figure 5.2.2). Melanin production during pregnancy may also darken or discolor skin on the face to create a **chloasma**, or “mask of pregnancy.”

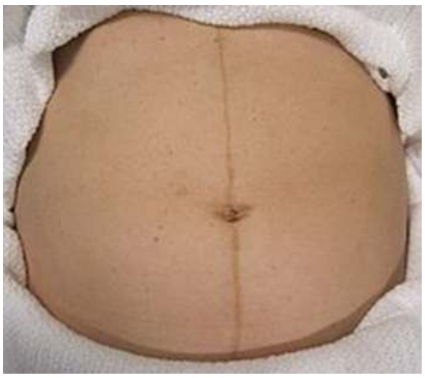


Figure 5.2.2 Linea Nigra - The linea nigra, a dark medial line running from the umbilicus to the pubis, forms during pregnancy and persists for a few weeks following childbirth.
Image Source: James Heilman. (2013). "Linea nigra as seen in a pregnant woman." Wikipedia.org. This work is distributed under a CC BY-SA 3.0 license. Available from Wikipedia.

5.2.2 Labor

Childbirth, or **parturition**, typically occurs within a week of the due date, unless the pregnancy involves more than one fetus, which usually causes labor to begin early. As a pregnancy progresses into its final weeks, several physiological changes occur in response to hormones that trigger labor.

First, recall that progesterone inhibits uterine contractions throughout the first several months of pregnancy. As the pregnancy enters its seventh month, progesterone levels plateau and then drop. Estrogen levels, however, continue to rise in the maternal circulation (Figure 5.2.3). The increasing ratio of estrogen to progesterone makes the **myometrium** (the uterine smooth muscle) more sensitive to stimuli that promote contractions (because progesterone no longer inhibits them). Moreover, in the eighth month of pregnancy, fetal cortisol rises, which boosts estrogen secretion by the placenta and further overpowers the uterine-calming effects of progesterone. Some people may feel the result of the decreasing levels of progesterone in late pregnancy as weak and irregular **peristaltic Braxton Hicks contractions**, also called false labor. These contractions can often be relieved with rest or hydration.[21]

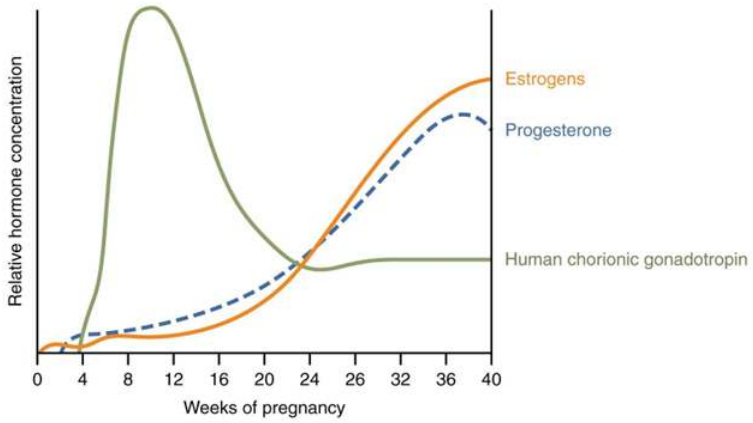


Figure 5.2.3 Hormones Initiating Labor - A positive feedback loop of hormones works to initiate labor.
Image Source: Betts, J. Gordon, Kelly A. Young, James A. Wise, Eddie Johnson, Brandon Poe, Dean H. Kruse, Oksana Korol, Jody E. Johnson, Mark Womble, Peter DeSaix. "Changes During Pregnancy, Labor, and Birth." Chapter 28.4 in *Anatomy and Physiology.* (2013). Open Stax, 2013 This work is distributed under a CC BY 4.0 license. Available from Open Stax

During pregnancy, a plug of mucus accumulates in the cervical canal, blocking the entrance to the uterus. Approximately 1–2 days before the onset of true labor, this plug loosens and is expelled into the vagina. The blood vessels in the cervix begin to rupture as it **effaces** and dilates, resulting in vaginal discharge with a small amount of blood, known as bloody show.

Meanwhile, the posterior pituitary has increased its secretion of **oxytocin**, a hormone that stimulates the contractions of labor. At the same time, the **myometrium** increases its sensitivity to oxytocin by expressing more receptors for this hormone. As labor nears, oxytocin begins to stimulate stronger, more painful uterine contractions, which—in a positive feedback loop—stimulate the secretion of prostaglandins from fetal membranes. Like oxytocin, prostaglandins

also enhance uterine contractile strength. The fetal **pituitary** also secretes oxytocin, which increases **prostaglandins**. Given the importance of oxytocin and prostaglandins to the initiation and maintenance of labor, it is not surprising that, when a pregnancy is not progressing to labor and needs to be induced, a pharmaceutical version of these compounds (called pitocin) is administered by intravenous drip.[22]

Finally, stretching of the myometrium and cervix by a full-term fetus in the vertex (head-down) position is regarded as a stimulant to uterine contractions. The sum of these changes initiates the regular contractions known as **true labor**, which become more powerful and more frequent with time.[23]

5.2.2.2 Stages of Childbirth

The process of childbirth can be divided into three stages: cervical dilation, expulsion of the newborn, and afterbirth (Figure 5.2.4).

- Cervical Dilation

For vaginal birth to occur, the cervix must dilate fully to 10 cm in diameter—wide enough to deliver the newborn's head. The **dilation** stage is the longest stage of labor and typically takes 6–12 hours. However, it varies widely and may take minutes, hours, or days, depending in part on whether the person has given birth before; in each subsequent labor, this stage tends to be shorter.

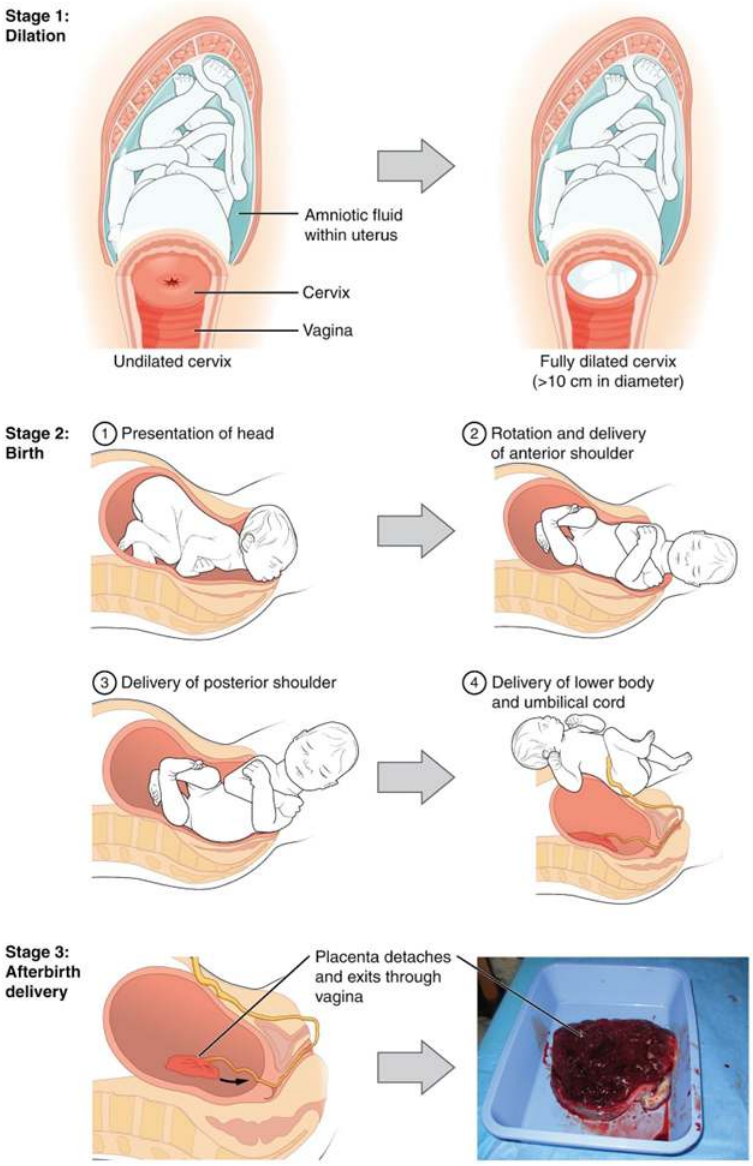


Figure 5.2.4 Stages of Childbirth - The stages of childbirth include Stage 1, early cervical dilation; Stage 2, full dilation and expulsion of the newborn; and Stage 3, delivery of the placenta and associated fetal membranes. (The position of the newborn's shoulder is described relative to the person giving birth.)

Image Source: Betts, J. Gordon, Kelly A. Young, James A. Wise, Eddie Johnson, Brandon Poe, Dean H. Kruse, Oksana Korol, Jody E. Johnson, Mark Womble, Peter DeSaix. "Changes During Pregnancy, Labor, and Birth." Chapter 28.4 in *Anatomy and Physiology.* (2013). Open Stax, 2013. This work is distributed under a CC BY 4.0 license. Available from Open Stax

True labor progresses in a positive feedback loop in which uterine contractions stretch the cervix, causing it to dilate and efface, or become thinner. Cervical stretching induces reflexive uterine contractions that dilate and efface the cervix further. In addition, cervical dilation boosts oxytocin secretion from the pituitary, which in turn triggers more powerful uterine contractions. When labor begins, uterine contractions may occur only every 3–30 minutes and last only 20–

40 seconds; however, by the end of this stage, contractions may occur as frequently as every 1.5–2 minutes and last for a full minute.[24]

Each contraction sharply reduces oxygenated blood flow to the fetus. For this reason, it is critical that a period of relaxation occur after each contraction. Fetal distress, measured as a sustained decrease or increase in the fetal heart rate, can result from severe contractions that are too powerful or lengthy for oxygenated blood to be restored to the fetus. Such a situation can be cause for an emergency birth with vacuum, **forceps**, or surgically by Caesarian section.[25]

The amniotic membranes rupture before the onset of labor in about 12 percent of people; they typically rupture at the end of the dilation stage in response to excessive pressure from the fetal head entering the birth canal.[26]

- Expulsion Stage

The **expulsion** stage begins when the fetal head enters the birth canal and ends with birth of the newborn. It typically takes up to 2 hours, but it can last longer or be completed in minutes, depending in part on the orientation of the fetus. The vertex presentation known as the occiput anterior vertex is the most common presentation and is associated with the greatest ease of vaginal birth. The fetus faces the maternal spinal cord and the smallest part of the head (the posterior aspect called the **occiput**) exits the birth canal first.[27]

In fewer than 5 percent of births, the infant is oriented in the breech presentation, or buttocks down. In a complete breech, both legs are crossed and oriented downward. In a frank breech presentation, the legs are oriented upward. Before the 1960s, it was common for breech presentations to be delivered vaginally. Today, most breech births are accomplished by Caesarian section.[28]

Vaginal birth is associated with significant stretching of the vaginal canal, the cervix, and the perineum. Until recent decades, it was routine procedure for an obstetrician to numb the perineum and perform an **episiotomy**, an incision in the posterior vaginal wall and perineum. The perineum is now more commonly allowed to tear on its own during birth. Both an episiotomy and a **perineal tear** need to be sutured shortly after birth to ensure optimal healing. Although suturing the jagged edges of a perineal tear may be more difficult than suturing an episiotomy, tears heal more quickly, are less painful, and are associated with less damage to the muscles around the vagina and rectum.[29]

Upon birth of the newborn's head, an obstetrician will aspirate mucus from the mouth and nose before the newborn's first breath. Once the head is birthed, the rest of the body usually follows quickly. The umbilical cord is then double-clamped, and a cut is made between the clamps. This completes the second stage of childbirth.

For more information

More information about vaginal birth can be found at "Vaginal Delivery" from National Library of Medicine StatPearls.

More information about the stages of labor can be found at "Stages of Labor" from National Library of Medicine StatPearls.

- Afterbirth

The delivery of the placenta and associated membranes, commonly referred to as the **afterbirth**, marks the final stage of childbirth. After expulsion of the newborn, the myometrium continues to contract. This movement shears the placenta from the back of the uterine wall. It is then easily delivered through the vagina. Continued uterine contractions then reduce blood loss from the site of the placenta. Delivery of the placenta marks the beginning of the postpartum period—the period of approximately 6 weeks immediately following childbirth during which the body gradually returns to a non-pregnant state. If the placenta does not birth spontaneously within approximately 30 minutes, it is considered retained, and the obstetrician may attempt manual removal. If this is not successful, surgery may be required.

It is important that the **obstetrician** examines the expelled placenta and fetal membranes to ensure that they are intact. If fragments of the placenta remain in the uterus, they can cause postpartum hemorrhage. Uterine contractions continue for several hours after birth to return the uterus to its pre-pregnancy size in a process called **involution**, which also allows the abdominal organs to return to their pre-pregnancy locations. Breastfeeding facilitates this process.

Although postpartum uterine contractions limit blood loss from the detachment of the placenta, the person who has recently given birth does experience a postpartum vaginal discharge called **lochia**. This is made up of uterine lining cells, **erythrocytes**, **leukocytes**, and other debris. Thick, dark, lochia rubra (**red lochia**) typically continues for 2–3 days, and is replaced by lochia serosa, a thinner, pinkish form that continues until about the tenth postpartum day. After this period, a scant, creamy, or watery discharge called lochia alba (white lochia) may continue for another 1–2 weeks.

Glossary Terms

Adrenal glands

Endocrine glands located at the top of each kidney that are important for the regulation of the stress response, blood pressure and blood volume, water homeostasis, and electrolyte levels.

Adrenocorticotropic (hormone)

An anterior pituitary hormone that stimulates the ADRENAL CORTEX and its production of CORTICOSTEROIDS. ACTH is a 39-amino acid polypeptide of which the N-terminal 24-amino acid segment is identical in all species and contains the adrenocorticotrophic activity. Upon further tissue-specific processing, ACTH can yield ALPHA-MSH and corticotrophin-like intermediate lobe peptide (CLIP).

Afterbirth

The third stage of childbirth, in which the placenta and associated fetal membranes are expelled.

Androgens

Compounds that interact with ANDROGEN RECEPTORS in target tissues to bring about effects similar to those of TESTOSTERONE. Depending on the target tissues, androgens can affect SEX DIFFERENTIATION; male reproductive organs, SPERMATOGENESIS; secondary male SEX CHARACTERISTICS; LIBIDO; and development of muscle mass, strength, and power.

Blastocyst

A post-MORULA preimplantation mammalian embryo that develops from a 32-cell stage into a fluid-filled hollow ball of over a hundred cells.

Braxton hicks contractions

weak and irregular peristaltic contractions that can occur in the second and third trimesters; they do not indicate that childbirth is imminent

Chloasma

A pigmentation disorder of the skin characterized by darker skin patches that primarily affect the face and other sun-exposed areas.

Corpus luteum

A transformed follicle after ovulation that secretes progesterone.

Decidual cells

Hyperplastic endometrial stromal cells that have transformed into large, eosinophilic, round-to-polygonal cells in response fo progestational influence followed by some type of irritation or trauma to the endometrium.

Dilation

The first stage of childbirth, involving an increase in cervical diameter.

Dyspnea

Difficult or labored breathing.

Effaces

The cervix stretches and gets thinner.

Endocrine

Glands and organs that make hormones and release them directly into the blood so they can travel to tissues and organs all over the body.

Endometrium

The inner lining of the uterus, part of which builds up during the secretory phase of the menstrual cycle and then sheds with menses.

Episiotomy

An incision made in the posterior vaginal wall and perineum that facilitates vaginal birth.

Erythrocytes

Red blood cells. Mature erythrocytes are non-nucleated, biconcave disks containing HEMOGLOBIN whose function is to transport OXYGEN.

Expulsion

The second stage of childbirth, during which the mother bears down with contractions; this stage ends in birth.

hCG

A chemical created by trophoblast tissue, tissue typically found in early embryos that will eventually be part of the placenta.

Involution

Postpartum shrinkage of the uterus back to its pre-pregnancy volume.

Leukocytes

White blood cells. These include granular **leukocytes** (BASOPHILS; EOSINOPHILS; and NEUTROPHILS) as well as non-granular **leukocytes** (LYMPHOCYTES and MONOCYTES)

Lightening

descent of the fetus lower into the pelvis in late pregnancy; also called “dropping.”

Lochia

Postpartum vaginal discharge that begins as blood and ends as a whitish discharge; the end of lochia signals that the site of placental attachment has healed.

Melanocyte-stimulating hormone

Peptides with the ability to stimulate pigmented cells (**MELANOCYTES** in mammals and MELANOPHORES in lower vertebrates). By **stimulating** the synthesis and distribution of MELANIN in these pigmented cells, they increase coloration of skin and other tissue.

Myometrium

The smooth muscle layer of uterus that allows for uterine contractions during labor and expulsion of menstrual blood.

Obstetrician

Qualified medical professionals who specialize in OBSTETRICS, a medical-surgical specialty concerned with management and care of women during pregnancy, parturition, and the puerperium.

Occiput

The back of the head or skull.

Oxytocin

The hypothalamic hormone stored in the posterior pituitary gland, important in stimulating uterine contractions in labor, milk ejection during breastfeeding, and feelings of attachment (also produced in males).

Parturition

Childbirth.

Perineal tear

Tears that happen spontaneously as the baby stretches the vagina and the perineum during birth.

Peristasis

A series of muscle contractions. These contractions occur in your digestive tract. Peristalsis is also seen in the tubes that connect the kidneys to the bladder

Pituitary

A small, unpaired gland situated in the SELLA TURCICA. It is connected to the HYPOTHALAMUS by a short stalk which is called the INFUNDIBULUM.

Placenta

A highly vascularized mammalian fetal-maternal organ and major site of transport of oxygen, nutrients, and fetal waste products. It includes a fetal portion (CHORIONIC VILLI) derived from TROPHOBLASTS and a maternal portion (DECIDUA) derived from the uterine ENDOMETRIUM. The placenta produces an array of steroid, protein and peptide hormones (PLACENTAL HORMONES).

Progesterone

A sex hormone important in regulating the reproductive cycle in those with ovaries and the maintenance of pregnancy.

Prostaglndins

A group of compounds derived from unsaturated 20-carbon fatty acids, primarily arachidonic acid, via the cyclooxygenase pathway. They are extremely potent mediators of a diverse group of physiological processes

Prolactin

The pituitary hormone that establishes and maintains the supply of breast milk; also important for the mobilization of maternal micronutrients for breast milk.

Striae

Stretch marks.

Thyrotopin

The master regulator of thyroid gland growth and function.

True labor

Regular contractions that immediately precede childbirth; they do not abate with hydration or rest, and they become more frequent and powerful with time.

Footnotes

10. Betts, J. Gordon, Kelly A. Young, James A. Wise, Eddie Johnson, Brandon Poe, Dean H. Kruse, Oksana Korol, Jody E. Johnson, Mark Womble, Peter DeSaix. "Changes During Pregnancy, Labor, and Birth." Chapter 28.4 in *Anatomy and Physiology.* (2013). Open Stax, 2013 This work is distributed under a CC BY 4.0 license. Available from Open Stax
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5.3: Changes in the Neonate

Learning Objectives

By the end of this section, learners will be able to

- Discuss the importance of an infant's first breath
- Explain the closing of the cardiac shunts
- Describe thermoregulation in the newborn
- Summarize the importance of intestinal flora in the newborn

Consider this:

From a fetal perspective, the process of birth is a crisis. In the womb, the fetus was snuggled in a soft, warm, dark, and quiet world. The placenta provided nutrition and oxygen continuously. Suddenly, the contractions of labor and vaginal childbirth forcibly squeeze the fetus through the birth canal, limiting oxygenated blood flow during contractions and shifting the skull bones to accommodate the small space. After birth, the newborn's system must make drastic adjustments to a world that is colder, brighter, and louder, and where they will experience hunger and thirst. The neonatal period (neo- = "new"; -natal = "birth") spans the first to the thirtieth day of life outside of the uterus.[30]

5.3.1 Respiratory Adjustments

Although the fetus "practices" breathing by inhaling amniotic fluid in utero, there is no air in the uterus and thus no true opportunity to breathe. (There is also no need to breathe because the placenta supplies the fetus with all the oxygenated blood it needs.) During gestation, the partially collapsed lungs are filled with amniotic fluid and exhibit very little metabolic activity. Several factors stimulate newborns to take their first breath at birth. First, labor contractions temporarily constrict umbilical blood vessels, reducing oxygenated blood flow to the fetus and elevating carbon dioxide levels in the blood. High carbon dioxide levels cause **acidosis** and stimulate the respiratory center in the brain, triggering the newborn to take a breath.[31]

The first breath typically is taken within 10 seconds of birth, after mucus is aspirated from the infant's mouth and nose. The first breaths inflate the lungs to nearly full capacity and dramatically decrease lung pressure and resistance to blood flow, causing a major circulatory reconfiguration. **Pulmonary alveoli** open, and **alveolar capillaries** fill with blood. Amniotic fluid in the lungs drains or is absorbed, and the lungs immediately take over the task of the placenta, exchanging carbon dioxide for oxygen by the process of respiration.[32]

5.3.2 Circulatory Adjustments

The process of clamping and cutting the umbilical cord collapses the umbilical blood vessels. In the absence of medical assistance, this occlusion would occur naturally within 20 minutes of birth because the **Wharton's jelly** within the umbilical cord would swell in response to the lower temperature outside of the mother's body, and the blood vessels would constrict. Natural occlusion has occurred when the umbilical cord is no longer pulsating. For the most part, the collapsed vessels in the newborn atrophy and become fibrotic remnants, existing in the mature circulatory system as ligaments of the abdominal wall and liver. The ductus venosus degenerates to become the ligamentum venosum beneath the liver. Only the proximal sections of the two umbilical arteries remain functional, taking on the role of supplying blood to the upper part of the bladder (Figure 5.3.1).[33]

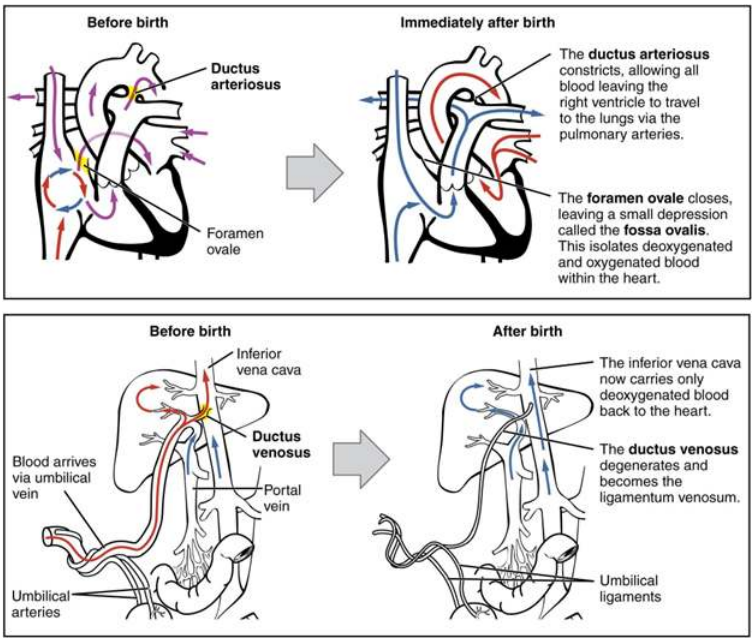


Figure 5.3.1 Neonatal Circulatory System - A newborn's circulatory system reconfigures immediately after birth. The three fetal shunts have been closed permanently, facilitating blood flow to the liver and lungs.
Image Source: Betts, J. Gordon, Kelly A. Young, James A. Wise, Eddie Johnson, Brandon Poe, Dean H. Kruse, Oksana Korol, Jody E. Johnson, Mark Womble, Peter DeSaix. "Adjustments of the Infant at Birth and Postnatal Stages." Chapter 28.5 in *Anatomy and Physiology.* (2013). Open Stax, 2013 This work is distributed under a CC BY 4.0 license. Available from Open Stax

The newborn's first breath is vital to initiate the transition from the fetal to the neonatal circulatory pattern. Inflation of the lungs decreases blood pressure throughout the pulmonary system, as well as in the right atrium and ventricle. In response to this pressure change, the flow of blood temporarily reverses direction through the **foramen ovale**, moving from the left to the right atrium, and blocking the shunt with two flaps of tissue. Within one year, the tissue flaps usually fuse over the shunt, turning the foramen ovale into the fossa **ovalis**. The ductus arteriosus constricts as a result of increased oxygen concentration and becomes the

ligamentum **arteriosum**. Closing of the ductus arteriosus ensures that all blood pumped to the pulmonary circuit will be oxygenated by the newly functional neonatal lungs.[34]

5.3.3 Thermoregulatory Adjustments

The fetus floats in warm amniotic fluid that is maintained at a temperature of approximately 98.6°F with very little fluctuation. Birth exposes newborns to a cooler environment in which they have to regulate their own body temperature. Newborns have a higher ratio of surface area to volume than adults. This means that their body has less volume throughout which to produce heat, and more surface area from which to lose heat. As a result, newborns produce heat more slowly and lose it more quickly. Newborns also have immature musculature that limits their ability to generate heat by shivering. Moreover, their nervous systems are underdeveloped, so they cannot quickly constrict superficial blood vessels in response to cold. They also have little **subcutaneous fat** for insulation. All these factors make it harder for newborns to maintain their body temperature.[35]

Newborns, however, do have a special method for generating heat: **nonshivering thermogenesis**, which involves the breakdown of **brown adipose tissue**, or brown fat, which is distributed over the back, chest, and shoulders. Brown fat differs from the more familiar white fat in two ways:

- It is highly vascularized. This allows for faster delivery of oxygen, which leads to faster cellular respiration.
- It is packed with a special type of mitochondria that are able to engage in cellular respiration reactions that produce less ATP and more heat than standard cellular respiration reactions.

The breakdown of brown fat occurs automatically upon exposure to cold, so it is an important heat regulator in newborns. During fetal development, the placenta secretes inhibitors that prevent metabolism of brown adipose fat and promote its accumulation in preparation for birth.[36]

5.3.4 Gastrointestinal and Urinary Adjustments

In adults, the gastrointestinal tract harbors bacterial flora—trillions of bacteria that aid in digestion, produce vitamins, and protect from the invasion or replication of pathogens. In stark contrast, the fetal intestine is sterile. The first consumption of breast milk or formula floods the neonatal gastrointestinal tract with beneficial bacteria that begin to establish the bacterial flora.[37]

The fetal kidneys filter blood and produce urine, but the neonatal kidneys are still immature and inefficient at concentrating urine. Therefore, newborns produce very dilute urine, making it particularly important for infants to obtain sufficient fluids from breast milk or formula.[38]

5.3.5 Homeostatic Imbalances

5.3.5.1 Homeostasis in the Newborn: Apgar Score

In the minutes following birth, a newborn must undergo dramatic systemic changes to be able to survive outside the womb. An obstetrician, midwife, or nurse can estimate how well a newborn is doing by obtaining an Apgar score. The Apgar score was introduced in 1952 by the anesthesiologist Dr. Virginia Apgar as a method to assess the effects on the newborn of anesthesia given to the person giving birth. Healthcare providers now use it to assess the general well-being of the newborn, whether or not analgesics or anesthetics were used.[39]

Five criteria—skin color, heart rate, reflex, muscle tone, and respiration—are assessed, and each criterion is assigned a score of 0, 1, or 2. Scores are taken at 1 minute after birth and again at 5 minutes after birth. Each time that scores are taken, the five scores are added together. High scores (out of a possible 10) indicate the baby has made the transition from the womb well, whereas lower scores indicate that the baby may be in distress.[40]

The technique for determining an Apgar score is quick and easy, painless for the newborn, and does not require any instruments except for a stethoscope. A convenient way to remember the five scoring criteria is to apply the mnemonic APGAR, for “appearance” (skin color), “pulse” (heart rate), “grimace” (reflex), “activity” (muscle tone), and “respiration.”[41]

Of the five Apgar criteria, heart rate and respiration are the most critical. Poor scores for either of these measurements may indicate the need for immediate medical attention to resuscitate or stabilize the newborn. In general, any score lower than 7 at the 5-minute mark indicates that medical assistance may be needed. A total score below 5 indicates an emergency situation. Normally, a newborn will get an intermediate score of 1 for some of the Apgar criteria and will progress to a 2 by the 5-minute assessment. Scores of 8 or above are normal.[42]

For more information

More information about the relationship between race and Apgar scores can be found online at PLOS Medicine.

Glossary Terms

Acidosis

A condition in which there is too much acid in the body fluids. It is the opposite of alkalosis (a condition in which there is too much base in the body fluids).

Alveolar capillaries

Very tiny blood vessels that connect the alveoli (millions of tiny air sacs scattered throughout the lungs) to larger blood vessels.

Arteriosum

The small ligament attaching the aorta to the pulmonary artery.

Brown adipose tissue

Highly vascularized fat tissue that is packed with mitochondria; these properties confer the ability to oxidize fatty acids to generate heat.

Foramen ovale

A shunt that directly connects the right and left atria and helps to divert oxygenated blood from the fetal pulmonary circuit.

Nonshivering thermogenesis

The process of breaking down brown adipose tissue to produce heat in the absence of a shivering response.

Pulmonary alveoli

Small polyhedral outpouchings along the walls of the alveolar sacs, alveolar ducts, and terminal bronchioles through the walls of which gas exchange between alveolar air and pulmonary capillary blood takes place.

Subcutaneous fat

The term "cutaneous" refers to the skin. Subcutaneous means beneath, or under, all the layers of the skin.

Wharton's jelly

Jelly-like connective tissue of the UMBILICAL CORD that contains MESENCHYMAL STEM CELLS.

Footnotes

30. Betts, J. Gordon, Kelly A. Young, James A. Wise, Eddie Johnson, Brandon Poe, Dean H. Kruse, Oksana Korol, Jody E. Johnson, Mark Womble, Peter DeSaix. "Adjustments of the Infant at Birth and Postnatal Stages." Chapter 28.5 in *Anatomy and Physiology.* (2013). Open Stax, 2013 This work is distributed under a CC BY 4.0 license. Available from Open Stax
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5.4: Lactation

Learning Objectives

By the end of this section, learners will be able to

- Describe the structure of the lactating breast
- Summarize the process of lactation
- Explain how the composition of breast milk changes during the first days of lactation and in the course of a single feeding

Lactation is the process by which milk is synthesized and secreted from the mammary glands of the postpartum female breast in response to an infant sucking at the nipple. Breast milk provides ideal nutrition and passive immunity for the infant, encourages mild uterine contractions to return the uterus to its pre-pregnancy size (i.e., **involution**), and induces a substantial metabolic increase in the postpartum person, consuming the fat reserves stored during pregnancy.[43]

5.4.1 Structure of the Lactating Breast

Mammary glands are modified sweat glands. The non-pregnant and non-lactating female breast is composed primarily of adipose and **collagenous tissue**, with mammary glands making up a very minor proportion of breast volume. The mammary gland is composed of milk-transporting lactiferous ducts, which expand and branch extensively during pregnancy in response to estrogen, growth hormone, cortisol, and prolactin. Moreover, in response to progesterone, clusters of breast alveoli bud from the ducts and expand outward toward the chest wall. Breast alveoli are balloon-like structures lined with milk-secreting cuboidal cells, or **lactocytes**, that are surrounded by a net of **contractile myoepithelial cells**. Milk is secreted from the lactocytes, fills the alveoli, and is squeezed into the ducts. Clusters of alveoli that drain to a common duct are called lobules; the lactating female has 12–20 lobules organized radially around the nipple. Milk drains from lactiferous ducts into lactiferous sinuses that meet at 4 to 18 perforations in the nipple, called nipple pores. The small bumps of the areola (the darkened skin around the nipple) are called **Montgomery glands**. They secrete oil to cleanse the nipple opening and prevent chapping and cracking of the nipple during breastfeeding.[44]

5.4.2 Process of Lactation

The pituitary hormone **prolactin** is instrumental in the establishment and maintenance of breast milk supply. It also is important for the mobilization of maternal micronutrients for breast milk.

Near the fifth week of pregnancy, the level of circulating prolactin begins to increase, eventually rising to approximately 10–20 times the pre-pregnancy concentration. We noted earlier that, during pregnancy, prolactin and other hormones prepare the breasts anatomically for the secretion of milk. The level of prolactin plateaus in late pregnancy, at a level high enough to

initiate milk production. However, estrogen, progesterone, and other placental hormones inhibit prolactin-mediated milk synthesis during pregnancy. It is not until the placenta is expelled that this inhibition is lifted and milk production commences.[45]

After childbirth, the baseline prolactin level drops sharply, but it is restored for a 1-hour spike during each feeding to stimulate the production of milk for the next feeding. With each prolactin spike, estrogen and progesterone also increase slightly.[46]

When the infant suckles, sensory nerve fibers in the areola trigger a neuroendocrine reflex that results in milk secretion from lactocytes into the alveoli. The posterior pituitary releases oxytocin, which stimulates myoepithelial cells to squeeze milk from the alveoli so it can drain into the lactiferous ducts, collect in the **lactiferous sinuses**, and discharge through the nipple pores. It takes less than 1 minute from the time when an infant begins suckling (the latent period) until milk is secreted (the let-down). Figure 5.4.1 summarizes the positive feedback loop of the **let-down reflex.**[47]

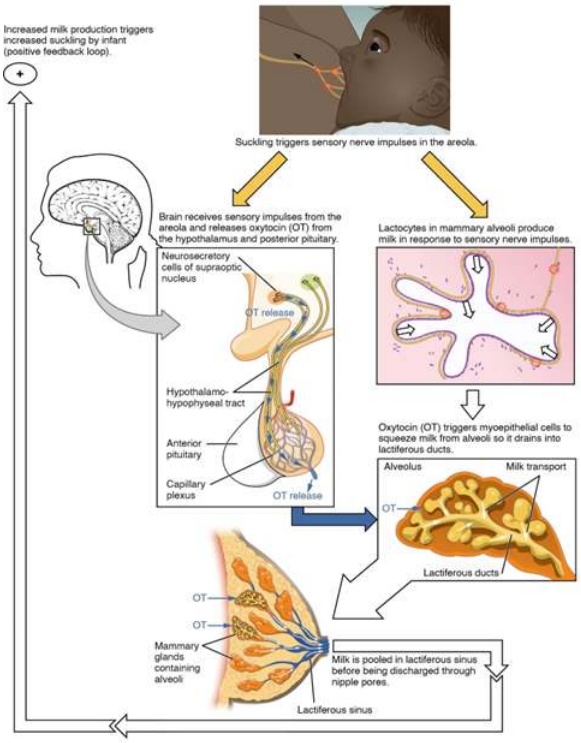


Figure 5.4.1 Let-Down Reflex - A positive feedback loop ensures continued milk production as long as the infant continues to breastfeed.

Image Source: Betts, J. Gordon, Kelly A. Young, James A. Wise, Eddie Johnson, Brandon Poe, Dean H. Kruse, Oksana Korol, Jody E. Johnson, Mark Womble, Peter DeSaix. "Lactation." Chapter 28.6 in *Anatomy and Physiology.* (2013). Open Stax, 2013 This work is distributed under a CC BY 4.0 license. Available from Open Stax

The prolactin-mediated synthesis of milk changes with time. Frequent milk removal by breastfeeding (or pumping) will maintain high circulating prolactin levels for several months. However, even with continued breastfeeding, baseline prolactin will decrease over time to its

pre-pregnancy level. In addition to prolactin and oxytocin, growth hormone, cortisol, parathyroid hormone, and insulin contribute to lactation, in part by facilitating the transport of maternal amino acids, fatty acids, glucose, and calcium to breast milk.[48]

5.4.3 Changes in the Composition of Breast Milk

In the final weeks of pregnancy, the alveoli swell with **colostrum**, a thick, yellowish substance that is high in protein but contains less fat and glucose than mature breast milk (Table 5.2). Before childbirth, some people experience leakage of colostrum from the nipples. In contrast, mature breast milk does not leak during pregnancy and is not secreted until several days after childbirth.

Table 5.2 Compositions of Human Colostrum, Mature Breast Milk, and Cow's Milk (g/L)

Table Source: Betts, J. Gordon, Kelly A. Young, James A. Wise, Eddie Johnson, Brandon Poe, Dean H. Kruse, Oksana Korol, Jody E. Johnson, Mark Womble, Peter DeSaix.
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	Human colostrum	Human breast milk	Cow's milk*
Total protein	23	11	31
Immunoglobulins	19	0.1	1
Fat	30	45	38
Lactose	57	71	47
Calcium	0.5	0.3	1.4
Phosphorus	0.16	0.14	0.9
Sodium	0.5	0.15	0.14

*Cow's milk should never be given to an infant. Its composition is not suitable, and its proteins are difficult for the infant to digest.

Colostrum is secreted during the first 48–72 hours postpartum. Only a small volume of colostrum is produced—approximately 3 ounces in a 24-hour period—but it is sufficient for the newborn in the first few days of life. Colostrum is rich with **immunoglobulins**, which confer gastrointestinal, and also likely systemic, immunity as the newborn adjusts to a nonsterile environment.[49]

After about the third postpartum day, the breast secretes transitional milk that represents an intermediate between mature milk and colostrum. This is followed by mature milk from approximately postpartum day 10 (see Table 2). As you can see in the accompanying table, cow's milk is not a substitute for breast milk. It contains less lactose, less fat, and more protein and minerals. Moreover, the proteins in cow's milk are difficult for an infant's immature digestive system to metabolize and absorb.[50]

The first few weeks of breastfeeding may involve leakage, soreness, and periods of milk engorgement as the relationship between milk supply and infant demand becomes established.

Once this period is complete, the lactating person will produce approximately 1.5 liters of milk per day for a single infant, and more if the person has twins or triplets. As the infant goes through growth spurts, the milk supply constantly adjusts to accommodate changes in demand. A person can continue to lactate for years, but once breastfeeding is stopped for approximately 1 week, any remaining milk will be reabsorbed; in most cases, no more will be produced, even if suckling or pumping is resumed.[51]

Mature milk changes from the beginning to the end of a feeding. The early milk, called **foremilk**, is watery, translucent, and rich in lactose and protein. Its purpose is to quench the infant's thirst. **Hindmilk** is delivered toward the end of a feeding. It is opaque, creamy, and rich in fat, and serves to satisfy the infant's appetite.[52]

During the first days of a newborn's life, it is important for meconium to be cleared from the intestines and for **bilirubin** to be kept low in the circulation. Recall that bilirubin, a product of erythrocyte breakdown, is processed by the liver and secreted in bile. It enters the gastrointestinal tract and exits the body in the stool. Breast milk has laxative properties that help expel meconium from the intestines and clear bilirubin through the excretion of bile. A high concentration of bilirubin in the blood causes jaundice. Some degree of jaundice is normal in newborns, but a high level of bilirubin—which is neurotoxic—can cause brain damage. Newborns, who do not yet have a fully functional blood–brain barrier, are highly vulnerable to the bilirubin circulating in the blood. Indeed, **hyperbilirubinemia**, a high level of circulating bilirubin, is the most common condition requiring medical attention in newborns. Newborns with hyperbilirubinemia are treated with phototherapy because UV light helps to break down the bilirubin quickly (J. Gordon Betts et al., Open Stax A&P second edition, 5.23.2023, 28.6).

For more information

Eunice Kennedy Shriver National Institute of Child Health and Human Development has information about breast milk, ongoing research on the impact of environmental exposures on breast milk safety, and the ecology of breast milk.

Glossary Terms

Bilirubin
: yellowish pigment found in bile, which is a fluid produced by the liver and stored in the gallbladder

Collagenous tissue
: Collagenous tissue may be rigid (bone) or compliant (tendon) or have a gradient from rigid to compliant.

Colostrum
: The first form of breastmilk released by the mammary glands after birth.

Foremilk
: Watery, translucent breast milk that is secreted first during a feeding and is rich in lactose and protein; quenches the infant's thirst.

Hindmilk
: Opaque, creamy breast milk delivered toward the end of a feeding; rich in fat; satisfies the infant's appetite.

Hyperbilirubinemia

A condition characterized by an abnormal increase of BILIRUBIN in the blood, which may result in JAUNDICE. Bilirubin, a breakdown product of HEME, is normally excreted in the BILE or further catabolized before excretion in the urine.

Immunoglobulins

Multi-subunit proteins that function in IMMUNITY. They are produced by B LYMPHOCYTES from the IMMUNOGLOBULIN GENES. They are comprised of two heavy (IMMUNOGLOBULIN HEAVY CHAINS) and two light chains (IMMUNOGLOBULIN LIGHT CHAINS) with additional ancillary polypeptide chains depending on their isoforms. The variety of isoforms include monomeric or polymeric forms, and transmembrane forms (B-CELL ANTIGEN RECEPTORS) or secreted forms (ANTIBODIES). They are divided by the amino acid sequence of their heavy chains into five classes (IMMUNOGLOBULIN A; IMMUNOGLOBULIN D; IMMUNOGLOBULIN E; IMMUNOGLOBULIN G; IMMUNOGLOBULIN M) and various subclasses.

Involution

Postpartum shrinkage of the uterus back to its pre-pregnancy volume.

Lactation

The process by which milk is synthesized and secreted from the mammary glands of the postpartum female breast in response to sucking at the nipple.

Lactocytes

Cells that make and store milk.

Let-down reflex

The release of milk from the alveoli, triggered by infant suckling

Mammary glands

Glands inside the breast that secrete milk.

Montgomery glands

Large sebaceous glands capable of secreting milk.

Prolactin

The pituitary hormone that establishes and maintains the supply of breast milk; also important for the mobilization of maternal micronutrients for breast milk.

Footnotes

43. Betts, J. Gordon, Kelly A. Young, James A. Wise, Eddie Johnson, Brandon Poe, Dean H. Kruse, Oksana Korol, Jody E. Johnson, Mark Womble, Peter DeSaix. "Lactation." Chapter 28.6 in *Anatomy and Physiology.* (2013). Open Stax, 2013 This work is distributed under a CC BY 4.0 license. Available from Open Stax
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5.5: Disorders of Pregnancy

5.5.1 Infections that affect pregnancy & fetal development

The following information is courtesy of Eunice Kennedy Shriver National Institute of Child Health and Human Development.[53]

5.5.1.1 Bacterial Vaginosis

Bacterial vaginosis is the most common vaginal infection in women of reproductive age. It increases the risk of contracting sexually transmitted infections (STIs) and may play a role in preterm labor. The condition results from a change in the balance of bacteria that normally live in the vagina. Having unprotected sex and douching can increase the risk of bacterial vaginosis. The Centers for Disease Control and Prevention (CDC) recommends that pregnant women get tested for bacterial vaginosis if they have symptoms and get treated if necessary.

5.5.1.2 Chlamydia

Chlamydia infection during pregnancy is associated with an increased risk of preterm birth and its complications. If the infection is present and untreated at the time of delivery, it can lead to eye infections or pneumonia in the infant.[2] In most hospitals, infants' eyes are routinely treated with an antibiotic ointment shortly after birth. The ointment can prevent blindness from exposure to chlamydia bacteria during delivery in case the pregnant woman had an undetected infection.

5.5.1.3 Cytomegalovirus (CMV)

Cytomegalovirus (CMV) is a common virus present in many body fluids that can be spread through close personal contact, such as kissing or sharing eating utensils, as well as sexual contact. The virus usually does not cause health problems, but once it is in a person's body, it stays there for life and can reactivate at different times. A pregnant woman may not even know she has the infection, and she may pass the virus on to her fetus, causing congenital CMV infection. Most infants with congenital CMV infection never show signs or have health problems. However, some infants have health problems such as hearing or vision loss, seizures, or intellectual disabilities that are apparent at birth or that develop later during infancy or childhood. Currently, routine screening for CMV during pregnancy is not recommended. Researchers are working on treatments for CMV and vaccines to try to prevent new infections during pregnancy and to reduce the risk of transmission to the infant. Congenital CMV infection can be diagnosed by testing a newborn baby's saliva, urine, or blood. Treatment with antiviral drugs may decrease the risk of health problems and hearing loss in some infected infants.

5.5.1.4 Fifth Disease

Fifth disease is caused by human parvovirus type B19. The virus causes a common childhood disease that spreads easily from person to person. Children who get it usually have a fever and a red rash on their cheeks. Parvovirus B19 usually does not cause problems for a pregnant individual or the fetus, but in rare cases, there might be a miscarriage, or the fetus could

develop anemia. There is no vaccine or treatment for fifth disease. You can reduce your chance of being infected with parvovirus B19 or infecting others by avoiding contact with people who have parvovirus B19 and by thoroughly and regularly washing your hands. Sometimes health care providers recommend testing pregnant individuals to see if they are immune to the virus already.

5.5.1.5 Gonorrhea

Untreated gonorrhea infection in pregnancy has been linked to miscarriage, preterm birth and low birth weight, premature rupture of the membranes surrounding the fetus in the uterus, and infection of the fluid that surrounds the fetus during pregnancy. Gonorrhea can also infect an infant during delivery as it passes through the birth canal. If untreated, infants can develop eye infections and blindness. In most hospitals, infants' eyes are routinely treated with an antibiotic ointment shortly after birth to prevent eye problems from exposure to gonorrhea during delivery, in case the pregnant woman had an undetected infection. Treating gonorrhea as soon as it is detected in pregnant individuals reduces the risk of transmission.

5.5.1.6 Group B Streptococcus (GBS)

Group B streptococcus (GBS) can cause serious health problems in infants. But giving antibiotics during labor can prevent the spread of GBS, so it's important to get tested for the infection during pregnancy.

For more information

More information about GBS and pregnancy can be found at the CDC "About Group B Strep Disease."

5.5.1.7 Genital Herpes

Pregnant women who get infected with genital herpes late in pregnancy have a high risk of infecting their fetus. The risk of infection is particularly high during delivery. Herpes infections in newborns are serious and potentially life-threatening. Infection with the herpes virus during pregnancy or at the time of delivery can lead to brain damage, blindness, and damage to other organs. Rarely, herpes infection during pregnancy can lead to serious complications in the mother, including severe liver damage and possibly death.

- If a pregnant woman has had genital herpes in the past, there are medications that she can take to reduce the chance that she will have an outbreak, which also reduces the risk to her fetus.
- If an individual has active herpes sores when they go into labor, the infant can be delivered by cesarean section to reduce the chance that the infant will come in contact with the virus.

5.5.1.8 Hepatitis B (HBV) & Hepatitis C (HCV)

If a woman is infected with hepatitis B virus (HBV) during pregnancy, the virus could infect her fetus. The likelihood of transmission depends on when during pregnancy the mother was

infected. If the mother gets the infection later in her pregnancy, the risk that the virus will infect her fetus is quite high. If the infection occurs early in pregnancy, the risk of the virus infecting the fetus is much lower. In infants, HBV can be serious and can lead to chronic liver disease or liver cancer later in life. In addition, infected newborns have a very high risk of becoming carriers of HBV and can spread the infection to others.

- In some cases, if a woman is exposed to HBV during pregnancy, she may be treated with a special antibody to reduce the likelihood that she will get the infection.
- All healthy infants should be vaccinated against HBV to give them lifelong protection.
- Infants born to women with evidence of ongoing HBV infection (HBV surface antigen positive) should also receive hepatitis B hyperimmune globulin as soon as possible after birth.

Hepatitis C virus (HCV). If a pregnant individual is infected with HCV during pregnancy, the virus could infect the fetus.

For more information

More information about Hep B during pregnancy can be found from the Centers for Disease Control and Prevention (CDC).

More information about HCV can be found from the CDC.

Hepatitis C virus (HCV). If a pregnant individual is infected with HCV during pregnancy, the virus could infect the fetus. More information from CDC about HCV can be found online.

5.5.1.9 HIV/AIDS

HIV/AIDS. HIV can be passed from mother to infant during pregnancy before birth, at the time of delivery, or after birth during breastfeeding.

5.5.1.10 Listeria

Listeria or listeriosis is a serious infection usually caused by eating food contaminated with a particular type of bacteria. Infection during pregnancy can lead to pregnancy loss, stillbirth, preterm birth, or life-threatening infection of the newborn. Listeriosis is most often associated with eating soft cheeses and raw milk, but recent outbreaks have been associated with fresh and frozen produce. Prevention recommendations include checking food labels to avoid eating unpasteurized cheese (made from raw milk) and other actions. Learn more about preventing listeria during pregnancy.

5.5.1.11 Rubella

Getting rubella (sometimes called German measles) during pregnancy can cause problems with the pregnancy as well as birth defects in the infant. Health care providers recommend that individuals get vaccinated against rubella before they get pregnant. Learn more about rubella and pregnancy.

5.5.1.12 Syphilis

Syphilis may pass from an infected pregnant individual to their fetus during pregnancy. The infection has been linked to preterm birth, stillbirth, and, in some cases, death shortly after birth. Untreated infants who survive tend to develop problems in many organs, including the brain, eyes, ears, heart, skin, teeth, and bones. All pregnant individuals should be screened for syphilis during their first prenatal visit. Pregnant individuals considered to be high risk should be screened again in the third trimester.

5.5.1.13 Toxoplasmosis

Toxoplasmosis is a disease caused by a parasite that can be present in cat feces or used cat litter. Cats get the parasite from eating small animals or birds. In humans, the disease is usually mild, but if the parasite passes from a pregnant individual to the developing fetus, it can cause intellectual disabilities, blindness, or other problems. Individuals who are trying to become pregnant or are pregnant can take steps to prevent exposure to the parasite, such as having someone else clean or change the cat litter box and wearing rubber gloves to handle cat litter or while gardening.

5.5.1.14 Trichomoniasis

Trichomoniasis is a common sexually transmitted infection, caused by a protozoan parasite. Pregnant individuals with trichomoniasis are more likely to deliver their baby prematurely and to have a baby with a low birth weight.

For more information

More information about trichomoniasis can be found from the CDC.

5.5.1.15 Zika

Zika is caused by a virus spread mainly by the bite of a certain type of mosquito, but it is also spread through sexual contact. Although its symptoms are usually mild, Zika infection during pregnancy can cause pregnancy loss and other pregnancy complications, as well as birth defects and other problems for the infant.

5.5.2 Meconium Aspiration

Throughout the second half of gestation, the fetal intestines accumulate a tarry, greenish black **meconium**. The newborn's first stools consist almost entirely of meconium; they later transition to seedy yellow stools or slightly formed tan stools as meconium is cleared and replaced with digested breast milk or formula, respectively. Unlike these later stools, meconium is sterile; it is devoid of bacteria because the fetus is in a sterile environment and has not consumed any breast milk or formula. Typically, an infant does not pass meconium until after birth. However, in 5–20 percent of births, the fetus has a bowel movement in utero, which can cause major complications in the newborn.[54]

The passage of meconium in the uterus signals fetal distress, particularly fetal hypoxia (i.e., oxygen deprivation). This may be caused by maternal drug abuse (especially tobacco or cocaine), maternal hypertension, depletion of amniotic fluid, long labor or difficult birth, or a defect in the placenta that prevents it from delivering adequate oxygen to the fetus. Meconium passage is typically a complication of full-term or post-term newborns because it is rarely passed before 34 weeks of gestation, when the gastrointestinal system has matured and is appropriately controlled by nervous system stimuli. Fetal distress can stimulate the vagus nerve to trigger gastrointestinal **peristalsis** and relaxation of the anal sphincter. Notably, fetal hypoxic stress also induces a gasping reflex, increasing the likelihood that meconium will be inhaled into the fetal lungs.[55]

Although meconium is a sterile substance, it interferes with the antibiotic properties of the amniotic fluid and makes the newborn and pregnant person more vulnerable to bacterial infections at birth and during the perinatal period. Specifically, inflammation of the fetal membranes, inflammation of the uterine lining, or neonatal sepsis (infection in the newborn) may occur. Meconium also irritates delicate fetal skin and can cause a rash.[56]

The first sign that a fetus has passed meconium usually does not come until childbirth, when the amniotic sac ruptures. Normal amniotic fluid is clear and watery, but amniotic fluid in which meconium has been passed is stained greenish or yellowish.[57]

Aspiration of meconium with the first breath can result in labored breathing, a barrel-shaped chest, or a low Apgar score. An obstetrician can identify meconium aspiration by listening to the lungs with a stethoscope for a coarse rattling sound. Blood gas tests and chest X-rays of the infant can confirm meconium aspiration. Inhaled meconium after birth could obstruct a newborn's airways leading to alveolar collapse, interfere with surfactant function by stripping it from the lungs, or cause pulmonary inflammation or hypertension. Any of these complications will make the newborn much more vulnerable to pulmonary infection, including pneumonia.[58]

For more information

More information about antepartum infections can be found in NLM StatPearls "Antepartum Infections."

5.5.3 Hypertensive Disorders

5.5.3.1 Preeclampsia and Eclampsia

The following information is courtesy of Eunice Kennedy Shriver National Institute of Child Health and Human Development.

Preeclampsia and **eclampsia** are pregnancy-related high blood pressure disorders. In preeclampsia, the pregnant person's high blood pressure reduces the blood supply to the fetus, which may get less oxygen and fewer nutrients. Eclampsia is when an individual with preeclampsia develops seizures or coma. Preeclampsia and eclampsia are part of the

spectrum of high blood pressure, or hypertensive, disorders that can occur during pregnancy. The condition can be serious and is a leading cause of preterm birth (before 37 weeks of pregnancy).[59]

For more information

Watch Video 5.1 -Preeclampsia (courtesy of MedlinePlus.gov)

More information about preeclampsia can be found online in NLM StatPearls "Preeclampsia."

5.5.4 Gestational Diabetes

The following information is courtesy of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK).

During pregnancy, the placenta releases **lactogen**. Lactogen reduces the normal function of insulin. This results in glucose in the blood rather than glucose going into the cells (insulin resistance). The body responds to this by producing more insulin. But some individuals are not able to make enough insulin to overcome the insulin resistance. These individuals develop gestational diabetes.

Gestational diabetes can cause an increased chance of having miscarriage or a stillborn baby. It is also more likely that the baby will be born prematurely or weigh too much, which can make delivery difficult and may increase the chance of having a cesarean section. People with gestational diabetes are also more likely to develop preeclampsia.

Usually, a person with gestational diabetes has no symptoms. Sometimes the symptoms are mild, such as being thirstier than normal or having to urinate more often. Testing for gestational diabetes usually occurs between 24 and 28 weeks of pregnancy and is diagnosed at that time. A blood test is used to determine how well the body uses glucose.

Some individuals with gestational diabetes can manage their blood glucose levels by following a healthy eating plan and being physically active. Some also may need insulin or other medications.

For more information

More information about insulin and gestational diabetes can be found in NLM StatePearls "Gestational Diabetes."

5.5.5 Preterm and Postterm Labor

Labor that begins before 37 weeks is called preterm labor (or premature labor). A birth that occurs before 37 weeks is considered a preterm birth. Preterm birth is the most common cause of infant death and is the leading cause of long-term disability related to the nervous system in children. Individuals with symptoms of preterm labor should go to the hospital immediately.

The causes of preterm labor and premature birth are numerous, complex, and only partly understood. Medical, psychosocial, and biological factors may all play a role in preterm labor and birth. There are a number of risk factors for preterm birth, including being pregnant with twins, triplets, or more.

Treatment varies depending upon the gestational age and stage of labor and starts with monitoring for fetal health and signs and symptoms of preterm labor. In some cases, patients are given medications that delay and suppress the contraction of the smooth muscle of the uterus. Delayed umbilical cord clamping results in better long-term outcomes for premature infants.60 More information about premature labor can be found online.

Post-term pregnancy is any pregnancy that extends beyond 42 weeks gestation. There is an increased risk of the baby being stillborn in a post-term pregnancy. Studies indicate that induction of labor by week 41 is associated with better outcomes for parent and child.[61]

5.5.6 Complications with Twins

Twin-to-twin transfusion syndrome (CTS) is a rare condition that occurs during pregnancy with identical twins. Abnormal vasculature in the placenta results in one twin receiving less blood (donor) than the other twin (recipient). The donor twin may have poor growth, **anemia**, and dehydration. The recipient twin may be larger, with too much blood, and increased blood pressure, and an increased risk for heart failure. Untreated, this situation can be fatal for both twins. Once identified, the amount of amniotic fluid and pressure can be decreased and/or a laser can be used to close the abnormal vessels in the placenta.

For more information

Watch Video 5.2 - Twin-to-Twin Transfusion Syndrome (courtesy of MedlinePlus.gov)

More information about TTTS can be found in NLM StatPearls "Twin-to-twin Transfusion Syndrome."

Footnotes

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5.6: Pregnancy that does not result in a Child

Learning Objectives

By the end of this section, learners will be able to

- Identify emergencies associated with miscarriages
- Outline typical history, physical, and laboratory evaluation of miscarriages
- Summarize the management options available for miscarriages
- Describe interprofessional team strategies for improving care coordination and communication to patients undergoing miscarriage

5.6.1 Miscarriage

5.6.1.1 Introduction

Spontaneous abortion or miscarriage is defined as the loss of pregnancy less than 20 weeks gestation. The American College of Obstetricians and Gynecologists (ACOG) estimates it is the most common form of pregnancy loss. It is estimated that as many as 26% of all pregnancies end in miscarriage and up to 10% of clinically recognized pregnancies.[62] Moreover, 80% of early pregnancy loss occurs in the first trimester.[63] The risk of miscarriage decreases after 12 weeks gestation.

The terms miscarriage and abortion are used interchangeably. The term abortion refers to a termination of a pregnancy either natural or induced. There are several terms that describe different states of pregnancy loss. These terms include *threatened, inevitable, complete,* and *missed* abortion. Threatened abortion is the presence of vaginal bleeding in early pregnancy, but on pelvic exam, the **cervical os** is closed, and the transvaginal ultrasound shows a viable fetus.[64] Inevitable abortion is when there is vaginal bleeding, but on the pelvic exam, the cervical os is open, meaning that the fetus or products of conception are expected to pass through the cervix in the near future. On transvaginal ultrasound, there can be either be a viable fetus or not.[65] Complete abortion is when there is initially vaginal bleeding and passing of products of conception through the cervix. On transvaginal ultrasound, there would be no remaining products of conception in the uterus. A missed abortion refers to when there was vaginal bleeding and perhaps some passage of tissue or products of conception. On pelvic exam, the cervical os would be closed. On transvaginal ultrasound, there would be retained products of conception, and there would not be a viable fetus.

Watch this video

Video 5.3 - Ultrasound

MedlinePlus [Internet]. Bethesda (MD): National Library of Medicine (US); [updated 2020 Jun 24]. "Ultrasound." [updated Jan 22, 2022]

5.6.1.2 Etiology

The most common cause of spontaneous pregnancy loss in the first trimester is chromosomal abnormalities. In most cases, it is too early to determine the exact cause of the abnormality. The risk of early pregnancy loss decreases with increasing gestational age and is relatively low after 15 weeks gestation in a genetically normal fetus.[66]

5.6.1.3 Epidemiology

The risk of miscarriage is multivariate, and while some maternal risk factors tend to be more important than others, there is no one predictor of future pregnancy loss. Maternal age is an important predictor of the risk of miscarriage. In women aged 20 to 30, the risk of miscarriage at less than 20 weeks gestation is 8.9%. This increases to 74.7% for women over 40.[67] Another important predictor in the risk of early pregnancy loss is prior obstetrical history. The risk of miscarriage in a future pregnancy is approximately 20% after 1 miscarriage, 28% after 2 consecutive miscarriages, and 43% after 3 or more consecutive miscarriages.[68]

Maternal comorbidities such as **thrombophilia**, **antiphospholipid antibody syndrome**, extremes of maternal weight, and hypertension also increase the risk of miscarriage. Additional maternal risk factors have been identified such as cigarette smoking, large amounts of caffeine use, trauma, and malnutrition.[69]

5.6.1.4 History and Physical

Signs of early pregnancy loss vary and can often be confused with complications or symptoms of a normal intrauterine pregnancy as well as **ectopic pregnancy**. Most commonly patients present with pelvic and abdominal cramping with or without vaginal bleeding and a positive pregnancy test or missed or abnormal menstrual cycle.

5.6.1.5 Evaluation

The most important determination when evaluating a pregnant patient with symptoms of miscarriage is whether or not this is a true loss, an ectopic pregnancy, **molar pregnancy**, or a viable pregnancy with complications.

Ultrasound is the gold standard for examining intrauterine contents and viability. This, paired with a quantitative **human chorionic** (hCG) hormone level, can help determine viability. hCG levels should double in 48 hours on serial exams.[70]

At hCG levels between 1000 to 2000, it has been determined that transvaginal ultrasound (TVUS) is the most sensitive study for identifying intrauterine contents such as a gestational sac with or without a fetus or embryo. There have been multiple studies that reveal a correlation between hCG levels and the stage of embryonic development seen on ultrasound. For instance, at a range of serum hCG between 800 to 1500 UI/I, a 1 to 3 mm gestational sac should be visible on TVUS. A yolk sac should be detectable within the range hCG level of 4500 to 7500 UI/I, with fetal heart motion visible at a range of 8650 to 12,200 U/I.[71]

Cardiac activity should be identifiable at a crown-rump length of 5 mm or greater.[72]

Findings suggestive of but not definitive of early pregnancy loss on transvaginal ultrasound are a crown-rump length (CRL) of 7 mm or greater without fetal cardiac activity or an empty gestational sac with no embryo of 16 to 24 mm or greater in diameter.[73]

The American College of Obstetricians and Gynecologists (ACOG), therefore, recommends serial hCG levels as well as serial ultrasounds to determine viability.[74]

5.6.1.6 Treatment/Management

Treatment options include expectant management, medication, or surgical interventions.

Decisions are often made jointly with the patient and the obstetrician as to which path to choose. As long as patients are **hemodynamically** stable and do not require emergency surgery, there is no difference in long-term outcomes when comparing these treatment options.

Expectant management is typically limited to those miscarrying in the first trimester because of lack of studies beyond that timeframe and presumed increased risk of bleeding complications beyond that. Approximately 80% of patients achieve complete passage of intrauterine contents within 8 weeks. [75]

Medical management can be used in the absence of contraindications, including severe **anemia**, bleeding disorders, or infection.[76] **Misoprostol**, a **prostaglandin** analog, is given in 1 or 2 doses to achieve induced passage of intrauterine contents. Misoprostol can be taken in the oral form, sublingually, or as a vaginal suppository. Most women will achieve complete expulsion within 3 days, and very few need subsequent uterine **curettage**.

Surgical evacuation is another option in the treatment of early pregnancy loss and is achieved either with sharp curettage or suction curettage. Surgical evacuation is preferred in women who present with hemorrhage, hemodynamic instability, or signs of infection because these conditions require urgent treatment.[77] This is also the preferred method of treatment for women with comorbid conditions such as cardiovascular disease, infection, severe anemia, or bleeding disorders.

Success rates for surgical evacuation reach 99%[78]. The risk of complications among all 3 treatment options remains low and is equivocal in patients without **comorbid** conditions or contraindications to one form or another. Hemorrhage and infection appear to be the 2 most common complications across all three treatment types.

Another important consideration that must be taken into account when evaluating pregnant females with complaints consistent with miscarriage is their **Rh status**. This is important because the fetus could differ in Rh type from the mother. If mother and fetus have different Rh types, this sets up a scenario where the mother could be exposed to a differing Rh from exposure to the fetal blood type. This could cause the mother to produce antibodies against the different Rh to which it was exposed. These antibodies can then cross the placenta and affect the fetus. This can present serious consequences to the fetus and cause the fetus to develop a high output cardiac failure state known as **hydrops fetalis**, which is nearly 100% fatal. All

women who have a blood type that is Rh(D) negative who are diagnosed with early pregnancy loss and have not been sensitized should receive Rh(D)-immune globulin 50 micrograms (or 300 micrograms if available) to prevent **alloimmunization**. Rh(D)-immune globulin should be administered as early as possible, within 72 hours, of diagnosis of miscarriage and immediately following surgical intervention.

To date, there exists no proven strategy to prevent early pregnancy loss. Suggestions such as pelvic rest and hormone administration have not been proven. However, some physicians advocate progestin administration early to women who have experienced multiple prior miscarriages. **Anticoagulants** or aspirin administration has only been proven to be beneficial in women with antiphospholipid antibody syndrome.[79]

5.6.1.7 Differential Diagnosis

The **differential** for early pregnancy loss includes ectopic pregnancy, viable pregnancy with implantation bleeding, molar pregnancy, and viable pregnancy with complications. There are also non-uterine causes of bleeding that can be mistaken for miscarriage such as vaginal trauma.

5.6.1.8 Deterrence and Patient Education

Patient education is important in early pregnancy loss as this can be an emotionally difficult diagnosis. Patient education should focus on maternal health and preparing for future pregnancy. There has been no data to support delaying conception after an early pregnancy loss to prevent subsequent miscarriage or complications.[80]Although most physicians recommend abstaining from vaginal intercourse for 1 to 2 weeks after the passage of tissues, there is no data to support this recommendation.[81]

Patients should also be provided with education regarding contraception after a miscarriage including the use of an intrauterine device or hormonal contraception as both have been deemed safe for use immediately following an early pregnancy loss.[82]

It is important to provide each Rh(D) negative patient education on alloimmunization and risk of future pregnancy with regards to receiving Rh(D) immune globulin.

Most importantly, while there are no proven strategies to reduce the risk of subsequent pregnancy loss after a miscarriage, patient education on maternal health is important. Patients should be provided with education on managing blood pressure, extremes of weight, and cigarette smoking cessation.

5.6.1.9 Enhancing Healthcare Team Outcomes

Treating patients who experience pregnancy loss requires close coordination between all members of the care team. Follow-up care with an **obstetrician** needs to be coordinated. Clear and concise discharge instructions need to be given to the patient. This experience for the patient can be very emotionally taxing and must be handled with extreme compassion and sensitivity.

Pearls and Other Issues

- Miscarriage is the loss of a pregnancy before 20 weeks gestation.
- Before 12 weeks gestation, most pregnancy loss is due to chromosomal abnormalities.
- Maternal health such as high blood pressure, obesity, and cigarette smoking may increase the risk of miscarriage.
- Advanced maternal age has been proven to increase the risk of miscarriage with risks as high as 74% for women over age 40.
- It is important to evaluate using transvaginal ultrasound to determine whether or not a pregnancy is viable.
- For women with no comorbid conditions, all 3 miscarriage treatment options (medical, surgical, or expectant management) have been proven equally safe and effective.

5.6.2 Abortion

Learning Objectives

- Describe options available to a patient with a positive pregnancy test
- Explain the methods of abortion available and describe the pros and cons of each method
- Outline the steps of medical abortion, identify complications, and explain how these can be managed
- Review steps of aspiration or surgical abortion, identify complications, and explain how these can be managed

5.6.2.1 Introduction

Abortion is one of the common procedures performed among women. In the US, in 2014, 1 in 5 pregnancies ended in abortion, and 1 in 4 women are estimated to have an abortion in their lifetimes.[83] Globally, 1 in 4 pregnancies ends in abortion. It is important that all providers understand the **prevalence** of abortion, the options available, the safety, the restrictions, and the access issues associated with abortion to be able to provide safe and optimal quality of care to the patients. This activity reviews the options available to the patient when they have a positive pregnancy test, describes the various methods of safe abortion care, outlines the indications and contraindications of the various methods of abortion, explains the techniques of performing an abortion, and outlines the complications and steps that help manage these complications.

A committee of the National Academies of Sciences, Engineering, and Medicine reviewed the data available and confirmed in their report in 2018 that all forms of abortion, including medication and aspiration abortion, are safe and effective and that the only factors decreasing safety are those decreasing access.84 First trimester abortions pose no long-term risk of infertility, ectopic pregnancy, spontaneous abortion, or breast cancer. Abortion does not pose a hazard to a patient's mental health.[85]

Abortion can be completed with medication or by a procedure which is often called surgical abortion or aspiration abortion. The reasons for terminating a pregnancy may be maternal factors or fetal indications. Preabortion workup often includes obtaining a complete blood count, **coagulation** profile, type and crossmatch, sexually transmitted infection screen, human chorionic gonadotropin levels, and a pelvic ultrasound to confirm that the pregnancy is intrauterine. Medication abortion can be completed at home. The aspiration abortion is usually performed in a clinic or hospital under local anesthesia, with or without conscious sedation.[86]

5.6.2.2 Anatomy and Physiology

Understanding the normal anatomy of the female genital tract helps manage complications of medication abortion and performing the aspiration or surgical abortion.

5.6.2.3 Indications

According to the National Abortion Federation 2020 Clinical Policy Guidelines for Abortion Care, any patient choosing to have an abortion must be counseled in a nonjudgmental manner about their options. The patient's desires must be explored, and options including continuing the pregnancy, parenting, adoption, and termination of pregnancy should be discussed during this time. If the patient desires to end the pregnancy, then the benefits, risks, and details of the process need to be discussed.

Early medication abortion is noninvasive, avoids the risks of a surgical procedure and anesthesia, and can be done up to 11 weeks. It allows for more privacy and control for the patient. It usually involves the use of medications such as **mifepristone** and **misoprostol,** and rarely, **methotrexate.**[87] Medication abortion after the first trimester can also be performed safely and effectively by trained clinicians in settings that are equipped to support the patient. Induced fetal demise may be necessary for later gestational ages.

Aspiration or surgical abortion involves a procedure and the use of instruments in the vagina, cervix, and uterus to remove the pregnancy. The procedure is usually short. Aspiration abortion might be needed if medication abortion fails or the woman bleeds heavily during the medication abortion. According to the 2020 National Abortion Federation Clinical Policy Guidelines for Abortion Care, the **incidence** of aspiration after medication abortion is 2-9% for >63 days LMP and even less to less than 1 to 3% when the second dose of misoprostol is used. The other indication for aspiration or surgical abortion is suspected molar pregnancy.[88]

5.6.2.4 Contraindications

Contraindications to medication abortion include:

- **IUD** in place - may be removed before the medication abortion
- Allergy to medication used
- **Chronic adrenal failure**, especially in patients who are on long-term systemic corticosteroid therapy
- Suspected ectopic pregnancy

- **Hemorrhagic** disorders
- Anticoagulant therapy, excluding aspirin
- **Hemodynamic** instability
- Inherited **porphyria**

Anemia, seizures, asthma on steroid inhalers, obesity, breastfeeding, HIV or AIDs, and sexually transmitted infection are not considered **contraindications**.

Exercise care in case of any **coagulopathy** or any other bleeding disorder, but these are not contraindications for surgical or aspiration abortion. In case the products of conception are not confirmed on the **aspirate** after a surgical abortion, trend the HCG levels to ensure ectopic pregnancy or pregnancy of unknown location is ruled out and treated if this is the case.

5.6.2.5 Equipment

Equipment used for aspiration abortion includes:

- Vacuum single valve aspirator/Manual vacuum aspirator plus
- Locking 60 cc syringe
- **Cannula**
- Specimen cup
- Standard Graves speculum
- Single tooth **tenaculum**
- Ring forceps with cotton
- **Small polyp forceps**
- **Pratt cervical dilators**
- Gauze
- Curette

5.6.2.6 Preparation

- Medical Abortion

Once the pregnancy test is positive and the patient has opted for abortion, take the following steps to ensure the patient is eligible for **medication abortion**.

Confirm the last menstrual period (LMP) and estimate the gestational age(GA). The first day of LMP alone is an accurate means of estimating the gestational age through the mid-first trimester. If the LMP is not known or unreliable, obtain an ultrasound to date the pregnancy. There is no need for an ultrasound prior to medication abortion in all cases.[89]

Take a detailed medical history from the patient, including allergies, review of medical conditions, medications, and substance use. Complete a physical exam if indicated by the patient's history and symptoms. Patients choosing medication abortion with a definite LMP do not need a pelvic exam. The pelvic and **bimanual** exams may be performed prior to the procedure. Patients with no medical conditions do not need routine pre-abortion lab testing. Labs that are recommended include glucose for patients with **Insulin Dependent Diabetes**

Mellitus, INR for those on anticoagulants (warfarin) beyond 12 weeks of GA, rhesus D testing for consenting patients beyond 56 days from LMP and unknown Rh status, **hemoglobin** and **hematocrit** only for those with history or symptoms of anemia, gonorrhea and chlamydia testing for those at increased risk or less than 25 years of age. When clinical dating is uncertain, an ultrasound scan is performed to confirm the location and viability of the pregnancy. Combined **mifepristone/**misoprostol regimens are more effective than misoprostol alone or methotrexate/misoprostol**.**[90]

According to the National Abortion Federation (NAF) 2020 guidelines, after counseling the patient about the methods and the pros and cons of the procedure, determine pregnancy dating and eligibility for medication abortion by one of the following.

1. LMP< or = 77 days from the anticipated date of mifepristone use and
    i. First positive pregnancy test was less than 6 weeks ago
    ii. No ectopic risk factors, including previous ectopic pregnancy, history of Pelvic Inflammatory Disease, Intra Uterine Device in place at the time of conception, bleeding since LMP, or unilateral pelvic pain
    iii. Regular menses with no hormonal contraception use 2 months prior to LMP
2. LMP and physical examination, including a bimanual examination if needed
3. Pelvic ultrasound to date the pregnancy

Ensure the patient has no contraindications for medication abortion. Obtain signed informed consent, including the manufacturer's patient agreement and medication guide from the patient, after discussing the risks involved in medication abortion and the side effects of the medication.

Side effects of mifepristone mainly include vaginal bleeding. Side effects of misoprostol include nausea, vomiting, diarrhea, low-grade fever, and muscle aches that resolve within 6 hours of use. If the mifepristone or misoprostol are vomited after less than 15 to 30 minutes of use, repeating the dosing can be considered. **Antiemetic** medications can help manage nausea and vomiting. Vaginal bleeding usually starts 4 to 6 hours after misoprostol use and can be heavy with clots. Patients bleeding heavier than 2 pads per hour or for over 2 hours need to be evaluated by the clinician. Bleeding lasts from 1 to 45 days. Patients need to be informed of the risks, including heavy bleeding that may need additional doses of misoprostol, NSAIDs, the need for aspiration in some cases, the small risk for **endometritis**, failure of medication abortion needing additional doses of misoprostol or aspiration, and **teratogenicity** of misoprostol. The patient's phone number or email is confirmed. Lastly, transportation for follow-up is ensured.

- Surgical Abortion

After taking a detailed medical history, pregnancy must be confirmed, and gestational age must be assessed. Ultrasound is often used to confirm the location of the pregnancy. Baseline vitals, including pulse and blood pressure, must be performed for all, and a physical exam for those

indicated by patient symptoms and history. Confirm and arrange all the instruments required for the procedure ahead of time.

5.6.2.7 Technique

- Medical Abortion - Mifepristone/Misoprostol protocol

Mifepristone - one 200mg tablet is swallowed on day 1 in the clinic or at home. Misoprostol can be administered in the following routes

1. **Buccally**: Four 200mcg tablets are placed between gum and cheek for 30 minutes and swallowed thereafter, 24 to 48 hours after mifepristone administration.
2. Vaginal: Four 200mcg tablets of misoprostol can also be placed in the vagina 6 to 48 hours after the mifepristone
3. Sublingual: Two to four 200mcg tablets of misoprostol under the tongue for 30 minutes

According to the NAF 2020 guidelines, if a patient is > 63 days from LMP, a second dose of 800mcg misoprostol can be administered 4 hours after the first dose. If the patient more than 70 days from LMP, a second dose of 800mcg misoprostol is recommended 4 hours after mifepristone.

NSAIDs help pain management for the patient while at home,[91] and the routine prescription of opiates is not necessary. A short prescription for **opiates** may be prescribed in case NSAIDs are not tolerated or cannot be used due to an allergy. **Prophylactic** antibiotics are not routinely recommended for medical abortion. Contraception can be discussed if the patient is willing to engage at this time.

The patient is instructed to contact the provider if

1. Bleeding heavily, soaking 2 or more pads in 2 or more consecutive hours
2. Severe pain that is not responding to the medication prescribed
3. Fever of more than 100.4 degrees Fahrenheit (38 C) for more than 24 hours after misoprostol
4. No bleeding within 24 hours of misoprostol
5. Nausea, vomiting, diarrhea, abdominal pain more than 24 hours after misoprostol

According to the NAF 2020 guidelines, an ultrasound is not needed to confirm the completion of a successful abortion if using clinical history and home pregnancy tests.92 It can be performed by checking baseline serum HCG on the day of mifepristone and one after misoprostol. A decrease of hCG of 50% from baseline by 72 hours, 60% by 4-5 days,[93] and 80% by 7 days from initiating treatment94 are confirmative of a successful **MAB**. It can also be confirmed by ultrasound examination before and after medication administration. An absence of the gestational sac or embryo confirms the success of the abortion.

According to the NAF 2020 guidelines, when methotrexate and misoprostol are used, an evidence-based regimen of oral or intramuscular methotrexate followed in three to five days with vaginal misoprostol is recommended for gestations up to 63 days.

- Surgical/Aspiration Abortion

Aspiration abortion is performed up to 16 weeks.

Technique: Don gloves, perform a bimanual examination, and confirm the uterine position and size. Confirm you have all the equipment you need. Adjust table and light, insert the speculum, and evaluate and collect samples for infection screening and testing. Apply the antiseptic solution to the cervix. Administer a **paracervical block** if the patient is awake. Place the tenaculum on the cervix. Dilate the cervix to the size of the cannula you will be using (gestational age in weeks + or - 1 to 2 mm). The cervix is dilated using tapered dilators like Pratt or Denniston dilators.[95] Misoprostol can also be used for cervical preparation prior to the procedure.[96] Osmotic dilators are used when cervical dilation is expected to be difficult. Insert cannula through the cervix with gentle but firm traction on the cervix using the tenaculum. Connect the aspirator to the cannula. The procedure is completed by aspiration of the uterus using a manual or electric vacuum and not by sharp curettage. The procedure is considered complete when the uterus is empty. Ultrasound can be used to confirm the completion of the procedure. Remove the tenaculum and the speculum. Check for the adequacy of the products of conception. If molar pregnancy is suspected, send the tissue to the pathologist for examination. Inform the patient of the complete procedure and the recovery process. The procedure usually takes 5 to 10 minutes, and antibiotics are given at the end of the procedure to avoid infection.

Dilatation and evacuation are performed beyond 16 weeks by experienced clinicians in appropriate clinical settings. **Intravenous** access should be established prior to the procedure. If induced fetal demise is used, appropriate evidence-based protocols must be followed. **Osmotic dilators** including **Dilapan** and **laminaria**, misoprostol, mifepristone, and or other cervical agents are used to achieve adequate dilation. Osmotic dilators may be placed in the cervix prior to the procedure. All instruments entering the uterine cavity must be sterile. Ultrasound should be used during the procedure to locate fetal parts, visualize instruments, and verify the completion of the procedure, thus reducing the risk of uterine perforation and shortening the procedure.[97] **Uterotonics** must be used to help control uterine bleeding during and after the procedure.

5.6.2.8 Complications

Complications of Medication abortion[98] and the management options when these arise include the following:

1. Heavy bleeding and or severe cramping.
    i. Repeat misoprostol/NSAIDs
    ii. Uterine aspiration
    iii. Blood transfusion99

2. Failure of medication abortion
    i. Uterine aspiration
    ii. Repeat misoprostol100
3. Infection - **endometritis** (fever>24 hours after misoprostol, abdominal and pelvic pain, vaginal discharge, uterine/adnexal tenderness)
    1. Uterine aspiration if retained pregnancy tissue in the uterus and antibiotics per CDC guidelines
    2. Immediate admission to the hospital will be required if hemodynamically unstable and aggressive treatment with antibiotics.
4. Ectopic pregnancy
    i. Treat or refer for the next steps

5.6.2.9 Aspiration **Abortion** 101

1. **Vasovagal** episode
    1. Cool compresses
    2. Elevate legs above the chest
    3. Isometric extremity contractions
    4. Atropine IM 0.4mg or 0.2mg IV, max dose 2mg
2. Heavy bleeding - remember 6 Ts102
    i. Tone - Uterine massage and consider uterotonics like methergine, misoprostol
    ii. Tissue - Ensure there is no retained tissue in the uterus
    iii. Trauma - Identify the source of bleeding and address it, especially cervical and vaginal tears
    iv. Thrombin - review the history of bleeding and consider additional tests like CBC, coagulation tests, clotting test
    v. Treatment - Consider IV fluid bolus and uterine tamponade with a **foley's catheter bulb**
    vi. Transfer - to the hospital if need be, monitor vitals closely

5.6.2.10 Perforation

1. Stop the suction, examine the contents of the aspirate for omentum, bowel, products of conception
2. If stable, continue and complete the procedure under ultrasound guidance. Consider uterotonics and antibiotics. Observe for 1.5 to 2 hours post-procedure.
3. If the patient is unstable, transfer
4. Incomplete abortion
    i. Offer misoprostol or
    ii. Reaspiration if bleeding, in pain or have signs of infection
5. Accumulation of blood in the uterus post-procedure - patient usually complains of pain and rectal pressure, and this is usually accompanied by hypotension and or **vasovagal syncope**

i. Uterine aspiration or uterotonics

6. Endometritis (fever, pain, vaginal discharge, leukocytosis)
   i. Antibiotics per the CDC **PID** regimen
   ii. Ultrasound +/- aspiration procedure
   iii. Test for gonorrhea and chlamydia
7. Ectopic Pregnancy - suspect if **POC** inadequate at the time
   i. Transfer to hospital for treatment with methotrexate vs. surgical management

5.6.2.11 Clinical Significance

Any patient with a positive pregnancy test should be counseled about thier options at the time of the consultation in a nonjudgemental manner. Abortion is an overall safe and effective procedure. Providers should be aware of the prevalence of abortion, the restrictions, and the access issues associated with abortion and strive to provide safe care to patients seeking an abortion.

5.6.2.12 Enhancing Healthcare Team Outcomes

Abortion is safer when the laws regarding abortion are less restrictive and in countries where the gross national income is higher. The stigma associated with abortion is another recognized barrier to accessing safe abortion and can contribute to the maternal mortality rate worldwide. Overall, ensuring women have better access to reproductive health care, including modern methods of contraception, can ensure the care provided is safe and help reduce maternal and infant mortality rates.

Glossary Terms

Alloimmunization
: **i**mmune response to foreign antigens after exposure to genetically different cells or tissues

Anemia
: condition in which the body does not have enough healthy red blood cells. Red blood cells provide oxygen to body tissues

Anticoabulants
: agents that prevent BLOOD CLOTTING

Antiemetic
: drug used to prevent NAUSEA or VOMITING

Antiphospholipid antibody syndrome
: condition *in which the immune system mistakenly creates antibodies that attack tissues in the body*

Aspirate
: aspiration means to draw in or out using a sucking motion

Buccally
: *buccal means relating to or located in the cheeks*

Cannula
: short, hollow cylinders or tubes for insertion into a canal, vessel, or body cavity

Cervical os
: opening between the cervix and the corpus

Coagulopathy

blood's ability to coagulate (form clots) is impaired

Coagulation

process of the interaction of BLOOD COAGULATION FACTORS that results in an insoluble FIBRIN clot

Comorbid

diseases or medical conditions that are simultaneously present in a patient

Contrainidcations

specific situation in which a medicine, procedure, or surgery should not be used because it may be harmful to the person

Curretage

scraping, usually of the interior of a cavity or tract, for removal of new growth or other abnormal tissue, or to obtain material for tissue diagnosis. It is performed with a curet (curette), a spoon-shaped instrument designed for that purpose

Dilipan

mechanical cervical dilator designed for gentle and predictable cervical ripening in the induction of labor

Dilation

first stage of childbirth, involving an increase in cervical diameter

Ectopic pregnancy

implantation of an embryo outside of the uterus

Endometritis

inflammation of the ENDOMETRIUM, usually caused by intrauterine infections. Endometritis is the most common cause of postpartum fever

Foley catheter

medical device that helps drain pee from your bladder

Hematocrit

Hematocrit is a blood test that measures how much of a person's blood is made up of red blood cells. This measurement depends on the number of and size of the red blood cells

Hemodynamics

movement and the forces involved in the movement of the blood through the CARDIOVASCULAR SYSTEM

Hemoglobin

protein in red blood cells that carries oxygen

Hemorrhagic disorders

hemorrhage is the medical term for bleeding. It most often refers to excessive bleeding. Hemorrhagic diseases are caused by bleeding, or they result in bleeding (hemorrhaging)

Human chorionic hormone (hCG)

hormone produced primarily by syncytiotrophoblastic cells of the placenta during pregnancy

Hydrops fetalis

occurs when abnormal amounts of fluid build up in two or more body areas of a fetus or newborn; it is a symptom of underlying problems

Incidence

the number of new cases of a condition, symptom, death, or injury that develop during a specific time period, such as a year. Incidence shows the likelihood that a person in a certain population will be newly affected by that condition in a specific period of time

Intravenous

means "within a vein;" most often it refers to giving medicines or fluids through a needle or tube inserted into a vein - this allows the medicine or fluid to enter your bloodstream right away

IUD

intrauterine device (IUD) is a small plastic T-shaped device used for birth control; it is inserted into the uterus where it stays to prevent pregnancy

MAB

medical abortion

Methodrexate

antineoplastic antimetabolite with immunosuppressant properties; it is an inhibitor of TETRAHYDROFOLATE DEHYDROGENASE and prevents the formation of tetrahydrofolate, necessary for synthesis of thymidylate, an essential component of DNA

Mifepristone

Mifepristone (Korlym) is used to treat hyperglycemia (high blood sugar) in people with a certain type of Cushing's syndrome in which the body makes too much cortisol (a hormone) and who have failed surgery or cannot have surgery to treat this condition

Misoprostol

used to prevent ulcers in people who take certain arthritis or pain medicines, including aspirin, that can cause ulcers; it protects the stomach lining and decreases stomach acid secretion

Molar pregnancy

rare complication of pregnancy involving unusual growth of cells called trophoblas

Obstetrician

qualified medical professionals who specialize in OBSTETRICS - a medical-surgical specialty concerned with management and care of women during pregnancy, parturition, and the puerperium

Opiates

drugs used to treat pain

Ostmoci dilators

medical implements used to dilate the uterine cervix by swelling as they absorb fluid from surrounding tissue

Paracervical block

nerve block used during obstetric and gynecologic procedures

Porphyria

group of rare disorders that result from a buildup of natural chemicals called porphyrins in the body

Prevalence

total number of cases of a given disease in a specified population at a designated time; it is differentiated from INCIDENCE, which refers to the number of new cases in the population at a given time

Prophylactic

medicine or course of action used to prevent disease

Prostaglandin

group of compounds derived from unsaturated 20-carbon fatty acids, primarily arachidonic acid, via the cyclooxygenase pathway; they are extremely potent mediators of a diverse group of physiological processes

Rh status

blood-type classification based on the presence or absence of the antigen Rh on the erythrocyte membrane surface

Syncope

loss of consciousness for a short period of time

Tenaculum

surgical instrument, usually classified as a type of forceps

Teratogenecity

ability to cause defects in a developing fetus

Thrombophilia

disorder of HEMOSTASIS in which there is a tendency for the occurrence of THROMBOSIS

Uterotonics

medication used to induce contraction or greater tonicity of the uterus to prevent or reduce hemorrhage

Vasovagal syncope

loss of consciousness due to a reduction in blood pressure that is associated with an increase in vagal tone and peripheral vasodilation

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5.7: Glossary

To review common anatomical and directional terms, please see Chapter 1. Anatomy of the Female Reproductive System.

Acidosis - Acidosis is a condition in which there is too much acid in the body fluids. It is the opposite of alkalosis (a condition in which there is too much base in the body fluids). [6]

Adrenal glands - endocrine glands located at the top of each kidney that are important for the regulation of the stress response, blood pressure and blood volume, water homeostasis, and electrolyte levels. [1]

Adrenocorticotropic - An anterior pituitary hormone that stimulates the ADRENAL CORTEX and its production of CORTICOSTEROIDS. ACTH is a 39-amino acid polypeptide of which the N-terminal 24-amino acid segment is identical in all species and contains the adrenocorticotrophic activity. Upon further tissue-specific processing, ACTH can yield ALPHA-MSH and corticotrophin-like intermediate lobe peptide (CLIP). [7]

Afterbirth - third stage of childbirth in which the placenta and associated fetal membranes are expelled. [3]

Anemia - Anemia is a condition in which the body does not have enough healthy red blood cells. Red blood cells provide oxygen to body tissues. [6]

Alloimmunization

alveolar capillaries

Androgens - Male sex hormones; for example, testosterone. [10]

Antiemetic - Drug used to prevent NAUSEA or VOMITING. [7]

Anticoagulants - Agents that prevent BLOOD CLOTTING. [7]

Antispholipid antibody syndome

Apgar Score - Apgar is a quick test performed on a baby at 1 and 5 minutes after birth. The 1-minute score determines how well the baby tolerated the birthing process. The 5-minute score tells the health care provider how well the baby is doing outside the mother's womb. It also helps measure how well the baby responds if resuscitation is needed right after birth. [6]

Aspirate - Aspiration means to draw in or out using a sucking motion. [6]

Bile - Bile is a fluid that is made and released by the liver and stored in the gallbladder. Bile helps with digestion. It breaks down fats into fatty acids, which can be taken into the body by the digestive tract. [6]

Bilirubin - Bilirubin is a yellowish pigment found in bile, which is a fluid produced by the liver and stored in the gallbladder. [6]

Bimanual

Blastocyst - A post-MORULA preimplantation mammalian embryo that develops from a 32-cell stage into a fluid-filled hollow ball of over a hundred cells. A **blastocyst** has two distinctive tissues. The outer layer of trophoblasts gives rise to extra-embryonic tissues. The inner cell mass gives rise to the embryonic disc and eventual embryo proper. [7]

Braxton Hicks - weak and irregular peristaltic contractions that can occur in the second and third trimesters; they do not indicate that childbirth is imminent. [3]

Brown adipose tissue - highly vascularized fat tissue that is packed with mitochondria; these properties confer the ability to oxidize fatty acids to generate heat. [4]

Bucally

Cannula - Short, hollow cylinders or tubes for insertion into a canal, vessel, or body cavity. [7]

Capillary - smallest of blood vessels where physical exchange occurs between the blood and tissue cells surrounded by interstitial fluid. [1]

carotid arteries - **T**wo principal arteries on both sides of the neck that supply blood to the head and neck; each divides into two branches, the internal carotid artery and the external carotid artery. [7]

cervical os - Neck portion of the UTERUS between the lower isthmus and the VAGINA forming the cervical canal.

chloasma

Chronic adrenal failure

Coagulation - The process of the interaction of BLOOD COAGULATION FACTORS that results in an insoluble FIBRIN clot.

Coagulopathy

collagenous tissue

Comorbid

contractile myoepithelial cells

Contraindication - A contraindication is a specific situation in which a medicine, procedure, or surgery should not be used because it may be harmful to the person. [6]

Corpus luteum - transformed follicle after ovulation that secretes progesterone. [1]

Curettage - A scraping, usually of the interior of a cavity or tract, for removal of new growth or other abnormal tissue, or to obtain material for tissue diagnosis. It is performed with a curet (curette), a spoon-shaped instrument designed for that purpose. [7]

decidual cells

Diabetes Mellitus - A heterogeneous group of disorders characterized by HYPERGLYCEMIA and GLUCOSE INTOLERANCE. [7]

Differential diagnosis - Determination of which one of two or more diseases or conditions a patient is suffering from by systematically comparing and contrasting results of diagnostic measures. [7]

Dilapan

Dilation - first stage of childbirth, involving an increase in cervical diameter. [3]

Ductus Arteriosus - shunt in the fetal pulmonary trunk that diverts oxygenated blood back to the aorta Ductus Venosus. [1]

dyspnea - Difficult or labored breathing. [7]

eclampsia - Eclampsia is the new onset of seizures or coma in a pregnant woman with preeclampsia. These seizures are not related to an existing brain condition. [6]

Ectopic pregnancy - implantation of an embryo outside of the uterus. [2]

effaces

Endometrium - inner lining of the uterus, part of which builds up during the secretory phase of the menstrual cycle and then sheds with menses. [1]

Endometritis - Inflammation of the ENDOMETRIUM, usually caused by intrauterine infections. Endometritis is the most common cause of postpartum fever. [7]

Endothelium - A layer of epithelium that lines the heart, blood vessels, lymph vessels, and the serous cavities of the body. [7]

Episiotomy - incision made in the posterior vaginal wall and perineum that facilitates vaginal birth. [3]

Erythrocyte - Red blood cell. Mature erythrocytes are non-nucleated, biconcave disks containing HEMOGLOBIN whose function is to transport OXYGEN. [7]

Expulsion - second stage of childbirth, during which the mother bears down with contractions; this stage ends in birth. [3]

foley catheter

Foramen Ovale - shunt that directly connects the right and left atria and helps to divert oxygenated blood from the fetal pulmonary circuit. [1]

Foremilk - watery, translucent breast milk that is secreted first during a feeding and is rich in lactose and protein; quenches the infant's thirst. [5]

Gestation

Hematocrit - Hematocrit is a blood test that measures how much of a person's blood is made up of red blood cells. This measurement depends on the number of and size of the red blood cells. [6]

Hemodynamics - The movement and the forces involved in the movement of the blood through the CARDIOVASCULAR SYSTEM. [7]

Hemoglobin - Hemoglobin is a protein in red blood cells that carries oxygen. The hemoglobin test measures how much hemoglobin is in your blood. [6]

Hemorrhagic - Hemorrhage is the medical term for bleeding. It most often refers to excessive bleeding. Hemorrhagic diseases are caused by bleeding, or they result in bleeding (hemorrhaging). [6]

hyperbilirubinemia - A condition characterized by an abnormal increase of BILIRUBIN in the blood, which may result in JAUNDICE. Bilirubin, a breakdown product of HEME, is normally excreted in the BILE or further catabolized before excretion in the urine. [7]

Hindmilk - opaque, creamy breast milk delivered toward the end of a feeding; rich in fat; satisfies the infant's appetite. [5]

human chorionic (hCG) hormone

Hydrops fetalis - Hydrops fetalis is a serious condition. It occurs when abnormal amounts of fluid build up in two or more body areas of a fetus or newborn. It is a symptom of underlying problems. [6]

Iliac artery - Either of two large arteries originating from the abdominal aorta; they supply blood to the pelvis, abdominal wall and legs. [7]

Immunoglobulins - Multi-subunit proteins which function in IMMUNITY. They are produced by B LYMPHOCYTES from the IMMUNOGLOBULIN GENES. They are comprised of two heavy (IMMUNOGLOBULIN HEAVY CHAINS) and two light chains (IMMUNOGLOBULIN LIGHT CHAINS) with additional ancillary polypeptide chains depending on their isoforms. The variety of isoforms include monomeric or polymeric forms, and transmembrane forms (B-CELL ANTIGEN RECEPTORS) or secreted forms (ANTIBODIES). They are divided by the amino acid sequence of their heavy chains into five classes (IMMUNOGLOBULIN A; IMMUNOGLOBULIN D; IMMUNOGLOBULIN E; IMMUNOGLOBULIN G; IMMUNOGLOBULIN M) and various subclasses. [7]

Incidence - Incidence is the number of new cases of a condition, symptom, death, or injury that develop during a specific time period, such as a year. Incidence shows the likelihood that a person in a certain population will be newly affected by that condition in a specific period of time. [6]

Intrauterine device (IUD) - An intrauterine device (IUD) is a small plastic T-shaped device used for birth control. It is inserted into the uterus where it stays to prevent pregnancy. [6]

Intravenous - Intravenous means "within a vein." Most often it refers to giving medicines or fluids through a needle or tube inserted into a vein. This allows the medicine or fluid to enter your bloodstream right away. For example, your health care provider may prescribe medicines to be given through a vein, or an intravenous (IV) line. [6]

Involution - postpartum shrinkage of the uterus back to its pre-pregnancy volume. [3]

Lactation - process by which milk is synthesized and secreted from the mammary glands of the postpartum female breast in response to sucking at the nipple. [5]

lactiferous sinuses

lactocytes

lactogen

Laminaria - A genus of BROWN ALGAE in the family Laminariaceae. Dried pencil-like pieces may be inserted in the cervix where they swell as they absorb moisture, serving as osmotic dilators.

lanugo

Let-down reflex - release of milk from the alveoli triggered by infant suckling. [5]

Leukocyte - White blood cell. These include granular **leukocytes** (BASOPHILS; EOSINOPHILS; and NEUTROPHILS) as well as non-granular **leukocytes** (LYMPHOCYTES and MONOCYTES). [7]

Lightening - descent of the fetus lower into the pelvis in late pregnancy; also called “dropping”. [3]

linea nigra

Lociha - postpartum vaginal discharge that begins as blood and ends as a whitish discharge; the end of lochia signals that the site of placental attachment has healed

Mammary glands - glands inside the breast that secrete milk. [2]

Meconium - fetal wastes consisting of ingested amniotic fluid, cellular debris, mucus, and bile. [2]

Melanocyte-stimulating hormone - Peptides with the ability to stimulate pigmented cells **MELANOCYTES** in mammals and MELANOPHORES in lower vertebrates. By **stimulating** the synthesis and distribution of MELANIN in these pigmented cells, they increase coloration of skin and other tissue. [7]

Medical abortion (MAB)

Mesoderm - The middle germ layer of an embryo derived from three paired mesenchymal aggregates along the neural tube.

Methotrexate - An antineoplastic antimetabolite with immunosuppressant properties. It is an inhibitor of TETRAHYDROFOLATE DEHYDROGENASE and prevents the formation of tetrahydrofolate, necessary for synthesis of thymidylate, an essential component of DNA. [7]

Mifepristone -Mifepristone (Korlym) is used to treat hyperglycemia (high blood sugar) in people with a certain type of Cushing's syndrome in which the body makes too much cortisol (a hormone) and who have failed surgery or cannot have surgery to treat this condition. Mifepristone is in a class of medications called cortisol receptor blockers. It works by blocking the activity of cortisol. Mifepristone is also available as another product (Mifeprex) that is used alone or in combination with another medication to end an early pregnancy. This monograph only gives information about mifepristone (Korlym) used to control hyperglycemia in people with a certain type of Cushing's syndrome. If you are using mifepristone to terminate a pregnancy, read the monograph entitled mifepristone (Mifeprex), which has been written about this product. [8]

Misoprostol - Misoprostol is used to prevent ulcers in people who take certain arthritis or pain medicines, including aspirin, that can cause ulcers. It protects the stomach lining and decreases stomach acid secretion. [8]

Molar pregnancy

Montgomery glands

Myometrium - smooth muscle layer of uterus that allows for uterine contractions during labor and expulsion of menstrual blood. [1]

Nonshivering thermogenesis - process of breaking down brown adipose tissue to produce heat in the absence of a shivering response. [4]

Obstetrician - Qualified medical professionals who specialize in OBSTETRICS - a medical-surgical specialty concerned with management and care of women during pregnancy, parturition, and the puerperium. [7]

Occiput

Opiates - Opiates or opioids are drugs used to treat pain. Opiates are derived from plants and opioids are synthetic drugs that have the same actions as opiates. The term narcotic refers to either type of drug. [6]

Osmotic dilators

ovalis

Oxytocin - hypothalamic hormone stored in the posterior pituitary gland and important in stimulating uterine contractions in labor, milk ejection during breastfeeding, and feelings of attachment (also produced in males). [1]

Parturition - childbirth. [3]

paracervical block

Pelvic inflammatory disease (PID) - Pelvic inflammatory disease (PID) is an infection of a woman's womb (uterus), ovaries, or fallopian tubes. [6]

Perineal tear

Peristalsis - Peristalsis is a series of muscle contractions. These contractions occur in your digestive tract. Peristalsis is also seen in the tubes that connect the kidneys to the bladder. [6]

Pituitary gland - A small, unpaired gland situated in the SELLA TURCICA. It is connected to the HYPOTHALAMUS by a short stalk which is called the INFUNDIBULUM. [7]

Placenta - A highly vascularized mammalian fetal-maternal organ and major site of transport of oxygen, nutrients, and fetal waste products. It includes a fetal portion (CHORIONIC VILLI) derived from TROPHOBLASTS and a maternal portion (DECIDUA) derived from the uterine ENDOMETRIUM. The placenta produces an array of steroid, protein and peptide hormones (PLACENTAL HORMONES). [7]

POC

Polyp forceps

Pratt cervical dilators

Preeclampsia - Preeclampsia is high blood pressure and signs of liver or kidney damage that occur in women after the 20th week of pregnancy. While it is rare, preeclampsia also may occur in a woman after delivering her baby, most often within 48 hours. This is called postpartum preeclampsia. [6]

Prevalence - The total number of cases of a given disease in a specified population at a designated time. It is differentiated from INCIDENCE, which refers to the number of new cases in the population at a given time. [7]

Prophylactic

Prophyria

Progesterone - sex hormone important in regulating the reproductive cycle in those with ovaries and the maintenance of pregnancy. [1]

prolactin - pituitary hormone that establishes and maintains the supply of breast milk; also important for the mobilization of maternal micronutrients for breast milk. [5]

Prostaglandins - A group of compounds derived from unsaturated 20-carbon fatty acids, primarily arachidonic acid, via the cyclooxygenase pathway. They are extremely potent mediators of a diverse group of physiological processes. [7]

Pulmonary alveoli - Small polyhedral outpouchings along the walls of the alveolar sacs, alveolar ducts and terminal bronchioles through the walls of which gas exchange between alveolar air and pulmonary capillary blood takes place. [7]

Pulmonary trunk - large arterial vessel that carries blood ejected from the right ventricle; divides into the left and right pulmonary arteries. [9]

Quickening - fetal movements that are strong enough to be felt by the mother [2]

RH status - blood-type classification based on the presence or absence of the antigen Rh on the erythrocyte membrane surface. [9]

Shunt - circulatory shortcut that diverts the flow of blood from one region to another. [2]

striae

subcutaneous fat - The term "cutaneous" refers to the skin. Subcutaneous means beneath, or under, all the layers of the skin. [6]

Tenaculum

Teratogenicity

Thrombophilia - A disorder of HEMOSTASIS in which there is a tendency for the occurrence of THROMBOSIS. [7]

thyrotropin

True labor - regular contractions that immediately precede childbirth; they do not abate with hydration or rest, and they become more frequent and powerful with time. [3]

Uterotonics

Vasovagal

vasovagal syncope - Loss of consciousness due to a reduction in blood pressure that is associated with an increase in vagal tone and peripheral vasodilation. [7]

Vena Cavae - The inferior (venous trunk which receives blood from the lower extremities and from the pelvic and abdominal organs) and superior (venous trunk which returns blood from the head, neck, upper extremities and chest) venae cavae. [7]

Vernix caseosa - waxy, cheese-like substance that protects the delicate fetal skin until birth. [2]

Wharton Jelly -Jelly-like connective tissue of the UMBILICAL CORD that contains MESENCHYMAL STEM CELLS. [7]

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CHAPTER OVERVIEW

6: Embryology

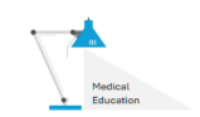
6.1: Week 1 Fertilization
6.2: Week 2 Implantation
6.3: Week 3 Gastrulation
6.4: Week 4 Neurulation

Chapter Curator: Judith Thorn, Ph.D.

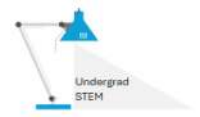
About this Chapter

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The content of this chapter is appropriate for, or easily adapted for the following audiences:







Learning Objectives

- WEEK 1
  - outline the steps of fertilization and interaction of egg (oocyte) and sperm (spermatozoa)
  - outline the steps of cleavage and blastocyst formation
- WEEK 2
  - Outline the process of implantation of the embryo to the endometrial wall of the uterus and formation of the bilaminar embryonic disc.
- WEEK 3
  - Outline the process of gastrulation and formation of the trilaminar embryo.
- WEEK 4
  - Outline the process of neurulation and the basics of embryo body folding

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6.1: Week 1 Fertilization

WEEK 1 of embryonic development starts with fertilization of the egg by a sperm.

This is different from how care providers count the weeks of pregnancy: WEEK 1 of pregnancy starts on the first day of the last menstrual period, which may be 1 to 2 weeks before WEEK 1 of development.

6.1.1 Egg & Sperm

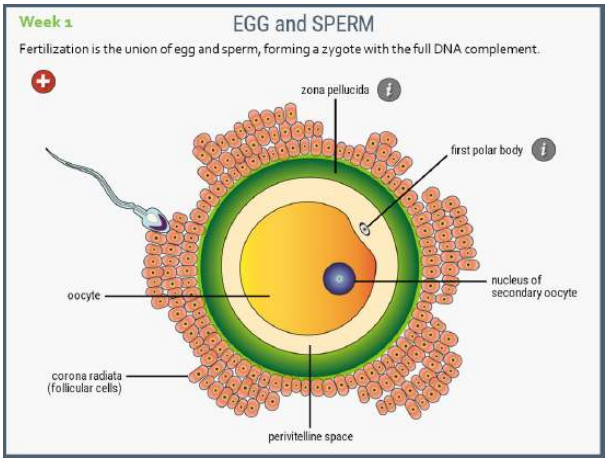
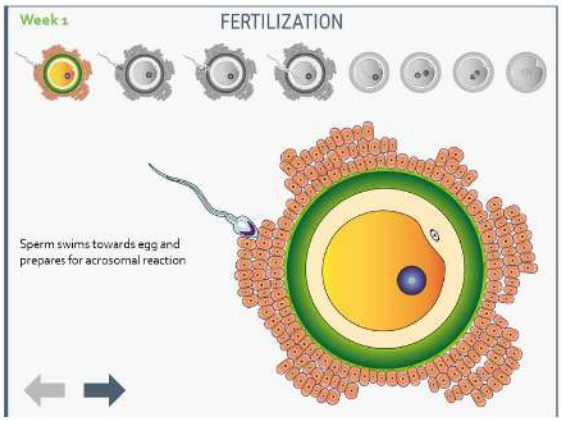
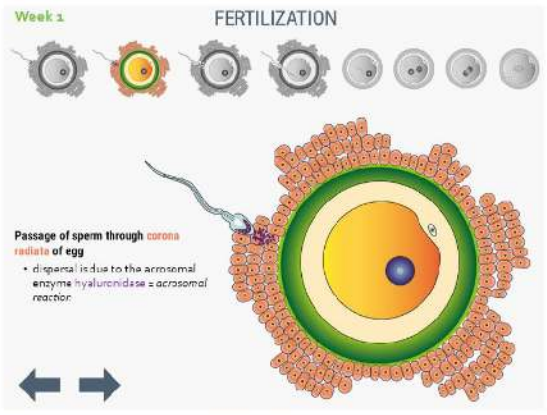


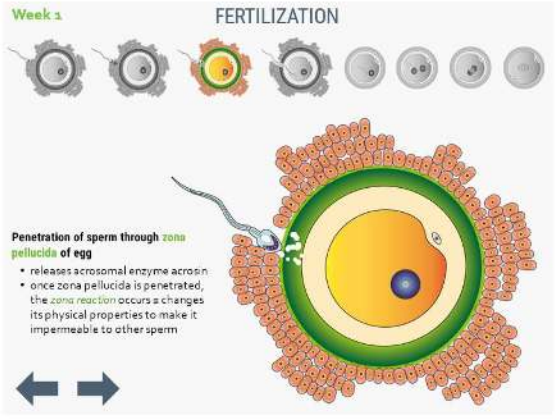
Figure 6.1 Egg & Sperm

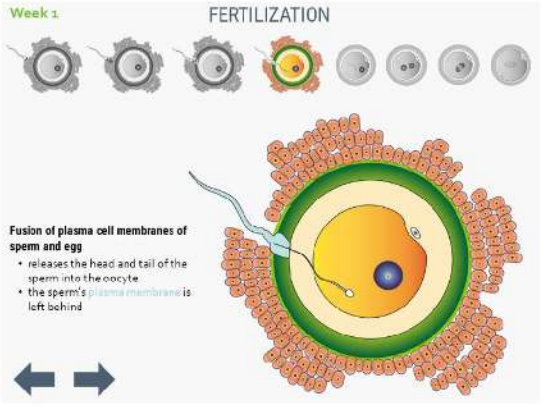
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6.1.2 Fertilization

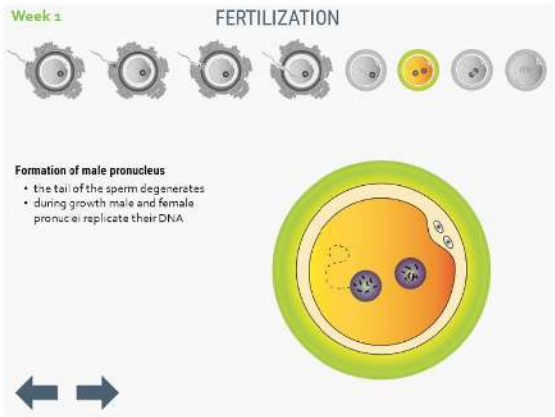

Week 1
FERTILIZATION
Sperm swims towards egg and prepares for acrosomal reaction

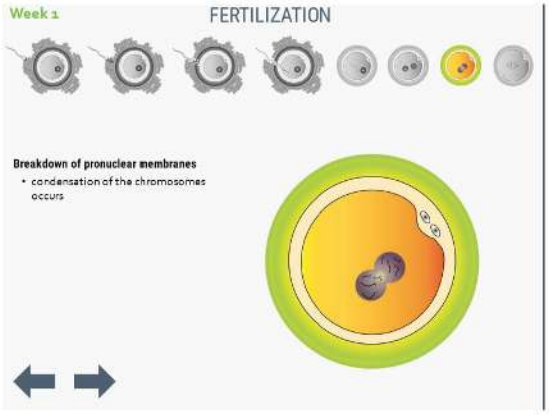

Week 1
FERTILIZATION
Passage of sperm through corona radiata of egg
• dispersal is due to the acrosomal enzyme hyaluronidase = acrosomal reaction


Week 1
FERTILIZATION
Penetration of sperm through zona pellucida of egg
• releases acrosomal enzyme acrosin
• once zona pellucida is penetrated, the zona reaction occurs a changes its physical properties to make it impermeable to other sperm


Week 1
FERTILIZATION
Fusion of plasma cell membranes of sperm and egg
• releases the head and tail of the sperm into the oocyte
• the sperm's plasma membrane is left behind


Week 1
FERTILIZATION
Completion of second mitotic division of the oocyte nucleus
• forms a mature oocyte and a second polar body
• nucleus becomes the female pronucleus


Week 1
FERTILIZATION
Formation of male pronucleus
• the tail of the sperm degenerates
• during growth male and female pronuclei replicate their DNA


Week 1
FERTILIZATION
Breakdown of pronuclear membranes
• condensation of the chromosomes occurs

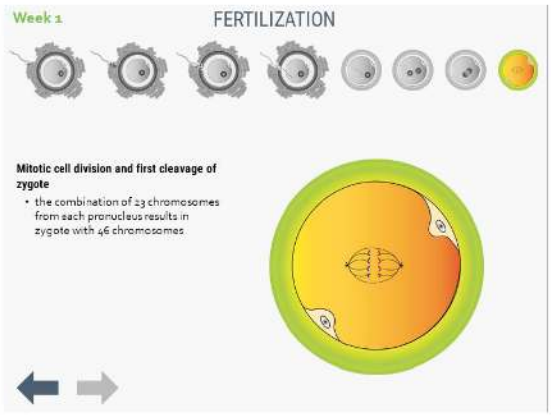

Week 1
FERTILIZATION
Mitotic cell division and first cleavage of zygote
• the combination of 23 chromosomes from each pronucleus results in zygote with 46 chromosomes

Figure 6.2 Process of Fertilization
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6.1.3 Cleavage

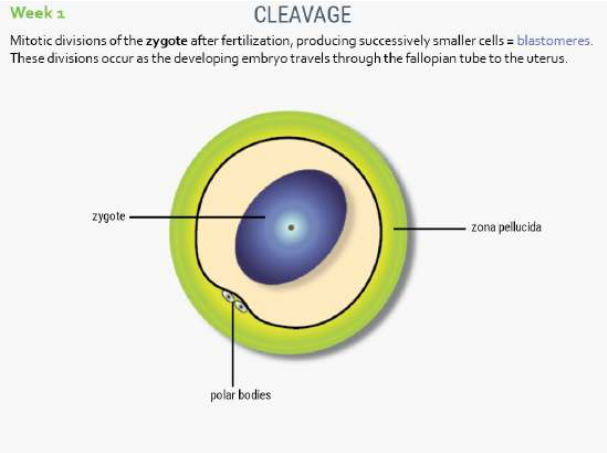


Figure 6.3 Cleavage
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6.1.3.1 Stages of Cleavage

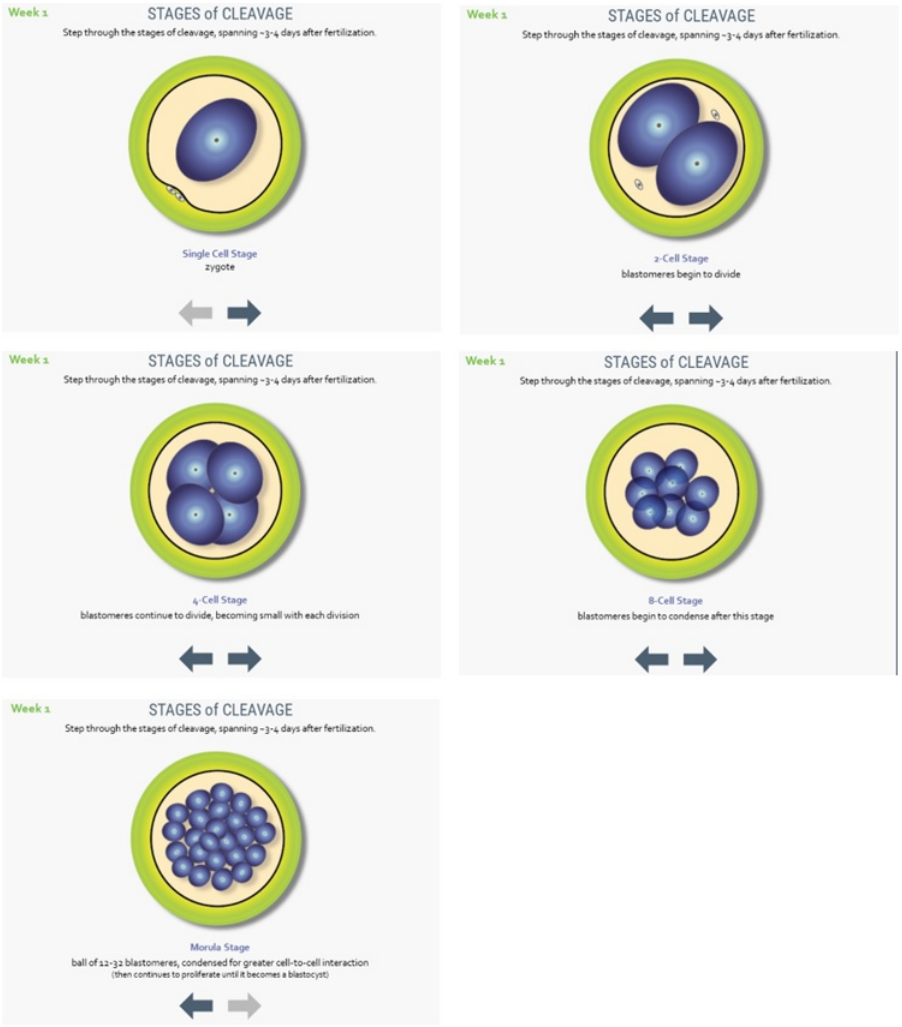


Figure 6.4 Stages of Cleavage

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6.1.4 Blastocyst Formation

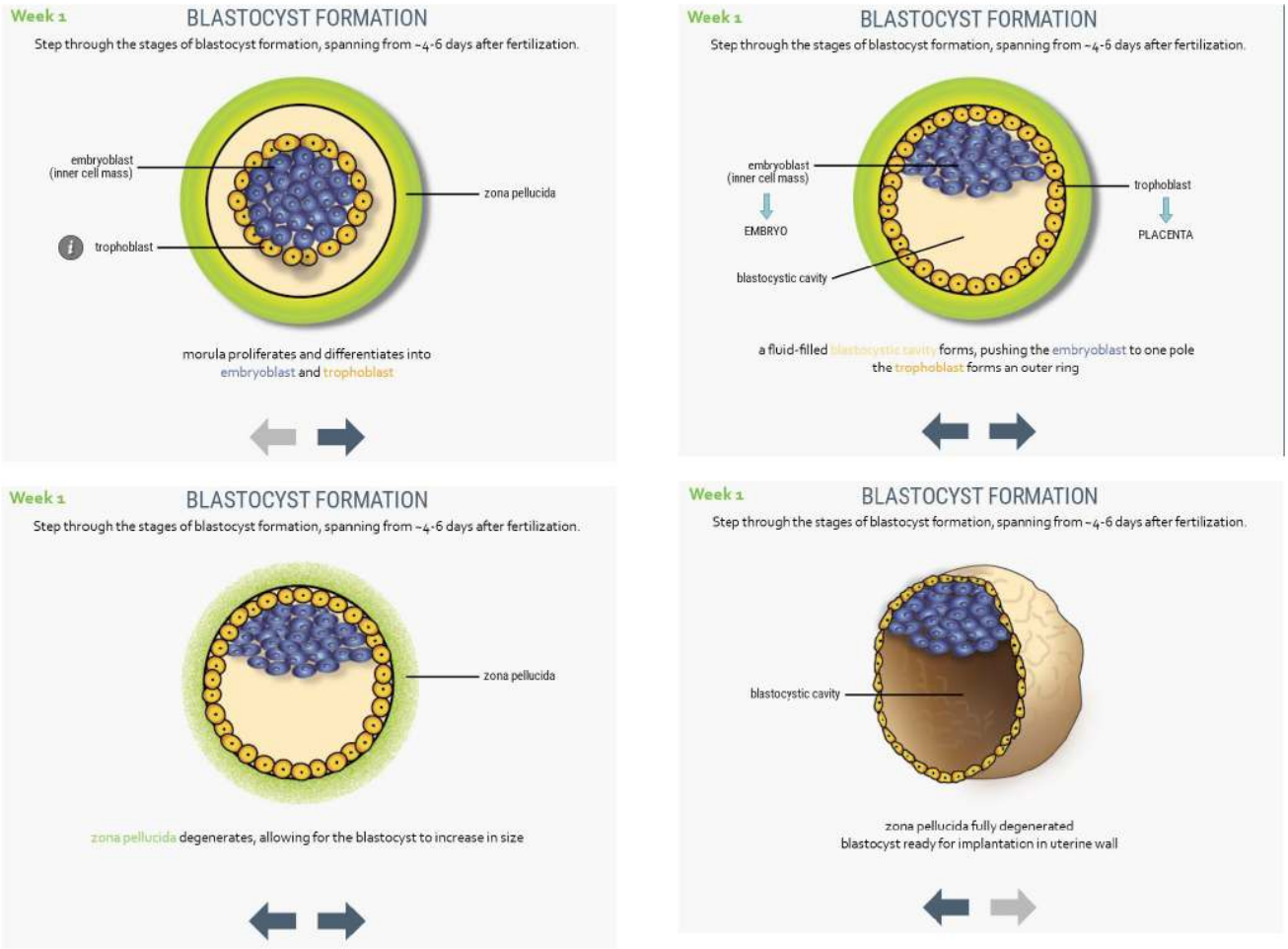


Figure 6.5 Blastocyst Formation

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Source Material

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6.2: Week 2 Implantation

6.2.1 Implantation

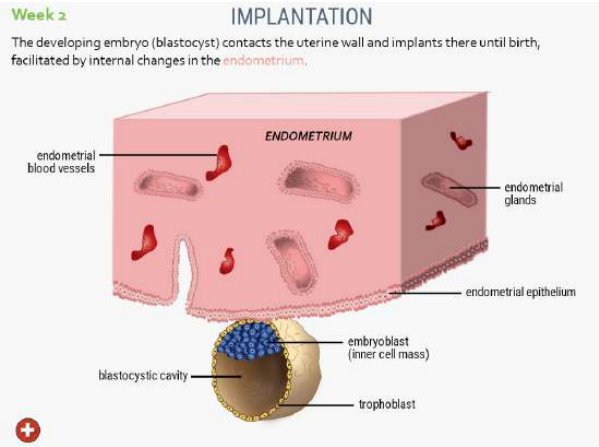


Figure 6.6 Implantation

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Ectopic pregnancy is a high-risk maternal medical condition that occurs if the blastocyst implants in a location outside the body of the uterus, such as the ovary, cervix, abdomen, or fallopian/uterine tube. The latter is the most common and is referred to as a tubal pregnancy.

6.2.1.1 Implantation Animation

Video 6.1

Watch IMPLANTATION video - From the Clinical Anatomy MENU, select Week 2 - 3.2 "Implantation Animation."

6.2.1.2 Implantation Stages

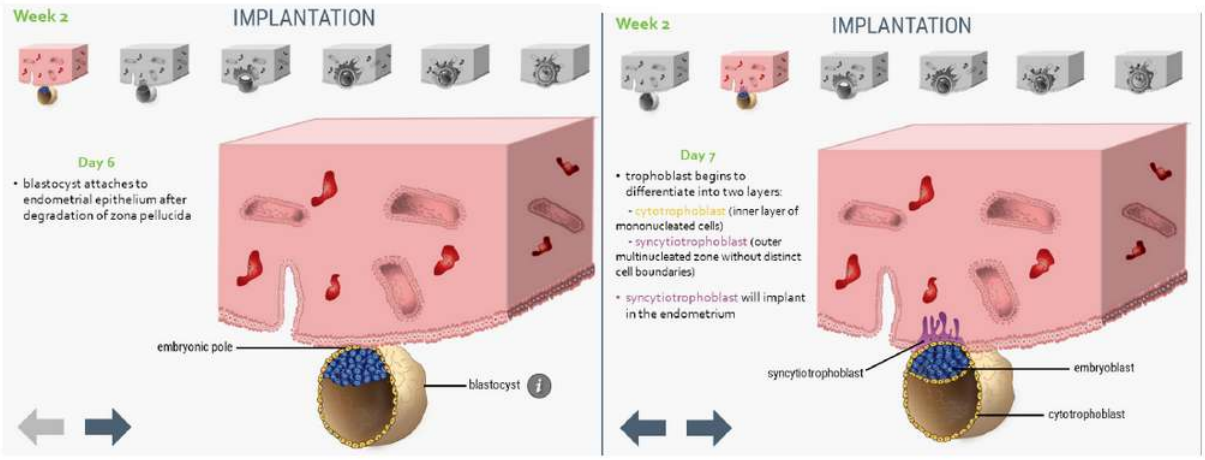


Figure 6.7 Stages of Implantation

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6.3: Week 3 Gastrulation

6.3.1 Gastrulation

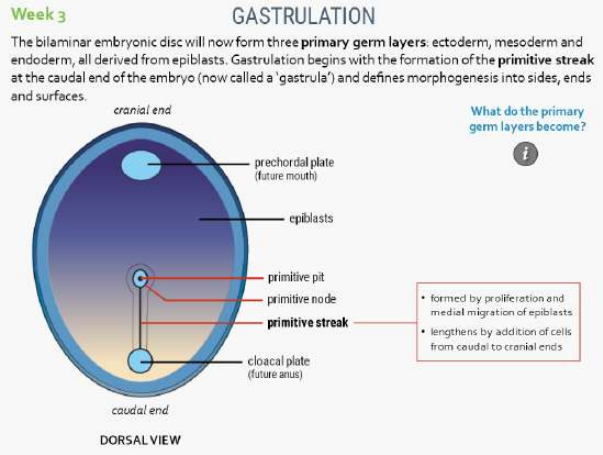


Figure 6.8 Gastrulation

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6.3.1.1 Gastrulation Animation

Video 6.2

Watch GASTRULATION Animation - From the Clinical Anatomy MENU, select Week 3 - 4.2 "Gastrulation Animation"

6.3.1.2 Gastrulation Stages

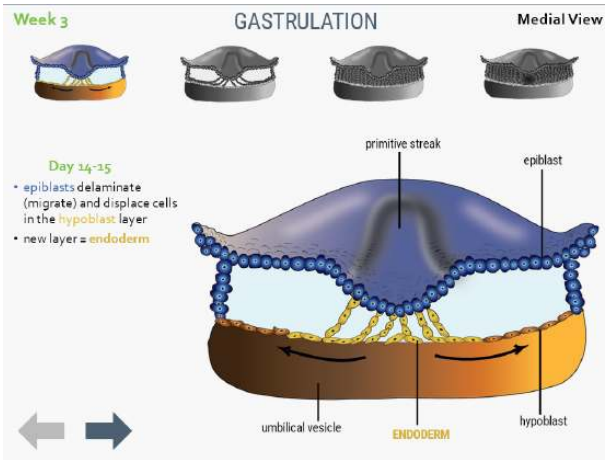


Figure 6.9 Gastrulation

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6.3.1.3 Notochord Animation

Video 6.3

Watch NOTOCHORD FORMATION Animation - From the MENU, select Week 3 - 4.4 "Notochord Animation"

Neurulation

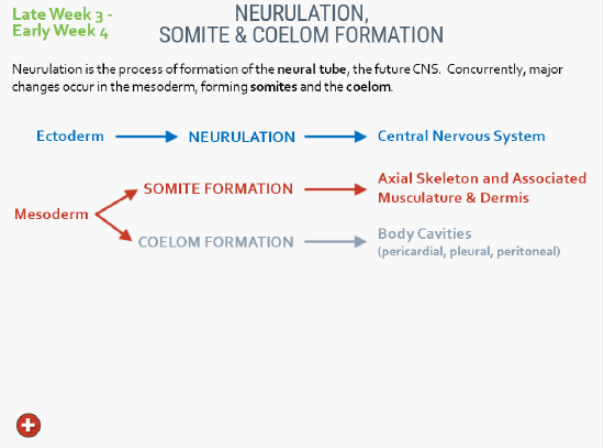


Figure 6.10 Neurulation

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Neural Tube Defects

During this period of rapid cell proliferation, pregnant women are recommended to take folic acid supplements to support DNA replication and decrease the chance of neural tube defects.

Failure to fully close the neural tube results in

- Cranial defects - anencephaly
- Caudal defect - spina bifida

6.3.1.4 Neurulation Stages

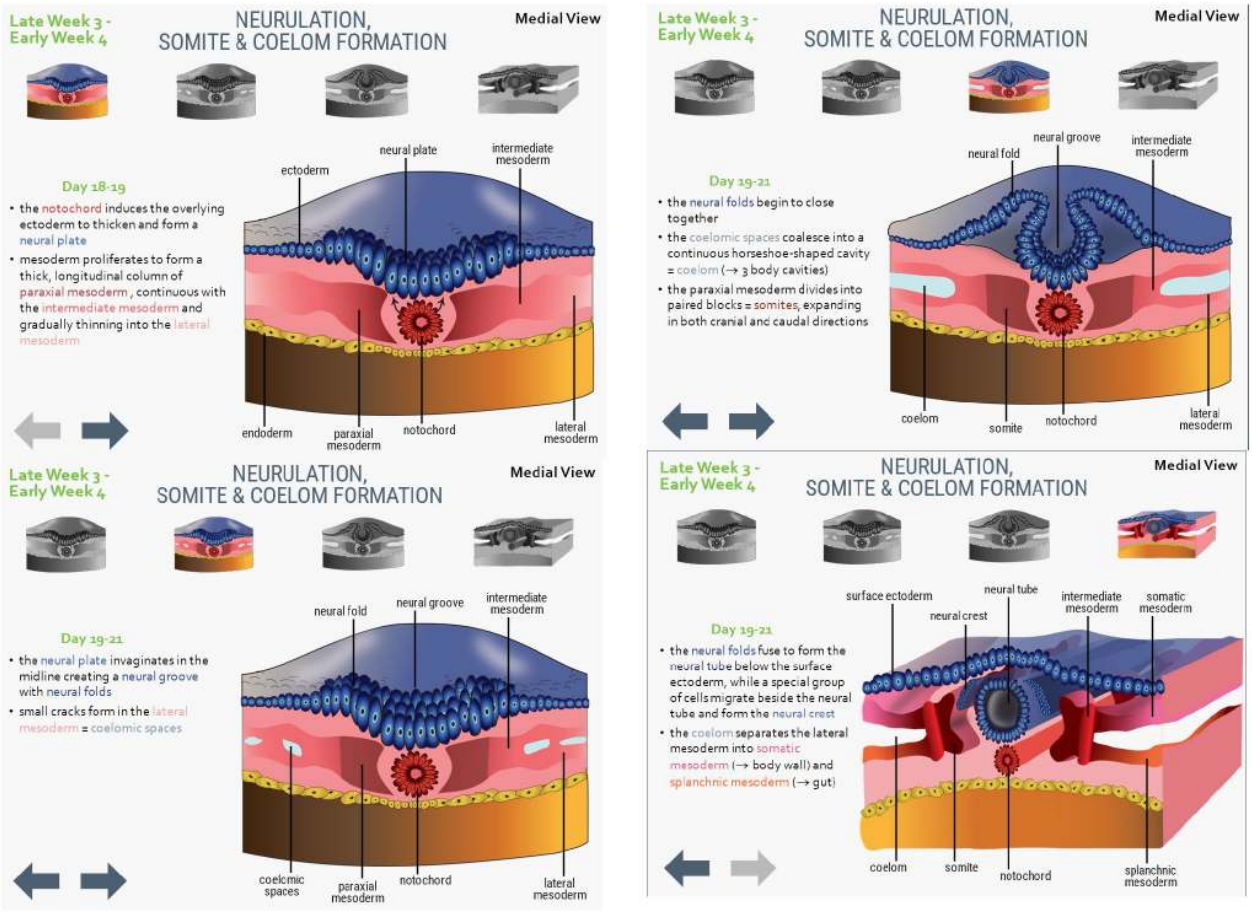


Figure 6.11 Stages of Neurulation

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Student Contribution

Melanocyte Development: How the Fetus Acquires Skin Color and Fetal Model Representation
Ava Vaccarella, Kailyn Storer, Sonia Lopez, and Judith Thorn

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6.4: Week 4 Neurulation

6.4.1 Embryonic Folding

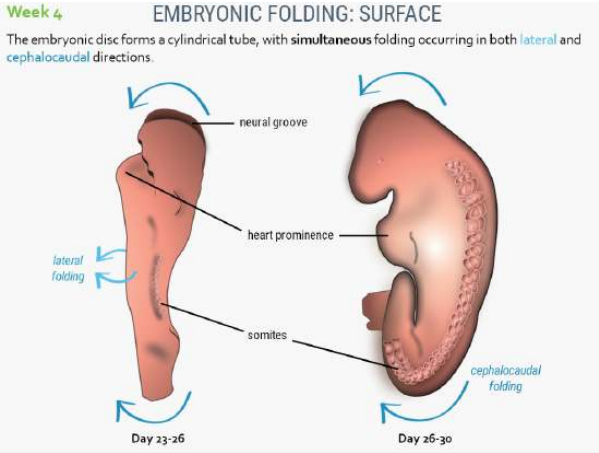


Figure 6.12 Embryonic Folding

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6.4.1.1 Folding Directions

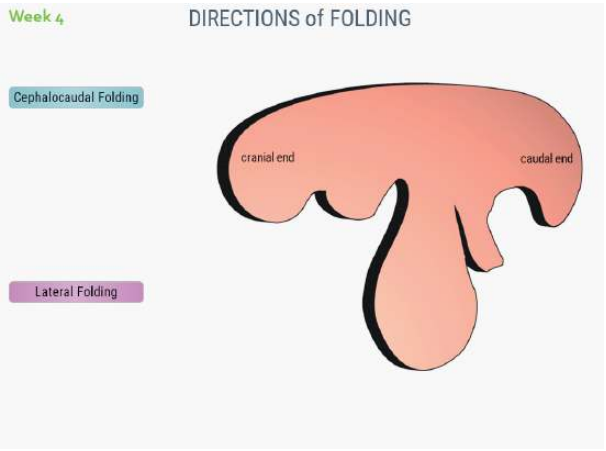


Figure 6.13 Folding Directions

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6.4.1.2 Lateral Folding

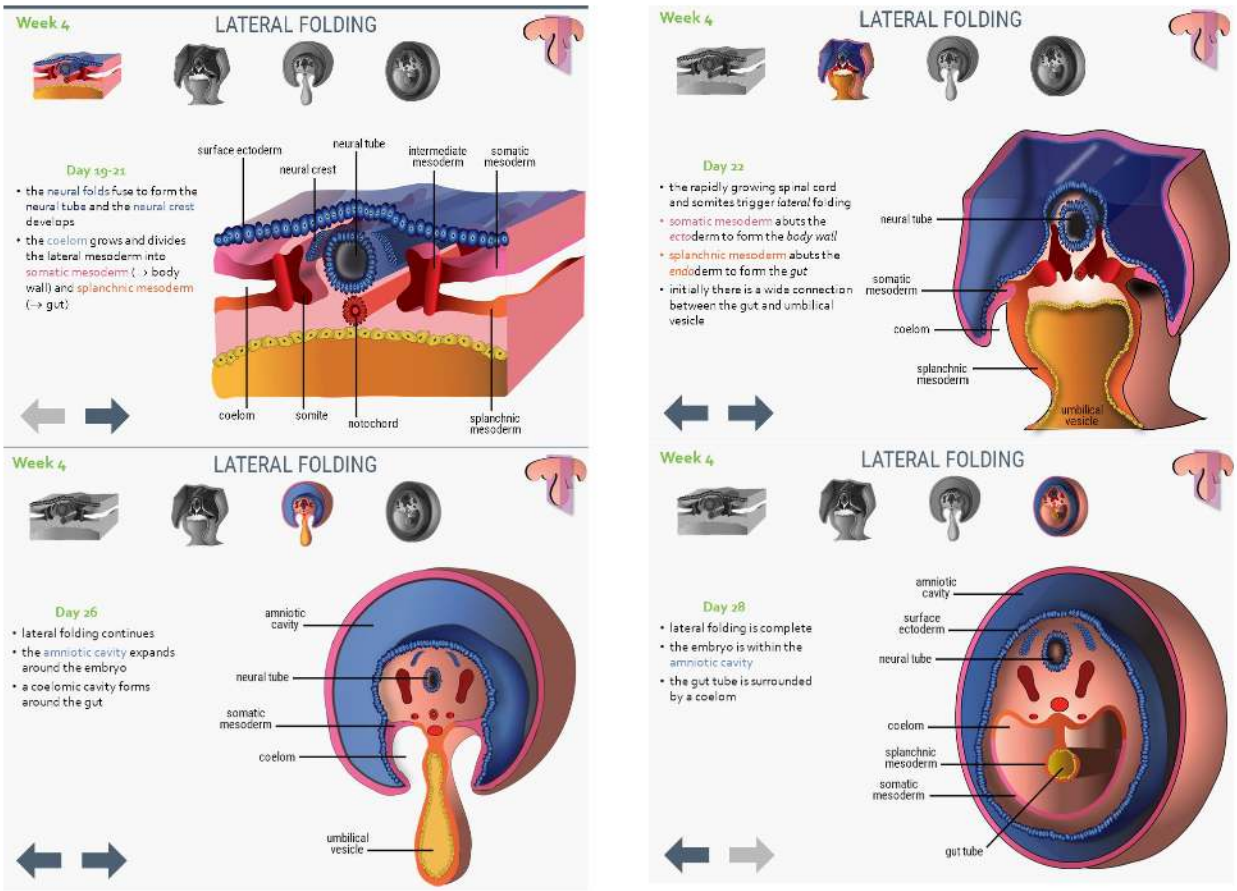


Figure 6.14 Lateral Folding

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6.4.1.3 Cephalocaudal Folding Animation

Video 6.4

Watch CEPHALOCAUDAL FOLDING Animation - From the Clinical Anatomy MENU, select Week 4 - 5.4 "Cephalocaudal folding animation"

6.4.1.4 Basic Body Plan

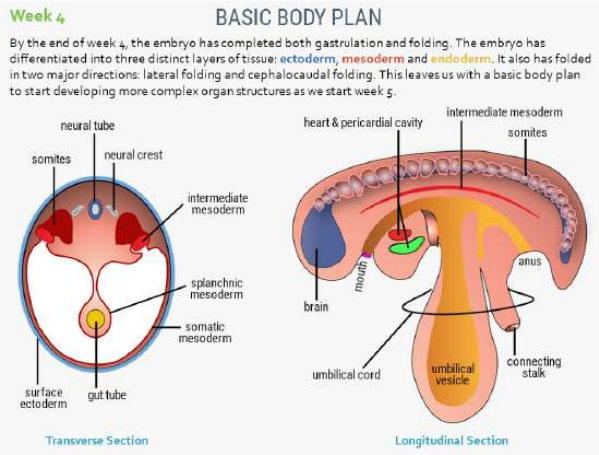


Figure 6.15 Basic Body Plan

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6.4.1.5 Embryo Layers

The embryo's three layers can further be divided into different types of tissues.

- Ectoderm

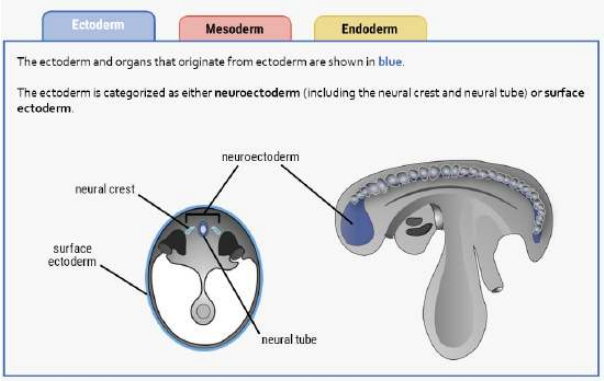


Figure 6.16 Ectoderm

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- Mesoderm

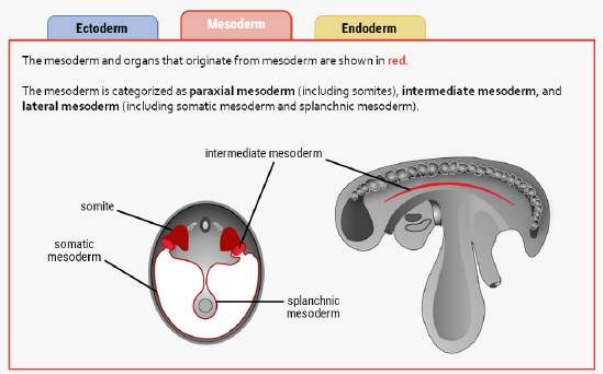


Figure 6.17 Mesoderm

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- Endoderm

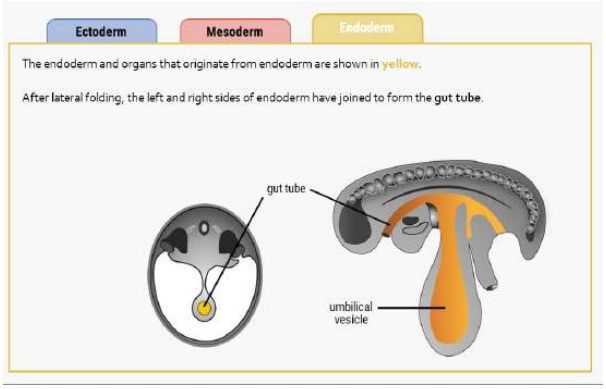


Figure 6.18 Endoderm

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CHAPTER OVERVIEW

7: Pregnancy and Beyond - Evidence-Based Perspectives on Maternal, Fetal, and Neonatal Care

7.1: Normal Pregnancy

7.2: Pregnancy Complications

7.3: Normal Labor and Delivery

7.4: Delivery Complications

7.5: Postpartum

Chapter content coming soon

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7.1: Normal Pregnancy

7.1.1 Introduction

Pregnancy is a complex and dynamic physiological process that encompasses conception, development, and birth. Spanning approximately forty weeks from the last menstrual period, it represents a period of remarkable anatomical, hormonal, and metabolic adaptations within the maternal body that support fetal growth and prepare for parturition. Understanding these changes is essential for recognizing normal progression, identifying potential complications, and providing comprehensive, evidence-based care. This chapter provides an overview of the fundamental biological mechanisms underpinning pregnancy, highlighting key clinical considerations relevant to medical students as they develop foundational knowledge in obstetrics and reproductive health.

7.1.2 Early Pregnancy

7.1.2.1 Diagnosis

In normal implantation, the blastocyst adheres to the uterine endometrium approximately 6 to 7 days after fertilization. Trophoblast cells at the periphery of the blastocyst begin to invade the decidualized endometrium, a process that establishes early maternal–fetal interface and ultimately gives rise to the placenta. The syncytiotrophoblast lineage synthesizes human chorionic gonadotropin (hCG), a glycoprotein hormone essential for the maintenance of early pregnancy. hCG supports the corpus luteum, enabling continued progesterone production, which is required to sustain the early gestational environment. By roughly 10 days after fertilization, circulating hCG concentrations are sufficient for detection in maternal serum, and by approximately 2 weeks, commercial home pregnancy tests can identify hCG in the urine. hCG consists of two subunits, alpha and beta. The alpha subunit is shared with other anterior pituitary hormones including thyroid stimulating hormone (TSH), follicle stimulating hormone (FSH), and luteinizing hormone (LH). Therefore, clinical pregnancy testing relies on assays that specifically detect the unique beta subunit of hCG.

As the pregnancy progresses, characteristic embryonic and extraembryonic structures become visible on transvaginal ultrasound. Between 4 and 5 weeks of gestation, a gestational sac containing a yolk sac can typically be visualized. By 5 to 6 weeks, the fetal pole becomes detectable, and by 6 to 7 weeks, cardiac electrical activity is generally apparent. (Figure 7.1) Because modern commercial pregnancy tests are highly sensitive, beta-hCG may be detectable in the urine before the embryo can be visualized sonographically. In such cases, serial quantitative beta-hCG measurements in conjunction with repeat ultrasound examinations may be required to confirm an intrauterine pregnancy and to distinguish it from an ectopic pregnancy or early pregnancy loss.



Figure 7.1 Fetal development from the 9th week to the 20th week.
Image Source: Thapaliya, Arbin, Alec Sithole, Michael Welsh and Gaston Dana. Ultrasound Physics and its Application in Medicine. This work is distributed under a CC BY 4.0. Availalbe from https://pressbooks.palni.org/ultraso...ioninmedicine/.

7.1.2.2 Gestational Age

Gestational age is defined as the time elapsed since the first day of the last menstrual period (LMP). In individuals with a typical 28-day menstrual cycle, the LMP precedes ovulation by approximately 14 days and implantation by roughly 3 weeks. Because pregnancy duration averages 40 weeks, or 280 days, from the LMP, an estimated due date can be calculated when the patient is able to recall the first day of her last menstrual period.

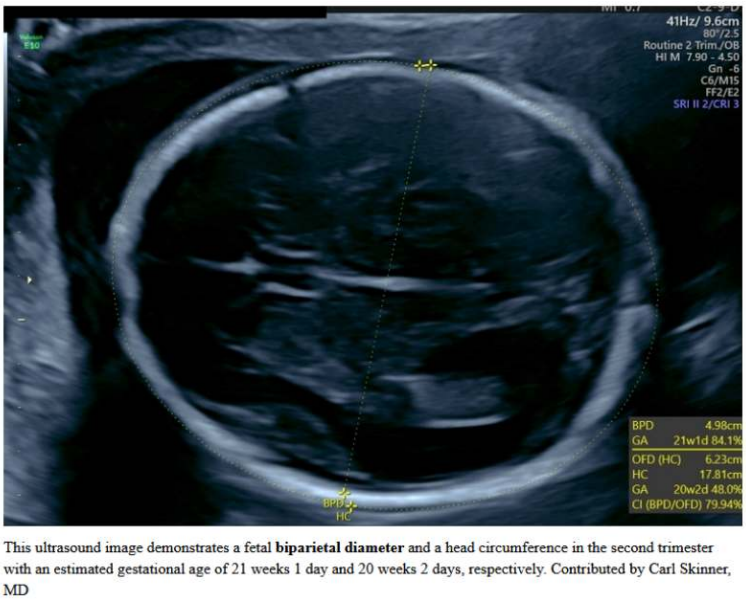
Because variation in menstrual cycle length can result in ovulation occurring earlier or later than the standard 14-day interval, reliance on LMP alone may lead to inaccurate estimation of gestational age. In early pregnancy, gestational age can instead be estimated using measurements of early embryonic and extraembryonic structures, such as the gestational sac and fetal pole. The crown rump length (CRL) of the fetal pole represents the most precise ultrasound parameter for dating a first-trimester pregnancy. (Figure 7.2) If the CRL-based gestational age differs substantially from that predicted by the LMP, the estimated due date should be recalculated using the CRL measurement.



Figure 7.2. Embryo at 7 weeks. An embryo at the end of 7 weeks of development is only 10mm in length, but its developing eyes, limb buds, and tail are already visible. (This embryo was derived from an ectopic pregnancy. Credit: Ed Uthman)

Source: Markell, Dawn. *Women's Health.* 2021. This work is distributed under a CC BY 4.0 license. Availalbe from https://mhcc.pressbooks.pub/he265/fr...ion-statement/

Some patients may not present for evaluation during the first trimester and therefore may not receive an early dating ultrasound. At and beyond 14 weeks of gestation, the CRL is no longer an accurate metric. Instead, gestational age estimation relies on a combination of biometric parameters, including biparietal diameter, head circumference, abdominal circumference, and femur length. (Figure 7.3) As pregnancy advances, biological variation in fetal size increases, leading to a gradual decline in the precision of ultrasound-based gestational age calculations.



This ultrasound image demonstrates a fetal **biparietal diameter** and a head circumference in the second trimester with an estimated gestational age of 21 weeks 1 day and 20 weeks 2 days, respectively. Contributed by Carl Skinner, MD

Figure 7.3 Fetal biparietal diameter and a head circumference in the second trimester with an estimated gestational age of 21 weeks 1 day.

Source: Skinner C, Mount CA. Sonography Assessment of Gestational Age. [Updated 2023 Apr 24]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. [Figure, This ultrasound image demonstrates a...] . This book is distributed under the terms of CC BY-NC-ND 4.0. Available from: https://www.ncbi.nlm.nih.gov/books/NBK570610/figure/article-128641.image.f1/.

Once the estimated due date is established, gestational age is tracked in weeks and days, expressed as a decimal fraction (for example, 32+3/7 weeks indicates 32 weeks and 3 days). Pregnancy is typically divided into trimesters based on gestational age. The first trimester spans from the LMP to 13+6/7 weeks. The second trimester extends from 14 weeks to 27+6/7 weeks. The third trimester includes 28 weeks through 41+6/7 weeks. Key gestational milestones include the designation of full-term pregnancy at 37 weeks, the estimated due date at 40 weeks, and the classification of post-term pregnancy at 42 weeks and beyond.

7.1.3 Placental and Umbilical Cord Anatomy

7.1.3.1 Placenta

The placenta is fundamental to normal fetal growth and development, and it plays a critical role in maintaining maternal physiological stability throughout pregnancy. Placental formation begins when trophoblast cells attach to the decidua at the blastocyst stage. As the embryo develops, cytotrophoblasts proliferate and fuse to form syncytiotrophoblasts that further invade the decidua, expand, and generate chorionic villi. These villous structures remodel the maternal spiral arteries within the endometrium, creating intervillous spaces that allow for efficient transfer of oxygen and nutrients from the mother to the fetus, as well as removal of fetal metabolic waste. (Figure 7.4) Abnormalities in the development of the maternal–fetal interface are implicated in several major pregnancy complications, including PRE ECLAMPSIA, STILLBIRTH, and FETAL GROWTH RESTRICTION.[1]

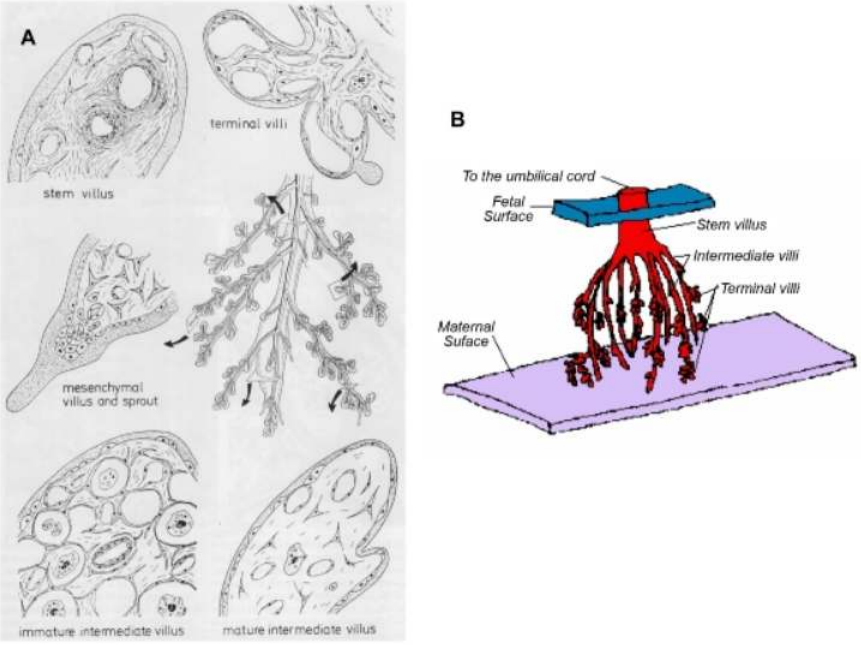


Figure 7.4: Architecture of different villous and vessel branches of a cotyledon. A: types of placental villi in human placenta. B: A villous tree connects to the fetal surface (chorionic plate) and the maternal surface (basal plate). The villous trees are so named because they resemble trees and their basic structure is established early in gestation. A “trunk” dives down into the placenta from the fetal surface vessels, as the stem villous, which divides into large branches, the intermediate villi, with nutrient gathering structures at their ends, followed by the terminal villi. However, during the second and third trimesters, the terminal villi continue to mature in such a way as to increase the quantity and quality of oxygen and nutrient exchange across the terminal villi between the maternal and fetal blood, in response to the demands of the growing fetus. (A is adapted from Benirschke et al. Fifth Edition of Pathology of the Human Placenta (page 123). Used with permission from Springer, and B is from http://showcase.netins.net/web/placenta/placentaltriage101.htm.). A: Reproduced from Pathology of the Human Placenta, Benirschke et al. with permission of Springer. B: Used with permission of DSM Pathworks Inc.
Source: Wang Y, Zhao S. Vascular Biology of the Placenta. San Rafael (CA): Morgan & Claypool Life Sciences; 2010. Figure 3.1, [Architecture of different villous and...]. Available from: https://www.ncbi.nlm.nih.gov/books/N...figure/fig3.1/

The mature placenta consists of two distinct surfaces. The maternal surface, known as the basal plate, is divided into lobulated units called cotyledons. The fetal surface, known as the chorionic plate, contains the site of umbilical cord insertion.[2] (Figure 7.5)

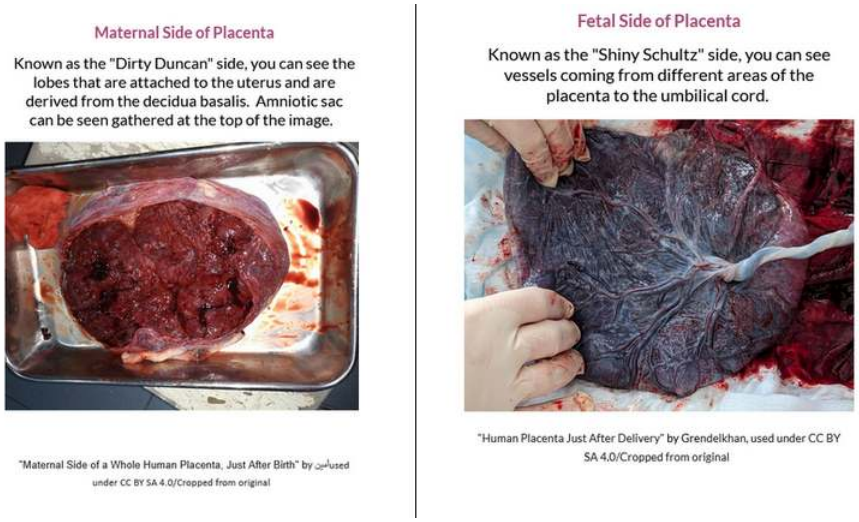


Figure 7.5: Maternal and Fetal Sides of Placenta.
Source: Smith, Deborah H. and Judith Rogers Fruiterman. Maternal-Infant Nursing Review. 2024. This work is distributed under a CC BY SA 3.0. Available from https://sites.google.com/view/maternitynursingreview/home.

7.1.3.2 Umbilical Cord

The umbilical cord serves as the essential anatomical connection between the fetus and the placenta, functioning as a bidirectional conduit for blood flow. It contains two umbilical arteries, one umbilical vein, and the obliterated allantois, also known as the urachus. These structures are embedded within Wharton jelly, a gelatinous protective matrix that cushions the vessels against compression.[3] (Figure 7.6 and Figure 7.7)

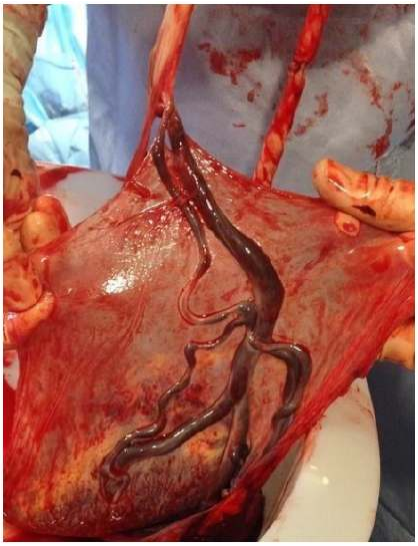


Figure 7.6: Velamentous Cord Insertion. The umbilical cord attaches to the membranes instead of the placental surface. Umbilical vessels travel unprotected between the amnion and chorion, without the surrounding Wharton jelly.
Source: Brahmandam G, Lipsett BJ. Anatomy, Abdomen and Pelvis: Umbilical Cord. [Updated 2025 Jul 26]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. This book is distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0) (http://creativecommons.org/licenses/by-nc-nd/4.0/) Available from: https://www.ncbi.nlm.nih.gov/books/NBK557389/

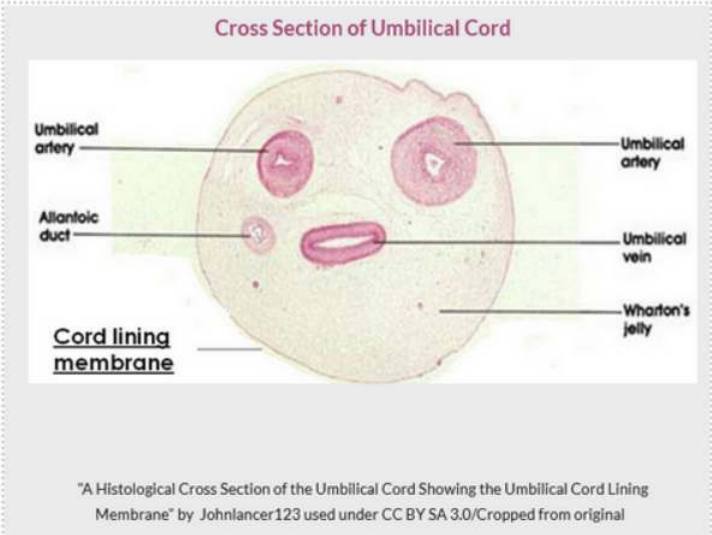


Figure 7.7 Umbilical cord cross section.
Source: Smith, Deborah H. and Judith Rogers Fruiterman. Maternal-Infant Nursing Review. 2024. This work is distributed under a CC BY SA 3.0. Available from https://sites.google.com/view/maternitynursingreview/home.

Oxygenated blood is transported from the placenta to the fetus through the umbilical vein, which subsequently enters the fetal circulation. A portion of this blood perfuses the developing

hepatic system, while a substantial amount is diverted to the inferior vena cava via the ductus venosus. De oxygenated blood returns to the placenta through the umbilical arteries.[4]

Clinical Correlation

The obliterated umbilical arteries can be visualized on the deep surface of the anterior abdominal wall within the medial umbilical folds.

Umbilical cord blood flow is closely tied to placental function. In cases of fetal growth restriction caused by uteroplacental insufficiency, Doppler evaluation of umbilical artery resistance can help assess disease severity and guide clinical management. Any occlusion of the umbilical vessels can compromise fetal perfusion. Acute interruptions in flow may result in fetal hypoxia or demise. As will be discussed in ANTENATAL FETAL SURVEILLANCE, intermittent cord compression can produce variable decelerations on fetal heart rate monitoring.[5]

7.1.4 Maternal Anatomy and Physiology

Sources used for this topic section:

Pascual ZN and MD Langakar. 2023[6]

Soma-Pillay P, C Nelson-Piercy, H Tolppanen and A. Mebazaa. 2016.[7]

7.1.4.1 Cardiovascular

Increased blood volume

Maternal blood volume increases by approximately 45% to 55% during pregnancy, driven largely by an expansion of plasma volume. This volume increase supports adequate uteroplacental perfusion and prepares the maternal circulation for the expected blood loss that accompanies delivery.

Decreased vascular resistance

Tp accommodate the expanded intravascular volume, systemic vascular resistance decreases, with the most pronounced decline occurring in the second trimester due to rising progesterone levels.

Clinical Correlation

The reduction in systemic vascular resistance predisposes patients to venous stasis. This stasis can contribute to lower extremity edema and increases the risk of venous thrombosis. (Figure 7.8 forthcoming) Any new elevation in blood pressure warrants evaluation for hypertensive disorders of pregnancy, including pre-eclampsia.

Blood pressure changes

Beginning in the second trimester, decreased systemic vascular resistance results in a reduction in systolic blood pressure by approximately 5 to 10 mmHg and in diastolic pressure by 10 to 15

mmHg. As plasma volume continues to expand in the late second trimester, blood pressure generally returns to pre-pregnancy levels. (Figure 7.9 forthcoming)

Clinical Correlation

The physiologic decline in blood pressure can lead to pre-syncopal symptoms. Patients may report lightheadedness when rising from a seated position or may experience syncope with prolonged standing.

Increased stroke volume and cardiac output

The increase in blood volume produces enhanced preload, resulting in increased stroke volume and a 30% to 60% rise in cardiac output. Mild maternal tachycardia later in pregnancy is considered physiologic as stroke volume plateaus.

Clinical Correlation

Due to the augmented stroke volume, benign systolic ejection murmurs are frequently auscultated in pregnant patients.

7.1.4.2 Hematologic

Increased plasma volume

As noted in the cardiovascular section, plasma volume expands significantly during pregnancy.

Clinical Correlation

Adequate maternal hydration is essential to support this physiologic expansion.

Increased red blood cell volume with dilutional anemia

Red blood cell mass increases by 15% to 25%, though this expansion is proportionally smaller than that of plasma volume, resulting in dilutional anemia. Anemia in pregnancy is defined by hemoglobin levels less than 11 g/dL (hematocrit levels less than 33%) in the first and third trimesters, and less than 10.5 g/dL (hematocrit level less than 32%) in the second trimester.[8] (Figure 7.10 forthcoming)

Clinical Correlation

All pregnant individuals undergo anemia screening in the first trimester and again between 24 and 28 weeks. Those with values below diagnostic thresholds should receive further evaluation. Iron deficiency anemia, the most common form of anemia in pregnancy, is treated with iron supplementation.[9]

Increased white blood cell volume

A mild leukocytosis is common in pregnancy, with white blood cell counts up to 15,000 per L considered within normal physiologic range.[10]

Increased coagulation factors

Concentrations of clotting factors and fibrinogen increase during pregnancy due to estrogen-induced hepatic stimulation. Although these changes promote hemostasis during delivery, they also heighten the risk of thromboembolic events during pregnancy and the postpartum period.[11]

7.1.4.3 Pulmonary

Physiologic changes in the pulmonary system accommodate increased oxygen demands and reduced intrathoracic space resulting from uterine enlargement.

Decreased Functional Residual Capacity (FRC)

Upward displacement of the diaphragm by up to 5cm occurs as the gravid uterus elevates abdominal contents, leading to mechanical lateral expansion of the chest wall. Despite this compensatory change, total functional capacity decreases by roughly 5%.

Increased tidal volume

Rising fetal CO2 production increases maternal ventilatory demands, resulting in a 30% to 40% increase in tidal volume.

Respiratory rate

Maternal respiratory rate remains similar to that of the non-pregnant state. (Figure 7.11)

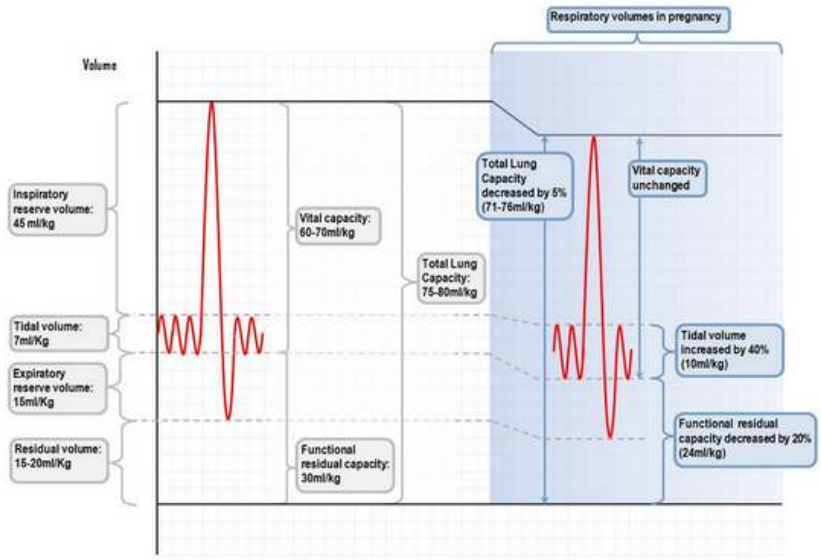


Figure 7.11. Tidal volume increases by 30-50%. Increased diaphragmatic excursion changes the tidal volume from (for example) 500ml in the first trimester to over 700ml in the third trimester. Respiratory rate increases from 15-17 on average. FEV_1/FVC remains essentially the same.
Source: Yartsev, Alex. Influence of pregnancy on respiratory function. In *Deranged Physciology.* 2023. Freely available resource: https://derantedphysiology.com/main/home.

Respiratory alkalosis

Increased minute ventilation lowers maternal CO2 levels, producing a slight respiratory alkalosis. Normal maternal pH ranges from 7.40 to 7.45, slightly higher than the non-pregnant

range of 7.35 to 7.45.

Clinical Correlation

Lower CO2 levels, increased tidal volume, and reduced total lung capacity may contribute to dyspnea of pregnancy. This sensation is most prominent in the third trimester, though oxygen saturation should remain normal.

7.1.4.4. Gastrointestinal

Nausea and vomiting

Elevated levels of hCG, progesterone, and estrogen in early pregnancy contribute to nausea and vomiting.

Clinical Correlation

Symptoms usually improve in the second trimester and may be managed with over-the-counter therapies. Severe vomiting with dehydration or electrolyte abnormalities may warrant hospitalization.

Slower gut motility

Progesterone reduces gastrointestinal smooth muscle activity, resulting in slowed gastric emptying and increased risk of constipation.

Esophageal sphincter relaxation

Progesterone also relaxes the lower esophageal sphincter. Combined with upward displacement of the stomach, this contributes to increased gastroesophageal reflux.

Hemorrhoids

Constipation, decreased systemic vascular resistance, and mechanical compression from the gravid uterus increase the incidence of hemorrhoids.

Gallstones

Elevated estrogen promotes cholesterol production and decreases bile salt synthesis, leading to bile supersaturation. Progesterone-induced gallbladder hypomotility promotes bile stasis, increasing gallstone formation.

Clinical Correlation

Cholelithiasis may be managed conservatively with dietary modification, although cholecystitis or choledocholithiasis may necessitate surgical intervention.

7.1.4.5 Renal and Urinary

Increased GFR

Increased plasma volume and decreased renal vascular resistance enhance renal perfusion, leading to up to a 50% rise in glomerular filtration rate (GFR). This increase contributes to lower maternal BUN and creatinine levels. Mild physiologic proteinuria may occur, but new onset proteinuria with elevation in blood pressure requires evaluation for pre-eclampsia.

Increased urination

Higher urine production and compression of the bladder by the gravid uterus contribute to urinary frequency.

Clinical Correlation

Nocturia is a common concern in pregnancy.

Increased risk of complicated urinary tract infection

Progesterone reduces ureteral motility, causing ureteral dilation and increasing the risk of reflux. Compression from the gravid uterus further enhances this risk, predisposing patients to pyelonephritis.

Clinical Correlation

Screening urine cultures are obtained early in pregnancy, and asymptomatic bacteriuria is treated to reduce risk of complications.

7.1.4.6 Endocrine

Thyroid

TSH shares an alpha subunit with hCG, so the peak of hCG in early pregnancy may weakly stimulate the thyroid to produce additional T3 and T4. This will transiently reduce TSH levels, while free T3 and T4 typically remain within normal range due to the simultaneous increase in thyroid-binding globulin.

Prolactin and Oxytocin

Rising estrogen levels stimulate prolactin production and increase uterine oxytocin receptor density. Oxytocin levels rise progressively during pregnancy and play an essential role in labor contractions, while prolactin promotes milk production.

Clinical Correlation

Synthetic oxytocin, known as Pitocin, is used to induce labor by augmenting uterine contractions.

7.1.4.7 Breast

Areolar enlargement

Most pregnancies involve enlargement and darkening of the areolae.

Breast tenderness and enlargement

Estrogen promotes ductal proliferation beginning in the first trimester, resulting in breast enlargement and tenderness. Although prolactin increases during pregnancy, elevated estrogen and progesterone inhibit milk production until after delivery.[1]

7.1.4.8 Uterus

Uterine growth

High maternal estrogen levels and fetal growth stimulate uterine enlargement and elongation. By the third trimester, uterine growth slows as musculature stretches to accommodate fetal size. Several weeks after delivery, the uterus returns to its pre-pregnancy dimensions.

Uterine quiescence

Progesterone maintains uterine relaxation throughout pregnancy by suppressing myometrial contractility.

7.1.5 Routine Prenatal Care

Prenatal care scheduling is designed to support the management of pre-existing medical conditions and to facilitate early detection of pregnancy related complications. As gestation advances, the incidence and complexity of potential complications increase, necessitating more frequent clinical encounters. Historically, prenatal care was conducted entirely through in-person visits, occurring every 4 weeks during the first and second trimesters, every 2 weeks from 28 to 36 weeks, and weekly from 36 weeks until delivery. The COVID-19 pandemic accelerated the adoption of alternative care strategies, including telehealth appointments, home blood pressure and fetal monitoring, and individualized adjustments in visit frequency based on risk stratification. Contemporary models of prenatal care increasingly incorporate these flexible approaches and may be tailored to the needs of each clinical practice and patient population.[13]

7.1.5.1 Components of Prenatal Visit

Blood pressure assessment

Blood pressure is measured at every prenatal visit. Elevated readings prior to 20 weeks gestation may suggest previously undiagnosed chronic hypertension. New onset elevations after 20 weeks require evaluation for pregnancy related hypertensive disorders, including pre-eclampsia.

Fundal height measurement

For low-risk pregnancies, fundal height measurement is initiated at 24 weeks. Using a tape measure, the clinician assesses the distance from the pubic symphysis to the uterine fundus, which in centimeters generally correlates with gestational age in weeks. Discrepancies greater than 3 centimeters warrant further evaluation with ultrasound to assess for abnormalities in AMNIOTIC FLUID or FETAL GROWTH. Certain conditions, such as HYPERTENSIVE DISORDERS (increasing risk for growth restriction) and GESTATIONAL DIABETES (increasing

risk for macrosomia) place a patient at high risk for growth disorders. Other disorders, such as, the presence of fibroids, MULTIFETAL GESTATION, or elevated maternal BMI, may render fundal height less reliable. In such individuals, serial growth ultrasounds at 3 to 4 week intervals are preferred.

Maternal weight

Expected weight gain in pregnancy is 25 to 35 pounds, with the majority occurring in the third trimester. Individuals with elevated pre-pregnancy BMI have lower recommended weight gain thresholds. Excessive weight gain is associated with increased risk of fetal macrosomia and cesarean delivery, while inadequate weight gain may indicate or contribute to fetal growth restriction.[14]

Fetal heart rate

Fetal heart rate is evaluated at each prenatal visit using a handheld doppler device. Patients at increased risk of stillbirth may require additional surveillance through non-stress tests, discussed further in ANTENATAL TESTING.

Assessment of fetal movement

Beginning when the patient can reliably perceive fetal movement, clinicians routinely inquire whether fetal activity feels normal for the individual. Evidence regarding the utility of formal kick count instruction is mixed, but any report of subjectively decreased fetal movement after viability warrants prompt evaluation.[15]

Assessment for miscarriage or preterm labor

At each visit, patients should be screened for vaginal bleeding, leakage of fluid, or uterine contractions, which may suggest miscarriage or preterm labor.

Assessment for pre-eclampsia

In addition to blood pressure monitoring, clinicians assess for symptoms suggestive of pre-eclampsia beginning in the second half of pregnancy. Symptoms include persistent headache, visual disturbance, right upper quadrant pain, dyspnea, and chest pain.

7.1.5.2 Ultrasounds

Source for this section topic:

ACOG. Ultrasound in Pregnancy. Practice Bulleting, No. 175. (December 2016). Restricted access, https://www.acog.org/clinical/clinic...d-in-pregnancy.[16]

First trimester ultrasound

As discussed in the EARLY PREGNANCY section, ultrasound evaluation in the first trimester is used to confirm intrauterine pregnancy, assess for multifetal gestation, and establish accurate gestational dating. Ideally, this scan is performed prior to 14 weeks gestation.

Anatomy ultrasound

A detailed fetal anatomy ultrasound is recommended between 18 and 22 weeks gestation. A standard examination includes evaluation of the fetal head, face, neck, chest, abdomen, spine, extremities, and genitalia. Placental location is recorded, and cervical length is often measured to assess risk for preterm birth. In pregnancies at increased risk for fetal anomalies, a more comprehensive targeted examination may be performed.

Growth ultrasounds

Serial growth ultrasounds may be obtained at 3 to 4 week intervals when there is concern for fetal growth abnormalities or when maternal body habitus or other factors limit the accuracy of fundal height measurements.

Additional ultrasound assessments

Specialized measurements such as biophysical profile, amniotic fluid index, umbilical artery dopplers, and middle cerebral artery dopplers may be performed when clinically indicated.

7.1.5.3 Immunizations

Source for this section topic:

ACOG. Maternal Immunization. *Practice Advisory* (October 2022). Availabe from: https://www.acog.org/clinical/clinic...l-immunization.[17]

Immunizations play a critical role in pregnancy by reducing the risk of maternal morbidity from infectious diseases and by providing passive immunity to the fetus and newborn. Pregnant patients should not receive live attenuated vaccines, including measles-mumps-rubella, varicella, and live attenuated influenza formulations. These vaccines carry theoretical risks of transplacental infection and are therefore contraindicated during pregnancy.

Tetanus toxoid, reduced diphtheria toxoid, and acelluar pertussis (Tdap)

All pregnant individuals should receive the Tdap vaccine between 27 and 36 weeks gestation in each pregnancy, regardless of prior vaccination history. Maternal vaccination during this window optimizes transplacental transfer of pertussis antibodies, providing passive immunity to the newborn for the first several months of life, when morbidity from pertussis infection is highest.

Hepatitis B

The American College of Obstetrics and Gynecology advises screening for hepatitis B surface antibody to assess immunity. Pregnant patients who are not immune may safely receive the hepatitis B vaccine series during pregnancy.

Influenza

Pregnancy increases the risk of severe complications from influenza infection, including pneumonia and preterm labor. Vaccination with an inactivated or recombinant influenza vaccine is recommended for all pregnant patients during influenza season.

COVID-19

Pregnant individuals experience higher risks of morbidity, mortality, and obstetric complications from COVID 19 infection. Vaccination is recommended for those who remain unvaccinated, and booster vaccination is advised for those who have previously completed a primary series.

Respiratory Syncytial Virus (RSV)

The American College of Obstetrics and Gynecology recommends administration of the bivalent RSV vaccine between 32 and 37 weeks gestation during respiratory virus season for individuals who have not yet received it. If the vaccine is not given during pregnancy, the newborn should receive the recommended monoclonal antibody for RSV prophylaxis if born during RSV season.

7.1.5.4 Laboratory

Complete blood count (CBC)

A CBC should be obtained during the first trimester and repeated between 24 and 28 weeks gestation. As noted in HEMATOLOGIC CHANGES OF PREGNANCY, physiologic hemodilution may result in mild anemia. Hemoglobin levels less than 11 g/dL in the first or third trimesters warrant evaluation for underlying causes, with iron deficiency representing the most common etiology.[18]

Platelet counts typically decrease slightly during pregnancy. Thrombocytopenia is conventionally defined as a platelet count less than 150×10^9 per L. The most frequent cause is gestational thrombocytopenia, a benign condition accounting for approximately 80% of cases and not requiring intervention. Platelet counts less than 100×10^9 per L are less likely to be gestational and warrant additional evaluation.[19]

Blood type

Maternal blood type should be determined in the first trimester. Red blood cell antigens are classified into the ABO and Rh systems. ABO incompatibility between mother and fetus may lead to neonatal jaundice and anemia. Rh D antigen incompatibility carries the risk of maternal alloimmunization, which can cause hydrops fetalis and stillbirth.

- If the patient is Rh D positive, repeat blood typing is generally unnecessary until delivery.
- If the patient is Rh D negative, preventative management is required to avoid alloimmunization, as detailed in ALLOIMMUNIZATION PREVENTION.

Antibody screen

An antibody screen is performed early in pregnancy to assess for maternal red blood cell antibodies. Although many antibodies do not result in clinically significant hemolytic disease,

others such as anti-D, anti-Kell, and anti-Duffy can cause severe fetal anemia. Pregnancies complicated by high-risk antibodies require serial fetal assessment throughout gestation.[20]

1-Hour oral glucose text

Source for this section topic:

ACOG. Gestational Diabetes Mellitus. *Practice Bulletin*, No. 190 (Febrary 2019). Restricted access, https://www.acog.org/clinical/clinical-guidance/practice-bulletin/articles/2018/02/gestational-diabetes-mellitus.[21]

Gestational diabetes is one of the most common medical complications of pregnancy and is discussed in detail in PREGNANCY COMPLICATIONS. Screening is recommended for all pregnant patients without a preexisting diabetes diagnosis between 24 and 28 weeks gestation.

All pregnant patients meeting these criteria should undergo an oral glucose tolerance screening with a 50 mg glucose load, followed by a venous blood glucose measurement 1 hour later. Institutional thresholds for abnormal values vary but are most commonly between 130 and 140 mg/dL.

Patients who fail the screening test undergo a diagnostic 3-hour glucose tolerance test. After an overnight fast, a fasting glucose level is obtained, followed by ingestion of a 100 mg glucose load. Venous glucose measurements are repeated at 1, 2, and 3 hours. Diagnostic cutoffs vary, and no universal consensus exists. A diagnosis of gestational diabetes is made when at least 2 of the 4 values exceed institutional thresholds. Emerging evidence suggests that even one abnormal value may confer increased risk, though current guidelines do not recommend treatment solely on this basis.

Hemoglobin A1c is not a reliable screening tool for gestational diabetes. Because gestational diabetes develops due to placental hormone mediated insulin resistance, which becomes more pronounced in the late second and early third trimesters, A1c may not reflect current glycemic status.

Select individuals at high risk for undiagnosed type 2 diabetes should undergo first trimester glucose screening. Risk factors include obesity, prior gestational diabetes, hypertension, dyslipidemia, family history of diabetes, high risk race or ethnicity, and history of a macrosomic infant.

7.1.5.5 Infection Screening

Rubella IgG

Rubella immunity is assessed during the first trimester of each pregnancy. Non-immune individuals should receive the measles-mumps-rubella vaccine in the postpartum period, as it is contraindicated during pregnancy.

Hepatitis B

Prenatal hepatitis B infection is a significant cause of chronic liver disease worldwide. Prophylaxis and antiviral therapy can markedly reduce neonatal transmission. All pregnant

individuals should undergo hepatitis B surface antigen (HBsAg) testing in the first trimester, regardless of prior vaccination or testing. Those who test positive should receive further testing, including hepatitis B virus DNA levels and hepatitis B core and surface antigens, to differentiate acute from chronic infection and determine the need for antiviral therapy. As mentioned previously, COG also recommends hepatitis B surface antibody (anti-HBs) and core antibody (anti-HBc) testing for pregnant patients over age 18 without documented prior screening. Individuals lacking surface antibodies are considered non-immune and may safely receive the hepatitis B vaccine series during pregnancy. Historically, hepatitis B vaccination has been administered to the infant immediately after delivery to reduce the risk of chronic hepatitis B infection acquired in infancy from household or caregiver exposure. This practice has significantly decreased the burden of childhood and lifelong liver disease. Although the CDC has recently modified its recommendations regarding routine neonatal vaccination, many medical institutions continue to endorse this approach based on longstanding evidence of its protective benefit.[22]

Hepatitis C

Universal screening for hepatitis C antibodies is recommended in each pregnancy. No current interventions have been demonstrated to reduce perinatal hepatitis C transmission.[23]

Human Immunodeficiency Virus (HIV)

All pregnant patients should be screened for HIV early in pregnancy. Repeat testing in the third trimester is recommended for high-risk individuals or in regions with high HIV incidence.[24]

Without treatment, perinatal HIV transmission rates range from 25% to 30%, but modern antiretroviral therapies can reduce transmission to less than 1%.[25]

For more information...

For more details about preventing perinatal HIV transmission, see Kalapila, Aly G. and David H. Spach. Preventing Perinatal HIV Transmission. *National HIV Curriculum*, Module 5, Lession 1. Available from: https://www.hiv.uw.edu/go/prevention/preventing-perinatal-transmission/core-concept/all.

Syphilis

Rates of congenital syphilis have risen substantially in the United States, with notable racial and ethnic disparities. Because early detection and treatment prevent most cases, universal screening is recommended in the first trimester. Many states also recommend repeat testing in the third trimester and again at delivery for high-risk populations.[26]

Gonorrhea and Chlamydia

Chlamydia (*Chlamydia trachomatis)* and Gonorrhea (*Neisseria gonorrhoeae)* are the most common sexually transmitted infections in the United States. In pregnancy, these infections can result in preterm rupture of membranes, preterm birth, and chorioamnionitis. During delivery,

these bacteria can cause neonatal conjunctivitis, resulting in permanent blindness, as well as neonatal sepsis. To prevent these complications, individuals considered high risk for sexually transmitted infections or patients with symptoms should be screened for gonorrhea and chlamydia in the first trimester with cervical swabs and treated if necessary. Universal erythromycin ointment is also recommended for neonates at the time of birth to prevent conjunctivitis in the case of undiagnosed infection.

Group B Streptococcus (GBS)

Source for this section topic:

ACOG. Prevention of Group B Streptococcal Early-Onset Disease in Newborns, Committee Opinion, Nov. 797 (February 2020). Available from: https://www.acog.org/clinical/clinical-guidance/committee-opinion/articles/2020/02/prevention-of-group-b-streptococcal-early-onset-disease-in-newborns.[27]

Streptococcus agalactiae colonizes the vaginal and rectal flora of 10% to 30% of pregnant individuals and is the leading cause of neonatal early-onset sepsis. Vertical transmission most commonly occurs during labor. All pregnant patients should undergo GBS screening with vaginal and anorectal swabs between 36 and 37 weeks gestation. Positive individuals should receive intrapartum antibiotic prophylaxis with penicillin or ampicillin, unless allergic, ideally at least 4 hours before delivery. Patients with a history of neonatal GBS sepsis do not require rescreening and should receive intrapartum antibiotics in all future pregnancies. Patients documented GBS bacteriuria at any point during the current pregnancy are considered positive and require intrapartum prophylaxis.

7.1.5.6 Alloimmunization Prevention

Alloimmunization occurs when an Rh-negative mother, who lacks the Rh D antigen on her red blood cells, is exposed to Rh positive fetal red blood cells and subsequently forms antibodies against the Rh D antigen. This immune response typically does not affect the current pregnancy. However, in subsequent pregnancies with an Rh-positive fetus, maternal anti-D antibodies can cross the placenta and destroy fetal erythrocytes, potentially resulting in hemolytic disease of the fetus and newborn.

To prevent alloimmunization in Rh negative patients, several approaches can be used to determine fetal Rh D status.

- **Cell-free DNA testing:** Advances in technology now allow noninvasive determination of fetal blood type through analysis of cell free fetal DNA in maternal blood.[28]
- **Paternal blood type testing:** If cell free DNA is unavailable and the father of the fetus is known, paternal Rh status may be assessed. Because the Rh D antigen is inherited in an autosomal dominant manner, an Rh-negative father will have only Rh-negative offspring.[29] (Figure 7.12)

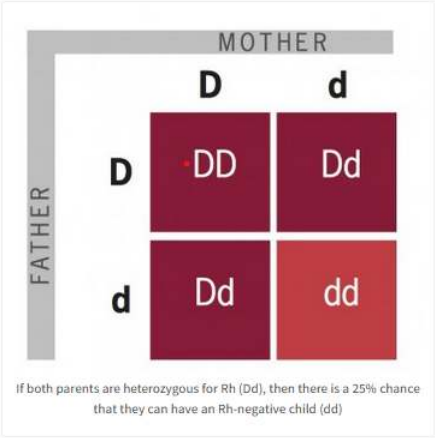


Figure 7.12. Simple Punnett Square
Source: Stanford Blood Center. Can two Rh-positive parents have an Rh negative child? (October 2018). Available from: https://stanfordbloodcenter.org/can-...egative-child/.

If fetal blood type cannot be definitively established, or if the fetus is determined to be Rh-positive, Rh-negative mothers should receive anti-D immune globulin at 28 weeks gestation and within 72 hours of any event associated with possible fetomaternal hemorrhage, such as abdominal trauma, vaginal bleeding, or invasive procedures like amniocentesis. Anti-D immune globulin binds fetal Rh positive red blood cells in maternal circulation, preventing maternal immune recognition and antibody formation.[30]

- **Early pregnancy events:** Recent evidence indicates that the volume of fetomaternal hemorrhage prior to 12 weeks gestation is insufficient to cause alloimmunization. As a result, anti-D immune globulin is no longer routinely recommended for miscarriages or pregnancy terminations before 12 weeks.[31]

After delivery, newborn blood type should be assessed. If the infant is Rh positive, the mother should receive an additional postpartum dose of anti-D immune globulin.

Patients who are already alloimmunized, indicated by the presence of maternal anti-D antibodies, require close surveillance throughout pregnancy to assess for fetal anemia.[32]

7.1.5.7 Antenatal Testing

Source for this section topic:

ACOG. Indications for outpatient antenatal fetal surveillance. *Committee Opinion,* No. 828 (June 2021). Available from: https://www.acog.org/clinical/clinical-guidance/committee-opinion/articles/2021/06/indications-for-outpatient-antenatal-fetal-surveillance.[33]

Certain pregnancies carry an elevated risk of stillbirth compared with the general obstetric population. These risks may arise from maternal factors (such as advanced maternal age, chronic hypertension, diabetes), fetal factors (such as multifetal gestation, fetal growth restriction, or congenital anomalies), or pregnancy-related conditions (such as chronic abruption or a history of prior stillbirth). Pregnancies associated with an estimated stillbirth risk

greater than 0.8 per 1,000, corresponding to a relative risk of at least 2.0, warrant closer fetal surveillance to identify early signs of hypoxia or compromise. Antenatal testing may begin at 32 weeks, 36 weeks, or after 39 weeks, depending on the magnitude and timing of risk.

The physiologic rationale behind antenatal testing is based on the sensitivity of fetal heart rate patterns, activity level, muscular tone, and amniotic fluid volume to hypoxia and acidemia. A fetus demonstrating normal activity, tone, and heart rate reactivity is unlikely to be acidemic at that point in time.

Nonstress Test (NST)

A reassuring fetal heart rate tracing at or beyond 32 weeks gestation includes temporary accelerations in heart rate that rise at least 15 beats per minute above baseline and persist for at least 15 seconds. An NST is performed by placing an external doppler transducer on the maternal abdomen to record fetal heart rate over a 20-to-40-minute period.

A normal (reactive) NST includes the following features:

- Baseline fetal heart rate between 110 and 160 beats per minute
- Baseline variability of 5 to 20 beats per minute
- At least two accelerations meeting the 15 beat per minute by 15 second criteria
- No decelerations in the fetal heart rate

Failure to meet these criteria may reflect fetal sleep cycles, but persistent abnormalities can signal hypoxia and warrant further evaluation.

Contraction Stress Test (CST)

Uterine contractions temporarily decrease blood flow to the placenta. A healthy fetus with normal placental reserve tolerates this reduction without evidence of compromise. However, when baseline placental perfusion is diminished or when cord compression is present, contractions may reveal fetal intolerance. A CST evaluates fetal heart rate patterns during contractions. Contractions may be stimulated through nipple stimulation or by administering intravenous oxytocin to achieve at least three contractions in a 10 minute interval.

Interpretation is as follows:

- Negative CST: No late decelerations are observed
- Positive CST: Late decelerations occur following at least 50 percent of contractions
- Equivocal CST: Variable decelerations or late decelerations occurring with less than 50 percent of contractions

A positive CST is concerning for uteroplacental insufficiency and generally requires prompt clinical assessment.

Biophysical Profile (BPP)

The biophysical profile combines ultrasound-based assessments of fetal well-being with the results of the NST. A non-hypoxic fetus should demonstrate adequate amniotic fluid, normal

tone, and ongoing gross movement. Each component of the BPP is assigned 2 points, for a maximum score of 10. Scores of 8 out of 10 or 10 out of 10 are considered reassuring.

The components are:

- NST: A reactive nonstress test
- Fetal breathing movements: At least one episode of rhythmic diaphragmatic movement lasting 30 seconds or longer within a 30-minute observation period
- Fetal body movements: At least three discrete movements of the body or limbs within 30 minutes
- Fetal tone: At least one episode of extension-flexion of a limb or opening-closing of a hand one episode of extension-flexion of a limb or opening-closing of a hand
- Amniotic fluid volume: A single deepest vertical pocket greater than 2 cm. A low BPP score may reflect fetal hypoxia and requires timely evaluation and possible intervention depending on gestational age and clinical context.

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Image Acknowledgements

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7.2: Pregnancy Complications

7.2.1 Early Pregnancy Complications

7.2.1.1 Hydatidiform Mole

Molar pregnancies are a form of gestational trophoblastic disease arising from abnormal fertilization. Although considered benign, hydatidiform moles are premalignant lesions with potential for malignant transformation and tissue invasion.[34]

Types

Source for this section content:

Cue, Lauren, Fabiola Farci, Sassan Ghassemzadeh, Michael Kang. [Updated 2024 Dec 11]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. [Updated 2024 Dec 11]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK459155/ Available from: https://www.ncbi.nlm.nih.gov/books/NBK45915.[35]

Complete hydatidiform mole:

A complete mole results from fertilization of an “empty” ovum that lacks maternal genetic material. This may occur when two sperm fertilize an empty egg, producing a 46 XX or 46 XY karyotype, though the more common mechanism is fertilization by a single 23X sperm followed by duplication of the paternal genome, producing a 46XX karyotype of entirely paternal origin. (Figure 7.13)

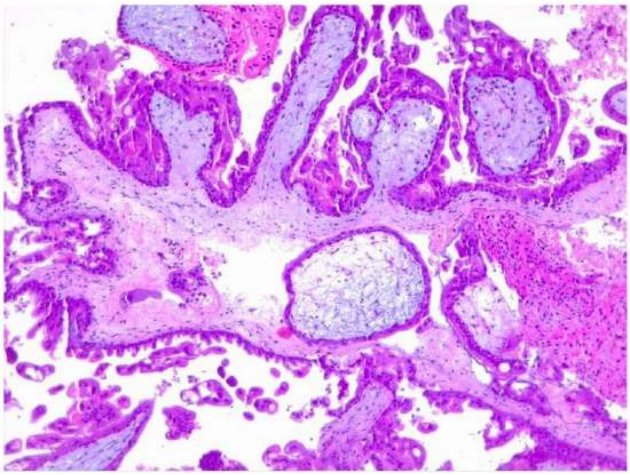


Figure. 7.13 Hydatiform Mole. Chorionic villi with hydropic change, formation of cystic spaces and exuberant villous trophoblastic hyperplasia. Contributed by F Farci, MD.
Source: Cue, Lauren, Fabiola Farci, Sassan Ghassemzadeh, Michael Kang. [Updated 2024 Dec 11]. In: *StatPearls* [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. [Updated 2024 Dec 11]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK459155/ Available from: https://www.ncbi.nlm.nih.gov/books/NBK459155/.

Partial hydatidiform mole:

A partial mole occurs when a normal 23X ovum is fertilized by either two sperm or one sperm that subsequently duplicates. This produces a triploid zygote with a 69XXX, 69XXY, or 69XYY karyotype. Because maternal DNA is present, partial moles may contain fetal tissue or fetal parts. Partial moles are less common than complete moles.(Figure 7.14)

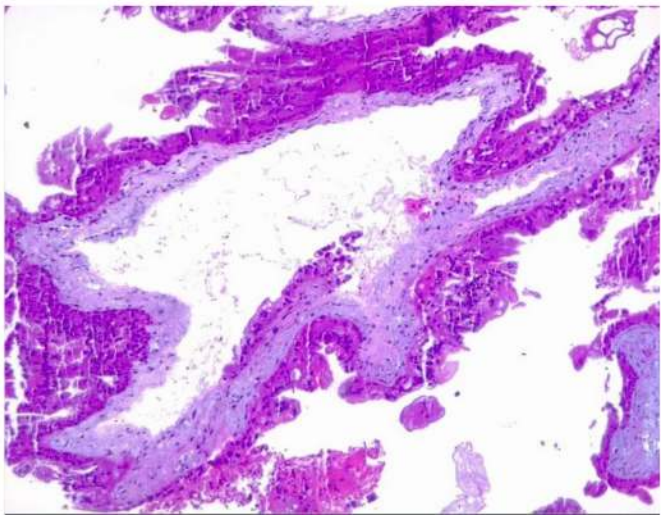


Figure 7.14. Partial Hydatiform Mole. Histologic image demonstrating irregular, indented villi with lace-like trophoblast proliferation, H/E 4×. Contributed by F Farci, MD

Source: Cue, Lauren, Fabiola Farci, Sassan Ghassemzadeh, Michael Kang. [Updated 2024 Dec 11]. In: *StatPearls* [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. [Updated 2024 Dec 11]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK459155/ Available from: https://www.ncbi.nlm.nih.gov/books/NBK459155/.

Diagnosis

Molar pregnancies are nonviable and characterized by trophoblastic hyperplasia. Rapid proliferation of abnormal villi produces markedly elevated hCG levels, often leading to severe nausea and vomiting and a uterine size larger than expected for gestational age. Vaginal bleeding is common due to separation of molar tissue from the decidua. Late clinical features may include symptoms of thyrotoxicosis, as hCG and TSH share an alpha subunit. Ultrasound classically demonstrates a “snowstorm” appearance composed of numerous cystic spaces resembling “grape clusters.” Partial moles may show fetal tissue. (Figure 7.15)



Figure 7.15. Ultrasound image of a molar pregnancy displaying a "snowstorm-like" appearance. Contributed by S Dulebohn, MD.

Source: Cue, Lauren, Fabiola Farci, Sassan Ghassemzadeh, Michael Kang. [Updated 2024 Dec 11]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. [Updated 2024 Dec 11]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK459155/ Available from: https://www.ncbi.nlm.nih.gov/books/NBK459155/.

Treatment

Management consists of evacuation via suction dilation and curettage. Hysterectomy is an option for individuals who have completed childbearing. Following evacuation, quantitative hCG levels should be monitored weekly until undetectable, then monthly for 1 to 3 months.[36]

Histopathology

Gross specimens show enlarged, cystic, “grape-like” villi. Microscopically, hydatidiform moles demonstrate hydropic villi with trophoblastic hyperplasia. Complete moles show diffuse villous enlargement, while partial moles show focal changes. (Figure 7.16)

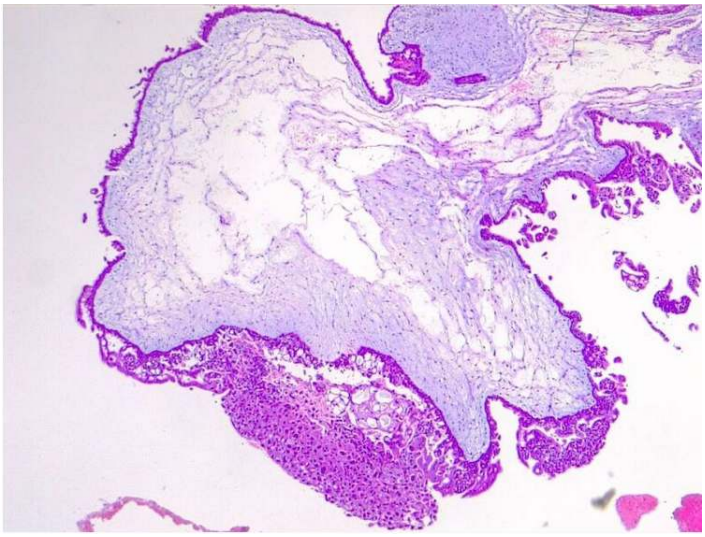


Figure 7.16. Hydropic Villi and Trophoblastic Proliferation. Microscopic examination of complete moles reveals poorly vascularized chorionic villi with hydropic swelling and myxomatous, edematous stroma, creating a florid cistern filled with stromal fluid, H/E 4×. Contributed by F Farci, MD.

Source: Cue, Lauren, Fabiola Farci, Sassan Ghassemzadeh, Michael Kang. [Updated 2024 Dec 11]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. [Updated 2024 Dec 11]. In: *StatPearls* [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK459155/ Available from: https://www.ncbi.nlm.nih.gov/books/NBK459155/.

7.2.1.2 Ectopic Pregnancy

An ectopic pregnancy results from implantation of the blastocyst outside the uterine cavity. The ampulla of the fallopian tube is the most common site, but implantation may also occur in the ovary, cervical canal, cesarean scar, cornua/interstitium, infundibulum, abdominal cavity, or peritoneum.(Figure 7.18)



Figure 7.18 An ectopic pregnancy adjacent to the left ovary.
Source: Ectopicleftmass by James Heilman, MD licensed under CC BY-SA 3.0. Available from: https://commons.wikimedia.org/wiki/File:Ectopicleftmass.PNG.

Ruptured Ruptured ectopic pregnancy is a life-threatening emergency and accounts for over 2% of pregnancy-related mortality.[37]

Risk Factors

Any condition associated with tubal damage or impaired ovum transport increases ectopic risk.

Examples include:

- Prior pelvic inflammatory disease
- Endometriosis
- Tubal occlusion or sterilization procedures
- Assisted reproductive technology
- Reproductive
- Congenital or acquired tubal abnormalities
- Smoking
- Advanced maternal age

Individuals with a prior ectopic pregnancy remain at elevated risk in subsequent pregnancies.[38]

Although the overall risk of pregnancy is low with intrauterine device (IUD) use, any pregnancy that occurs with an IUD in place carries approximately a 50% chance of being ectopic. [39]

Diagnosis

Symptoms typically include unilateral lower abdominal pain and vaginal bleeding. Pain may become diffuse with tubal rupture. Transvaginal ultrasound may demonstrate an adnexal yolk sac or fetal pole, although diagnosis often relies on the combination of imaging, beta-hCG levels, and clinical suspicion.[40] Signs of rupture include free intraperitoneal fluid and hemodynamic instability.

Pregnancy of unknown location

Sensitive pregnancy tests may reveal early pregnancy before an intrauterine gestation is detectable. Serial hCG measurements and ultrasound should be performed until a pregnancy

location is confirmed. Inappropriately rising hCG levels without visualization of an intrauterine pregnancy raise concern for ectopic pregnancy or early pregnancy loss. Management may involve uterine aspiration or methotrexate.[41]

Treatment

Methotrexate

Methotrexate is a folate antagonist that inhibits DNA synthesis in rapidly dividing cells. It is administered intramuscularly for hemodynamically stable patients. Close follow-up with serial hCG measurements is required. Contraindications include renal or hepatic dysfunction, bone marrow suppression, and active gastrointestinal disease. Higher initial hCG levels, fetal cardiac activity, or large ectopic size are associated with lower methotrexate success rates.[42]

Surgical Management

Patients who prefer definitive therapy or have contraindications to methotrexate may undergo surgical management.

- Salpingectomy removes the affected fallopian tube and eliminates future ectopic risk in the tube.
- Salpingostomy excises the ectopic pregnancy while preserving the tube but requires postoperative hCG monitoring and carries recurrent ectopic risk.

Treatment choice should incorporate patient preference, fertility considerations, and clinical stability.[43]

7.2.1.3 Miscarriage

Early pregnancy loss, also known as miscarriage or spontaneous abortion, is defined as pregnancy loss before 13 weeks gestation. It is common, occurring in 15% to 25% of clinically recognized pregnancies and up to 30% to 60% of all conceptions.[44]

Risk Factors

Approximately half of early pregnancy losses are due to chromosomal abnormalities. The most common risk factors are advanced maternal age and prior miscarriage. Additional contributors include uterine anomalies, antiphospholipid syndrome, diabetes, and certain infections, although the differential is broad.[45]

Diagnosis

Some patients are asymptomatic, with pregnancy failure detected on ultrasound. Others present with bleeding and cramping.

Diagnostic criteria include:

- Crown-rump length greater than 7 mm without cardiac activity
- Mean gestational sac diameter greater than 25 mm without an embryo
- Loss of previously documented embryo or cardiac activity

A significant drop in hCG may indicate pregnancy loss, but ectopic pregnancy must be excluded, especially in pregnancies of unknown location.[46]

Treatment

Management options include expectant, medical, and surgical approaches.

Expectant management

Appropriate for stable patients with counseling on what to expect. Up to 80% will spontaneously complete expulsion within 8 weeks. Signs of infection or hemorrhage require prompt intervention. Follow-up is necessary to confirm passage of all tissue.[47]

Medical management

Highly effective for most patients. The preferred regimen is oral mifepristone (anti-progesterone) followed by buccal, vaginal, or oral misoprostol (prostaglandin). Success rates approximate 95% When mifepristone is unavailable, misoprostol alone is approximately 83 percent effective.[48] Risks include heavy bleeding, incomplete expulsion, infection, and treatment failure. Follow-up is required.

Surgical management

Suction dilation and curettage is appropriate for patients who decline other options or have contraindications to medical or expectant management. The procedure may be performed in an outpatient or operating room setting. Risks include bleeding, infection, and uterine perforation.

7.2.2 Hypertensive Disorders of Pregnancy

Hypertensive disorders of pregnancy, including gestational hypertension and pre-eclampsia, are among the leading causes of maternal and perinatal morbidity and mortality worldwide. Their prevalence continues to rise in the United States, largely attributable to increasing maternal age, higher rates of obesity, and a growing burden of chronic health conditions.

7.2.2.1 Classification

Source for this section topic:

ACOG. Gestational Hypertension and Preeclampsia. *Practice Bulletin*, No. 222 (June 2020). Restricted access, https://www.acog.org/clinical/clinic...d-preeclampsia.[49]

Chronic Hypertension

Chronic hypertension is defined as the presence of elevated blood pressures before pregnancy. In individuals without prior medical care, blood pressure elevation diagnosed before 20 weeks gestation should be considered chronic hypertension.

Gestational Hypertension

Gestational hypertension is defined as new onset systolic blood pressure greater than 140 mmHg or diastolic blood pressure greater than 90 mmHg after 20 weeks gestation. Diagnosis requires two elevated measurements at least 4 hours apart.

Pre-eclampsia

Pre-eclampsia without severe features

This condition is diagnosed when gestational hypertension is accompanied by proteinuria.

Proteinuria criteria:

- Greater than 300 mg per 24 hours, or
- Protein/creatinine ratio greater than 0.3

Patients must not have severe range blood pressures or evidence of end organ dysfunction.

Pre-eclampsia with severe features

This diagnosis is made when any of the following are present:

- Severe range blood pressure (systolic greater than 160 mmHg or diastolic greater than 110 mmHg), or
- Signs of end organ damage:
  - Elevated liver transaminases at least twice normal
  - Persistent right upper quadrant or epigastric pain unresponsive to medication
  - Serum creatinine greater than 1.1 mg per dL or doubling of baseline
  - Platelet count less than 100×10^9 per L
  - Pulmonary edema
  - New onset headache unresponsive to medication
  - Visual disturbances

Proteinuria is no longer required for diagnosis if severe features are present.

HELLP Syndrome

HELLP syndrome is considered a variant of pre-eclampsia with severe features.

It is defined by:

- **H**emolysis (elevated LDH, elevated bilirubin, or schistocytes on smear)
- **E**levated **L**iver enzymes (LFTs twice normal)
- **LP**: Low platelets (less than 100×10^9 per L)

Although HELLP may occur in the absence of elevated blood pressure, it should be managed similarly to pre-eclampsia with severe features.

Eclampsia

Eclampsia is the most severe manifestation of hypertensive disease in pregnancy and is characterized by tonic clonic seizures without another identifiable cause. Prodromal symptoms may include blurred vision, severe headache, or altered mental status. Seizures may lead to trauma, hypoxia, and aspiration. Although eclampsia is typically considered a progression of pre-eclampsia, seizures may occur even in the absence of classic pre-eclampsia symptoms.

Causes

The precise etiology of pre-eclampsia is not fully understood. Current evidence suggests a multifactorial process beginning with abnormal placentation, which leads to systemic

endothelial dysfunction, increased vascular permeability, and vasoconstriction.

Risk Factors

Risk factors for the development of pre-eclampsia include chronic hypertension, pregestational diabetes, kidney disease, systemic lupus erythematosus, and antiphospholipid syndrome. Additional factors include nulliparity, multifetal gestation, advanced maternal age, obesity, and conception via assisted reproductive technology.

Prevention

Although no definitive method exists to prevent pre-eclampsia, daily low dose aspirin has been shown to reduce the risk in individuals with elevated baseline risk. Proposed mechanisms involve imbalance between prostacyclin, a vasodilator and inhibitor of platelet aggregation, and thromboxane A2, a vasoconstrictor and platelet activator. Low dose aspirin selectively inhibits COX 1, reducing thromboxane A2 production. Current recommendations advise initiation of 81 mg aspirin daily for individuals with one high risk factor or two moderate risk factors. Aspirin should be started between 12 and 28 weeks gestation, optimally before 16 weeks, and continued until delivery.[50]

Management

Gestational Hypertension and Pre-eclampsia without severe features

These conditions can be managed in an outpatient setting with close monitoring. Planned delivery at 37 weeks gestation is recommended.

Pre-eclampsia with Severe Features and HELLP Syndrome

Management should occur in an inpatient setting.

Key components include:

- Blood pressure control: Patients with severe range blood pressures should receive intravenous antihypertensives to maintain systolic blood pressure below 160 mmHg and diastolic blood pressure below 110 mmHg. Labetalol, nifedipine, and hydralazine are considered safe and effective.
- Seizure prophylaxis: Intravenous magnesium sulfate is recommended, as it prevents eclamptic seizures more effectively than other antiepileptics.
- Delivery: Delivery is indicated at 34 weeks gestation or earlier depending on maternal or fetal status. Betamethasone should be administered for fetal lung maturity when delivery is anticipated before 34 weeks. After 34 weeks, delivery should not be delayed for steroid administration.

Eclampsia

Acute management includes supportive measures during active seizure, including lateral positioning to prevent aspiration and oxygen supplementation as needed. Magnesium sulfate

should be administered promptly, and blood pressure should be controlled with intravenous antihypertensives if indicated. Delivery should occur once the patient is stabilized.

Postpartum Considerations

Pre-eclampsia, HELLP, and eclampsia may occur in the postpartum period. Individuals who present postpartum with new onset hypertension, laboratory abnormalities, or seizures should be evaluated for pre-eclampsia spectrum disorders.

Future Implications

Individuals with hypertensive disorders of pregnancy have an increased likelihood of recurrence in subsequent pregnancies. Counseling regarding optimal pregnancy spacing and early initiation of aspirin prophylaxis should occur at the postpartum visit. Long term, these individuals carry an elevated risk for chronic hypertension and cardiovascular disease. Annual follow up with a primary care clinician is recommended for cardiovascular monitoring and risk reduction through lifestyle modification.

7.2.3 Gestational Diabetes

Source for this section content:

ACOG. Gestational Diagetes Mellitus. Practice Bulleting, No. 190 (February 2018). Restricted access, https://www.acog.org/clinical/clinic...betes-mellitus.[51]

7.2.3.1 Causes and Risk Factors

During pregnancy, the placenta produces several hormones, including human placental lactogen, that induce significant insulin resistance. In response, maternal pancreatic beta cell mass ordinarily increases to augment insulin production and maintain euglycemia. Individuals who develop gestational diabetes are unable to compensate adequately, often due to underlying genetic susceptibility. Risk factors include a prior history of gestational diabetes, obesity, a family history of diabetes, hypertension, hyperlipidemia, and polycystic ovary syndrome.[5]

7.2.3.2 Diagnosis

As discussed in the ROUTINE PRENATAL CARE: LABORATORY section, all pregnant individuals without pre-existing diabetes undergo a 1 hour oral glucose screening test between 24 and 28 weeks gestation. Details of this diagnostic process are outlined in that section.

7.2.3.2 Complications

Maternal

Although gestational diabetes rarely leads to diabetic ketoacidosis, hyperosmolar hyperglycemic syndrome, or vascular complications during the pregnancy, it is associated with increased risk of pre-eclampsia.

Fetal

Because hyperglycemia in gestational diabetes typically develops after organogenesis, the risk of congenital anomalies is significantly lower compared with pregestational diabetes. However, poor glycemic control can result in multiple fetal complications. Chronic maternal hyperglycemia stimulates fetal hyperinsulinemia, which promotes excessive fetal growth. Macrosomia increases the risk of shoulder dystocia, cesarean birth, and birth trauma. Uncontrolled hyperglycemia also increases the risk of stillbirth.

Neonatal

Neonates of diabetic mothers experience a sudden drop in glucose levels after delivery when maternal glucose supply ceases. Persistently elevated fetal insulin levels can lead to neonatal hypoglycemia. Long term, these neonates have increased risk of childhood obesity and type 2 diabetes.

7.2.3.3 Management

Treatment of gestational diabetes has been shown to reduce the rates of maternal pre-eclampsia, macrosomia, shoulder dystocia, birth trauma, and perinatal death.[53]

Blood Glucose Control

Diet and Lifestyle

Nutritional counseling emphasizing controlled carbohydrate intake and regular exercise forms the cornerstone of treatment. Individuals whose glucose levels remain within target range with diet and exercise alone are classified as having A1GDM.

Medications

If lifestyle modifications are insufficient, pharmacologic therapy is required. Individuals who require medication are classified as having A2GDM.

- Insulin: Insulin is the first line therapy because of its efficacy and inability to cross the placenta.
- Metformin: Metformin is an option for individuals who cannot use or prefer to avoid insulin. It is effective but does cross the placenta, and long-term outcomes for exposed offspring are not fully characterized.

Delivery

Timing of delivery depends on degree of glycemic control and presence of complications.

- Poorly controlled gestational diabetes may warrant earlier delivery, individualized to the clinical picture.
- Well controlled gestational diabetes requiring medication should be delivered between 39 and 40 weeks.
- Well controlled gestational diabetes managed with diet alone may be delivered at 39 weeks but can be expectantly managed to 41 weeks.
- If the estimated fetal weight exceeds 4500 grams, the risk of shoulder dystocia increases. In such cases clinicians should offer counseling regarding elective cesarean birth.

Postpartum

All individuals should undergo postpartum screening with a 75 gram 2 hour oral glucose tolerance test to evaluate for persistent glucose intolerance. Individuals diagnosed with impaired glucose metabolism or diabetes should be referred for appropriate long term management.

Future Implications

Approximately half of individuals with gestational diabetes will develop type 2 diabetes later in life. For this reason, even those with normal postpartum testing should undergo repeat assessment of glycemic status every 1 to 3 years.

7.2.4 Preterm Birth and Preterm Prelabor Rupture of Membranes

7.2.5 Multifetal Gestation

7.2.6 Fetal Growth Disorders

7.2.7 Amniotic Fluid Disorders

7.2.8 Fetal Demise

7.2.9 Placental Disorders

7.2.9.1 Abruption

7.2.9.2 Placenta Accreta Spectrum

7.2.9.3 Placenta Previa and Vasa Previa

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7.3: Normal Labor and Delivery

7.3.1 Spontaneous Labor

7.3.2 Induction of Labor

7.3.3 Monitoring

7.3.4 Pain Control

7.3.5 Stages of Labor

7.3.6 Lacerations

7.3.7 Neonate

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7.4: Delivery Complications

7.4.1 Labor Dystocia

7.4.2 Cesarean Section

7.4.3 Postpartum Hemorrhage

7.4.4 Shoulder Dystocia

7.4.5 Intra-amniotic Infection

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7.5: Postpartum

7.5.1 Normal Postpartum Course

7.5.2 Uterine Changes

7.5.3 Lactation and Breastfeeding

7.5.4 Mood Changes

7.5.5 Contraception and Family Planning

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CHAPTER OVERVIEW

8: Aging and Reproductive Health

8.1: Growing Older and Reproductive Health
8.2: Menopause
8.3: Aging Related Cancers
8.4: Aging Related Abnormal and Disease Conditions
8.5: Glossary

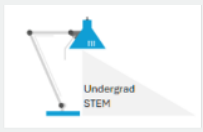
Chapter Author: Margaret (Peg) Burnette, MSLIS

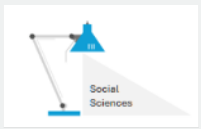
Audience

This chapter presents an overview of reproductive anatomical and physiological changes related to the aging process. Both normal and abnormal conditions are discussed.

The content of this chapter is appropriate for, or easily adapted for the following audiences:







Learning Objectives

By the end of this chapter, learners will be able to

- Define menopause and explain its significance with respect to the reproductive capabilities of women.
- Describe the overall effects of menopause and estrogen replacement therapy on the vagina, external genitalia, and breasts and describe consequences from these effects.
- Discuss cancers that can be associated with the aging process and reproductive health.

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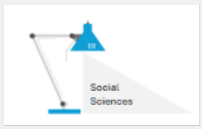
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8.1: Growing Older and Reproductive Health

This unit provides an overview of physical and hormonal changes that are commonly associated with the aging process in females and their effect on physical and mental wellbeing.

The content of this chapter is appropriate for, or easily adapted for the following audiences:





8.1.1 Introduction

Female **fertility** peaks when women are in their twenties, and is slowly reduced until a women reaches 35 years of age. After that time, fertility declines more rapidly, until it ends completely at the end of menopause. Menopause is the cessation of the menstrual cycle that occurs as a result of the loss of ovarian follicles and the hormones that they produce. A woman is considered to have completed menopause if she has not menstruated in a full year. After that point, she is considered postmenopausal. The average age for this change is consistent worldwide at between 50 and 52 years of age, but it can normally occur in a woman's forties, or later in her fifties. Poor health, including smoking, can lead to earlier loss of fertility and earlier menopause.1

8.1.2 Physical Changes Associated with Ageing

8.1.2.1 Ovaries

Before menopause, as more follicles ovulate or become **atretic**, the number of follicles capable of **ovulation** decreases, and by age 50 almost no viable follicles remain. While the number of viable follicles is decreasing, the follicles that develop during each ovarian cycle develop less completely, fewer of them ovulate and form a **corpus luteum**, and therefore less estrogen and progesterone are produced. Eventually no follicles mature fully, ovulation ceases, ovarian cycles disappear, and reproduction becomes impossible. Since the occurrence of menstrual cycles depends on the hormones produced by ovarian cycles, menstrual cycles also cease and menopause occurs.[2]

After menopause, the ovaries produce very small quantities of estrogen and progesterone , and this production gradually diminishes. These hormonal changes are responsible for many other changes, including most age changes in other parts of the reproductive system.[3]

8.1.2.2 Uterus

The most noticeable change in the **uterus** before menopause is a decrease in the degree of **endometrial** thickening during menstrual cycles. Since this decline is due to reduced ovarian

hormone production, this change is observed most frequently during menstrual cycles that accompany ovarian cycles with no ovulation.[4]

The menstrual flow resulting from cycles that have reduced endometrial thickening may be so slight that it is not viewed as constituting a true menstrual period. Menstrual cycles may seem to become very long because two or more cycles may occur before enough menstrual flow is produced to definitively mark the end of a cycle.[5]

As the proportion of ovarian cycles involving no ovulation increases, the time between menstrual periods also increases. When no periods happen for 1 year, menopause has occurred. Note that occasional periods may occur after menopause . However, pregnancy becomes impossible when ovulation ends or when the endometrium fails to thicken enough to form a **placenta** capable of supporting the development of an **embryo**.[6]

Both before and after menopause , the uterus often tips backward and settles lower in the abdominal cavity as its supporting **ligaments** weaken and surrounding structures shift. If the lowering of the uterus is excessive, it may descend into or through the **vagina**. This abnormal condition is called ***uterine prolapse***. Uterine prolapse may also develop as a complication from childbirth or from surgery in the pelvic area.[7]

After menopause , the entire uterus shrinks. It may decrease in size by 50 percent within 15 years after menopause and may eventually shrink to less than 2.0 cm in width.[8]

For more information

Clinical and cost-effectiveness of pessary self-management versus clinic-based care for pelvic organ prolapse in women: the TOPSY RCT with process evaluation.

Source: Bugge C, Hagen S, Elders A, et al. Clinical and cost-effectiveness of pessary self-management versus clinic-based care for pelvic organ prolapse in women: the TOPSY RCT with process evaluation. Southampton (UK): National Institute for Health and Care Research; 2024 May. (Health Technology Assessment, No. 28.23.) Available from: https://www.ncbi.nlm.nih.gov/books/NBK603985/ doi: 10.3310/NWTB5403

8.1.2.3 Vagina

Age changes have no significant effect on the reproductive functions of the vagina. However, they significantly reduce its role as a barrier against abrasion and microbes because as the vagina becomes smaller, thinner, and less elastic, it is more easily damaged by even mild physical trauma, such as friction during sexual intercourse. The increased risk of injury and the decline in lubrication are also more likely to result in pain from sexual intercourse. As the risk of vaginal injury rises, so does the risk of developing sores and vaginal infections. The risk of vaginal infections rises also because as age increases, the lining cells contain and release less **glycogen**. As glycogen declines, less acidic material is produced by healthful microbes and injurious microbes can flourish.[9]

Finally, since the **urethra** lies immediately in front of the vagina, thinning of the vaginal wall increases the frequency of urethral and bladder irritation and inflammation (**cystitis**) from agitation of the vagina during intercourse. Painful urination and temporary urinary incontinence may result.[10]

The rate of age changes in the vagina can be slowed by continued frequent sexual intercourse and by administered estrogen . Therefore, the undesirable consequences of these changes can be minimized. Topical application of estrogen -containing creams directly to the vagina is especially effective. In addition, because the postmenopausal vagina is relatively thin, much of the estrogen enters the blood and can have beneficial effects in other areas.[11]

8.1.2.4 External Structures

Though the changes in the vagina are the main reasons for the increased risk of developing vaginal infections, age -related shrinkage of the **labia majora** may also play a contributing role. This shrinkage causes the labia to remain separated more of the time, allowing microbes to enter the vagina more easily. [12]

8.1.2.5 Breasts

Age changes in the breasts result primarily from the decline in ovarian hormones after menopause . Shrinkage of glandular material, increases in fat, and weakening of fibrous materials in the breasts reduce their firmness and support, causing them to sag and droop rather than protrude from the chest (Figure 7.1.1). Breasts that have stretched fibers from years with little support from undergarments may show more sagging. These changes have significant cosmetic effects.[13]

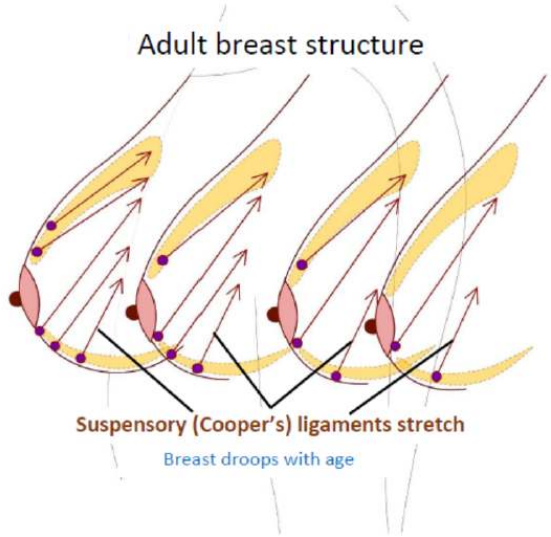


Figure 8.1.1 Age changes in the structure of the breast.
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8.1.2.6 Hormonal Changes

As a woman reaches the age of menopause, depletion of the number of viable follicles in the ovaries due to **atresia** affects the hormonal regulation of the menstrual cycle. During the years leading up to menopause, there is a decrease in the levels of the hormone **inhibin**, which normally participates in a negative feedback loop to the **pituitary** to control the production of **FSH**. The menopausal decrease in inhibin leads to an increase in FSH. The presence of FSH stimulates more follicles to grow and secrete estrogen. Because small, secondary follicles also respond to increases in FSH levels, larger numbers of follicles are stimulated to grow; however, most undergo atresia and die. Eventually, this process leads to the depletion of all follicles in the ovaries, and the production of estrogen falls off dramatically. It is primarily the lack of estrogens that leads to the symptoms of menopause.[14]

When menopause occurs, estrogen secretion by the ovaries and blood estrogen levels decline quickly. During the four years after menopause estrogen secretion by the ovaries dwindles to zero. Blood estrogen levels do not reach zero, however, because small amounts of estrogen are produced by conversion of **testosterone** and **androstenedione** to estrogen and by the **adrenal cortex**. In spite of this estrogen production, blood estrogen levels usually drop to slightly below the lowest levels that were present during premenopausal hormone cycles. Furthermore, postmenopausal estrogen levels may be less than 5 percent of those present during midcycle estrogen peaks before menopause. The low estrogen levels reached within a few years after menopause do not fluctuate cyclically.[15]

As menopause occurs, ovarian sex hormone levels plummet, causing many menopausal women to experience temporary signs and symptoms that are often considered part of menopause. Among these common phenomena, hot flashes involve sudden dilation of skin blood vessels in the head and neck, which often spreads downward over other regions. Affected women may feel a sense of pressure in the head, followed by sensations of heat or burning in areas where vessel dilation is occurring. The affected areas appear flushed, and profuse sweating may occur. Hot flashes seem to be caused by low estrogen levels.[16]

These flashes usually last approximately four minutes but may last from a few seconds to over 30 minutes. It is difficult to estimate the incidence among menopausal women because of the extreme individual variations in the intensity of hot flashes. Hot flashes in some women are barely noticeable, while other women may be briefly disabled or may be awakened by very intense flashes.[17]

A loss of estrogen also leads to an increased risk of **osteoporosis** (Aging changes in the female reproductive system, 2012), which is a condition in which bones become more brittle and are more at risk for fractures or breaks. There may also be an increased risk for urinary tract infections due to loss of bladder muscle tone. Loss of muscle tone in the pubic area could potentially lead to prolapsed bladder, vagina, or anus (Aging changes in the female

reproductive system, 2012), which is a condition in which these organs drop from their original position to the outside of the body.[18]

Other consequences of altered sex hormone levels during and shortly after menopause may include depression, anxiety, irritability, nervousness, fatigue, and impaired memory and ability to concentrate. Some of these psychological changes may result from sleep disturbances caused by low estrogen levels or nocturnal hot flashes. All these undesirable features usually subside. These and other effects from menopause vary greatly among different cultures.[19]

There may be a diminished sexual drive due to changes in hormones and physical changes within the vagina, but this is not necessarily the case. Many elderly women continue to have sexual desires and engage in sexual activity.[20]

8.1.3 Social Determinants of Health (SDOH) and Women's Reprodutive Health in Aging

As outlined in Healthy People 2030, there are five overarching social determinants of health domains—economic stability, education access and quality, health care access and quality, neighborhood and built environment, and social and community context.[21]

8.1.3.1 Economic Stability

Economic stability refers to the link between a person's finances and health and includes such factors as employment, income level, food security and housing stability (HHS). An epidemiological study among aging adults in Baltimore, the Healthy Aging in Neighborhoods of Diversity across the Life Span study, found that sociodemographic factors measured by living in poverty intersect with gender, with women reporting higher pain levels (Quiton et al., 2020). For example, the study found that White women living in poverty were more likely to report pain than White men (Quiton et al., 2020). Research has also shown that socioeconomic status, along with a variety of factors such as racism and health insurance status, is associated with health care related disparities for the treatment of headache disorders (Kiarashi et al., 2021).[22]

A handful of studies using data from the Health and Retirement Study have investigated the effects of early and later life socioeconomic status on osteoporosis. One study found that lower levels of childhood and adult socioeconomic status were associated with higher odds of developing osteoporosis (Gough Courtney et al., 2023). "Lower maternal investment," a term used to describe maternal social capital and that may be linked to childhood behaviors, was linked to greater odds of osteoporosis (Courtney et al., 2023).[23]

8.1.3.2 Neighborhood and Built Environment

Physical activity is an important lifestyle behavior that is associated with the developing and managing osteoporosis and other chronic conditions in women. Neighborhood environment plays a role in enhancing physical activity levels based on how walkable one's neighborhood is or amount of green space available (Zhu et al., 2023). One study found that neighborhood factors such as neighborhood socioeconomic status (poverty level), neighborhoods built in 1950–1969, and proximity to businesses and facilities influence the physical activity levels of

postmenopausal women (King, 2005). Another study showed that greater neighborhood walkability and green space in China were associated with fewer fractures; more studies addressing these issues are needed in the United States (Zhu et al., 2023).[24]

Key Takeaways

- Menopause occurs typically between 50 and 52 years of age. A woman is considered to have completed menopause if she has not menstruated in a full year.
- As women age, ovulation decreases and eventually ceases. These hormonal changes impact the entire reproductive system, including the uterus and vagina.
- The decline in ovarian hormones impact breast structure such as reduction in firmness and support.
- Significant hormonal changes occur with the aging process. Estrogen secretion declines, leading to increased risk of osteoporosis.
- Socioeconomic issues can significantly impact quality of life and access to healthcare during the aging process.

Glossary Terms

androstenedione
anabolic steroid - manmade hormone that are the same as, or similar to, androgens, the male-type sex hormones in the body.

atresia
absence or abnormal narrowing of an opening or passage in the body.

corpus luteum
transformed follicle after ovulation that secrets progesterone.

cystitis
Inflammation of the lining of the bladder.

embryo
group of blastocyst cells that will become an embryo and thus develop into a baby.

endometrial
related to the endometrium - the inner lining of the uterus, part of which builds up during the secretory phase of the menstrual cycle and then sheds with menses.

fertility
fertility refers to the *actual production of offspring*, rather than the physical capability to reproduce, which is termed fecundity.

FSH
anterior pituitary hormone that stimulates the production and maturation of sex cells.

glycogen
polysaccharide that is converted to glucose.

inhibin
hormone secreted by the gonads that inhibits FSH production by the anterior pituitary ischemia.

labia majora

folds of hair-covered skin that begin just posterior to the mons pubis.

ligaments

connective tissues that join bones to other bones.

menstrual cycle

menstrual cycle begins when you get your period or menstruate.

osteoporosis

disease characterized by a decrease in bone mass that occurs when the rate of bone resorption exceeds the rate of bone formation.

ovaries

female gonads that produce oocytes and sex steroid hormones (notably estrogen and progesterone.

ovulation

release of a secondary oocyte and associated granulosa cells from an ovary.

pituitary

bean-sized organ suspended from the hypothalamus that produces, stores, and secretes hormones in response to hypothalamic stimulation (also called hypophysis).

placenta

organ that supplies oxygen and nutrients to the fetus, excretes waste products, and produces and secretes estrogens and progesterone.

testosterone

potent androgenic steroid and major product secreted by the LEYDIG CELLS of the TESTIS. Its production is stimulated by LUTEINIZING HORMONE from the PITUITARY GLAND.

urethra

transports urine from the bladder to the outside environment.

uterine prolapse

occurs when the womb (uterus) drops down and presses into the vaginal area.

uterus

muscular organ that nourishes and supports the growing embryo.

vagina

muscular canal (approximately 10 cm long) that is the entrance to the reproductive tract.

Footnotes

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18. O'Hara-Leslie, Erin, Wade, Amdra C., McLain, Kimberly B. Aging and the Body. This work is distributed under a CC BY 4.0. Original source: https://milnepublishing.geneseo.edu/home-health-aide.
19. O'Hara-Lesie et al
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23. National Academies of Sciences, Engineering, and Medicine; Health and Medicine Division; Board on Population Health and Public Health Practice; Committee on a Framework for the Consideration of Chronic Debilitating Conditions in Women; Section 7.
24. National Academies of Sciences, Engineering, and Medicine; Health and Medicine Division; Board on Population Health and Public Health Practice; Committee on a Framework for the Consideration of Chronic Debilitating Conditions in Women; Section 7

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8.2: Menopause

8.2.1 Overview

Aging of the female reproductive system can be divided into two phases, which are separated from each other by menopause. **Menopause** is the time when age changes in the ovaries cause menstrual cycles to cease for at least 1 year. The average age at which menopause occurs is 51, though it can occur any time between ages 45 and 55. Women who have not experienced menopause are called **premenopausal**, and those who have passed through it are called **postmenopausal**.[1]

Menopause is important for two reasons. First, pregnancy, and therefore reproduction, is no longer possible because ovulation has stopped. Second, bodily structures and functions that are influenced by **estrogen** and **progesterone** undergo significant changes after menopause because blood levels of these hormones drop and stay low when **follicles** no longer mature. This section discusses general physiological changes of the reproductive system related to premenopausal, menopausal, and postmenopausal periods.[2]

8.2.2 Perimenopause

The earliest changes occur during the menopausal transition, often referred to as perimenopause, when a women's cycle becomes irregular but does not stop entirely. Although the levels of estrogen are still nearly the same as before the transition, the level of progesterone produced by the **corpus luteum** is reduced. This decline in progesterone can lead to abnormal growth, or **hyperplasia**, of the **endometrium**. This condition is a concern because it increases the risk of developing endometrial cancer. Two harmless conditions that can develop during the transition are **uterine fibroids**, which are benign masses of cells, and irregular bleeding. As estrogen levels change, other symptoms that occur are hot flashes and night sweats, trouble sleeping, vaginal dryness, mood swings, difficulty focusing, and thinning of hair on the head along with the growth of more hair on the face. Depending on the individual, these symptoms can be entirely absent, moderate, or severe.[3]

At about age 45 the length of each male cycle begins to shorten because the time between the end of one cycle and **ovulation** in the next cycle decreases. Since this phase of the cycle produces much estrogen, its shortening results in a decline in estrogen secretion, and estrogen levels fall. These levels become so low that an increasing number of cycles do not produce a positive feedback effect, and ovulation does not occur. These changes seem to be caused initially by a decrease in the responsiveness of the ovaries to **FSH** and **LH**.[4]

Because of these changes, there is less progesterone production, less development of the uterine lining, and an increasing number of cycles with little or no menstrual flow. Since menstrual flow is the most noticeable indicator of female cycles, the occasional absence of menstrual flow when it is expected indicates that the cycles are becoming irregular. By age 50

to 51 progesterone is essentially absent, menstrual flow happens less than once each year, ovarian and menstrual cycles (uterine cycles) have ended, and menopause has occurred.[5]

8.2.3 Menopause

Female fertility (the ability to conceive) peaks when women are in their twenties, and is slowly reduced until a women reaches 35 years of age. After that time, fertility declines more rapidly, until it ends completely at menopause. Menopause is the cessation of the menstrual cycle that occurs as a result of the loss of ovarian follicles and the hormones that they produce. A woman is considered to have completed menopause if she has not menstruated in a full year. After that point, she is considered postmenopausal. The average age for this change is consistent worldwide at between 50 and 52 years of age, but it can normally occur in a woman's forties, or later in her fifties. Poor health, including smoking, can lead to earlier loss of fertility and earlier menopause.[6]

Menopause can be divided into spontaneous or natural and induced, most commonly via surgical removal of both ovaries, radiation, or chemotherapy. Menopause is characterized by the changes in and decline of ovarian hormone levels and cessation of ovulation and menstruation. It is diagnosed when the menstrual cycle ceases for at least 1 year (Peacock et al., 2023). The transition preceding the final period is referred to as perimenopause, which is associated with physiological changes that vary among women (Santoro et al., 2020), with little investigation into that variation in terms of symptom experience, onset, duration, severity, and response to treatments. Postmenopause is the final stage of the menopause process.[7]

Women experience features of several conditions linked to the transition, including hot flashes, weight gain, and increased rate of diabetes, cardiovascular disease (CVD), cognitive decline, osteoporosis, and depression (El Khoudary et al., 2020; Jeong and Park, 2022; Lobo and Gompel, 2022; Sochocka et al., 2023). Increased anxiety has also been reported. Bromberger and colleagues (2013) found women with low levels of anxiety at study baseline had significantly higher odds of high anxiety at early perimenopause, later perimenopause, and postmenopause compared to the premenopause stage, after controlling for other risk factors.[8]

8.2.4 Postmenopause

When menopause occurs, estrogen secretion by the ovaries and blood estrogen levels decline quickly. During the four years after menopause estrogen secretion by the ovaries dwindles to zero. Blood estrogen levels do not reach zero, however, because small amounts of estrogen are produced by conversion of **testosterone** and **androstenedione** to estrogen and by the **adrenal cortex**. In spite of this estrogen production, blood estrogen levels usually drop to slightly below the lowest levels that were present during premenopausal hormone cycles. Furthermore, postmenopausal estrogen levels may be less than 5 percent of those present during midcycle estrogen peaks before menopause. The low estrogen levels reached within a few years after menopause do not fluctuate cyclically.[9]

After menopause, lower amounts of estrogens can lead to other changes. CVD becomes as prevalent in women as in men, possibly because estrogens reduce the amount of cholesterol in the blood vessels. When estrogen is lacking, many women find that they suddenly have problems with high cholesterol and the cardiovascular issues that accompany it. **Osteoporosis** is another problem because bone density decreases rapidly in the first years after menopause. The reduction in bone density leads to a higher incidence of fractures.[10]

As with testosterone levels in older men, estrogen levels among postmenopausal women show considerable variation. Obese women generally have higher levels because fat tissue converts much androstenedione to estrogen. In extreme cases these elevated estrogen levels may equal or exceed average levels in premenopausal women. However, the estrogen in postmenopausal women is not as potent as that in premenopausal women because most postmenopausal estrogen is **estrone** rather than **estriol**.[11]

Testosterone secretion from both the ovaries and the adrenal glands in postmenopausal women declines slightly, resulting in a small decrease in the already low blood levels. This testosterone has a greater impact, however, because the ratio of testosterone to estrogen increases.[12]

Since hot flashes and the psychological alterations accompanying menopause are almost always temporary, they do not seem to fit the definition of age changes. Other changes caused primarily by the paucity of estrogen after menopause are permanent unless estrogen levels are raised, and many of these changes intensify into very old age. They include shrinkage and decreased functioning of all reproductive system structures; alterations in secondary sex characteristics (e.g., shrinkage of the breasts, increase in visible facial hair, decrease in axillary and pubic hair); increases in **LDL**s and decreases in **HDL**s; and more rapid loss of bone matrix.[13]

The changes resulting from plunging estrogen levels and menopause are diverse. As for the reproductive system, the loss of childbearing ability is considered by some people to be a negative effect which can lead menopausal women into depression or other psychological disturbances. Others view the loss of childbearing ability as a positive outcome because it eliminates concerns about unwanted pregnancies. As a result, some women have an increase in sexual activity.[14]

Alterations in secondary sex characteristics after menopause are often considered cosmetically undesirable. Other changes in the skin include decreased secretion by **apocrine sweat glands** and **sebaceous glands** and an increased incidence of skin abnormalities. The changes in blood **lipoprotein**s raise the risk of developing **atherosclerosis** and its complications (e.g., heart attacks, strokes). Shrinkage of the urethra promotes urinary **stress incontinence**. Finally, the rapid loss of bone matrix is a main risk factor for type I osteoporosis.[15]

8.2.5 Hot Flashes

Although data are sparse and have not adequately included underserved populations, hot flashes, night sweats, and cold sweats—collectively termed vasomotor symptoms (VMS)—are classic menopausal symptoms that an estimated 80 percent of midlife women experience, with about one-third having frequent or severe VMS (El Khoudary et al., 2020; Gold et al., 2006). VMS affect quality of life over an average of 7–10 years and are one of the main reasons for midlife women to seek care (Avis et al., 2015; Freeman et al., 2011; Williams et al., 2007). Increased anxiety has also been reported.[16]

It is widely known that the reduction in estrogens contributes to hot flashes; however, the precise, underlying mechanisms are unclear. Estrogens have effects on brain structure and function, with the **hippocampal** and **prefrontal cortical regions** expressing a high density of estrogen receptors (ER) (Ishunina et al., 2007; Osterlund et al., 2000). Researchers have postulated that signaling originating in the brainstem triggers hot flashes, with different brain regions—the **insular cortex**, **prefrontal cortex**, and **anterior cingulate**—mediating the perception (Diwadkar et al., 2014). Other brain regions that research has implicated in hot flashes include those, such as the **hippocampus**, that are activated without external stimuli (Thurston et al., 2015).[17]

8.2.6 Hormone Replacement Therapy

Evidence points to the menopausal transition as an important life stage in a woman's life during which certain metabolic and CVD risks emerge (Lobo and Gompel, 2022). An increased propensity for cancer; cardiometabolic conditions, such as obesity, **metabolic syndrome**, diabetes, CVD, and stroke; and autoimmune disorders, including arthritis; and cognitive dysfunction, including Alzheimer's Disease (AD), have been attributed to the menopausal physiological changes. The transition should therefore be considered a critical time during which preventive strategies that reduce disease risks could determine health outcomes, improving quality of life and decreasing mortality in postmenopausal women (Lobo and Gompel, 2022). Two general approaches exist for treating VMS: hormone therapy and *NK3R* antagonists.[18]

Hormone therapy, if administered at the onset of menopause, can alleviate VMS (Manson et al., 2024) and improve bone, metabolic, and cardiovascular health (Manson and Martin, 2001). The evidence and beliefs about its benefits versus on the pace of aging and risk of chronic diseases in women have changed dramatically in the last few decades. Observational studies and randomized clinical trials illustrated that hormone treatment after menopause was associated with a reduced risk of several chronic diseases, including CVD, osteoporosis, cognitive decline, and dementia, and clinician-initiated hormone therapy in post-menopausal women (Manson et al., 2020). Women were normally prescribed estrogen, alone or with a progestin, to treat symptoms during the perimenopausal or early postmenopausal phase (Manson et al., 2020). However, from 2002–2004, results from the Women's Health Initiative

(WHI) clinical trial agreed with most observational study findings but contradicted observations regarding coronary heart disease (CHD) by showing an increased risk in women who initiated estrogen alone or in combination with a progestin at ages 50–79 years (Anderson et al., 2004; Manson et al., 2020; Rossouw et al., 2002). The trial of estrogen-progestin was stopped in 2002 after a median of 5.2 years to follow-up because the global index which summarized the balance of risks and benefits of major clinical outcomes showed that the harms exceeded benefits and should not be continued or initiated for primary prevention of CHD (Writing Group for the WHI Investigators, 2002). The trial of estrogens only was stopped for futility, after a median follow-up of 7.2 years, as no cardiovascular risk outcome was likely to become statistically significant by continuing the trial and the risk of stroke was elevated (Manson et al., 2020).[19]

The answer to the simple question of whether hormone therapy is protective or harmful for chronic diseases related to aging is quite complex and may vary across groups of women and depend on if menopause is spontaneous or induced. Investigators have suggested that a better understanding of the effects of hormone therapy on the risk of chronic conditions may come from considering the age of onset and type of menopause (Rocca et al., 2023).[20]

Hormone therapy (HT) employs medication (synthetic estrogens and progestins) to increase estrogen and progestin levels, and can alleviate some of the symptoms of menopause. In 2002, the Women's Health Initiative began a study to observe women for the long-term outcomes of hormone replacement therapy over 8.5 years. However, the study was prematurely terminated after 5.2 years because of evidence of a higher than normal risk of breast cancer in patients taking estrogen-only HT. The potential positive effects on cardiovascular disease were also not realized in the estrogen-only patients. The results of other hormone replacement studies over the last 50 years, including a 2012 study that followed over 1,000 menopausal women for 10 years, have shown cardiovascular benefits from estrogen and no increased risk for cancer. Some researchers believe that the age group tested in the 2002 trial may have been too old to benefit from the therapy, thus skewing the results. In the meantime, intense debate and study of the benefits and risks of replacement therapy is ongoing. Current guidelines approve HT for the reduction of hot flashes or flushes, but this treatment is generally only considered when women first start showing signs of menopausal changes, is used in the lowest dose possible for the shortest time possible (5 years or less), and it is suggested that women on HT have regular pelvic and breast exams.[21]

8.2.6.1 Estrogen Replacement Therapy

Since many target structures retain much of their responsiveness to estrogen, many postmenopausal changes can be slowed, stopped, or reversed by administering estrogenlike substances. This type of treatment is often called estrogen replacement therapy (ERT).[22]

8.2.6.2 Benefits

In many women ERT reduces or eliminates hot flashes. It also restores low LDL levels and high HDL levels, lowering the risk of atherosclerosis, and it seems to maintain cognitive functions and reduce the risk of getting Alzheimer's disease. To be most effective against osteoporosis, ERT should begin within six months after menopause, before significant bone loss has occurred. Furthermore, prevention of osteoporosis may require ERT for 10 or more years after menopause because stopping ERT allows the rate of bone resorption to increase to pretreatment levels. Postmenopausal prevention of osteoporosis may also require measures such as exercise, calcium supplements, and vitamin D supplements.[23]

8.2.6.3 Risks

Estrogen replacement therapy is especially recommended for women who have an early menopause and those at high risk for developing osteoporosis. Because ERT increases the risks of certain disorders (e.g., thrombus formation, breast cancer, gallbladder disease, endometrial cancer), it is not recommended for women with risk factors for certain conditions. These conditions include breast cancer or other reproductive system cancers; circulatory abnormalities such as high blood pressure, thrombus formation, and varicose veins; liver or gallbladder disease; or endometriosis. Women who are heavy smokers or are obese are also poor candidates for ERT.[24]

The risks from ERT can be greatly reduced in several ways. These include using small doses of estrogen; administering estrogen by injection rather than orally; administering estrogen in cycles that mimic natural cycles; and administering low levels of certain progesteronelike substances (progestins). Cyclic administration of estrogen, especially when supplemented with progestins, often results in continued uterine cycles and periodic menstrual flow, which is usually less than premenopausal menstrual flow. However, no egg cells are produced and pregnancy is impossible.[25]

In conclusion, ERT can relieve several serious consequences of low estrogen levels in postmenopausal women. Though ERT increases certain risks somewhat, it greatly reduces others. Therefore, the net effect in many women is an increase in the quality of life and life expectancy.[26]

8.2.6.4 Alternatives

For some women, the risks from estrogen supplementation are too high when compared with the possible benefits. Scientists have found artificial compounds that promote some beneficial effects from estrogen supplements (e.g., reduce risk of atherosclerosis, reduce bone thinning) while not increasing certain risks from estrogen supplements (e.g., blood clots, cancers). Examples include tamoxifen and raloxifene. Other alternatives to traditional estrogen supplement therapy are being developed and evaluated. These alternatives include using different methods of estrogen administration (e.g., skin patches, vaginal creams); minimizing other risk factors (e.g., high fat diet); increasing alternative beneficial practices (e.g., improved

diet; exercise; vitamin and calcium supplements; exercise; foods containing natural estrogens; herbal remedies).[27]

A more recent treatment approach for VMS targets the NK3R protein, and in May 2023, FDA approved Veozah (fezolinetant), an NK3R antagonist, as the second nonhormonal medication to treat VMS and help regulate body temperature (FDA, 2023). Studies in in vivo animal models have shown that NK3R activation and signaling resulting from lower circulating estradiol levels alters the brain's thermoregulatory systems, resulting in VMS (Krajewski-Hall et al., 2019; Rance et al., 2013). Given these promising findings, several clinical studies tested whether antagonists to NK3R improve VMS. Four phase 2 clinical trials have shown that NK3R antagonists significantly reduced VMS, similar to what was observed after hormone therapy (Depypere et al., 2019; Fraser et al., 2020; Prague et al., 2017; Rance et al., 2013; Trower et al., 2020). Several NK3R antagonists are in phase 3 clinical trials (Prague, 2021).[28]

Identifying NK3R as an important player in thermoregulation and VMS in menopausal women has provided an important proof of principle regarding the power of GWAS (see above section on "Genetic Factors Related to VMS"). Future identification of genes using GWAS experimental approaches should therefore be encouraged to uncover other VMS biological mechanisms, as this could lead to new therapies.[29]

8.2.7 Impacts of Menopause

Approximately 1.3 million U.S. women enter menopause each year (McCarthy and Raval, 2020). Natural or spontaneous menopause typically occurs between ages 45 and 51, with variability in the age of onset, duration, and degree of perceived symptoms (Harlow et al., 2012). In a progress report of menopause transition-related results from studies associated with the Study of Women's Health Across the Nation (SWAN), the investigators summarized findings on symptoms (El Khoudary et al., 2019):

- Up to 80 percent reported vasomotor symptoms (VMS) or hot flashes, with the highest reporting during the transition from early to late perimenopause (El Khoudary et al., 2019; Gold et al., 2006). White women had the highest unadjusted percentage of VMS of greater than 6 days at baseline at 43.5 percent, followed by African American women at 38.0 percent, Hispanic women at 10.5 percent, Chinese or Chinese American women at 4.7 percent and Japanese or Japanese American women at 3.3 percent. However, in models adjusting for a number of sociodemographic factors, African American women had a higher adjusted odds ratio (1.63) of VMS than White women in this longitudinal cohort. In addition, during menopausal transitions (e.g., premenopause to perimenopause, perimenopause to postmenopause), African American women had the highest reported unadjusted percentage of any VMS (Gold et al., 2006).
- Women in late perimenopause and natural postmenopause reported more sleep difficulties (43.2–45.4 percent), compared to premenopausal women (31.4 percent) (Kravitz et al., 2003). In addition, in pre- or early perimenopausal women, White women were significantly

more likely and Hispanic women less likely to wake up several times than women of other racial and ethnic groups. (Kravitz et al., 2008). In a more recent study of sleep difficulties (e.g., sleep duration, awake after sleep onset) in postmenopausal women, White women reported better sleep quality than Black or Hispanic women. Differences were mediated by factors, such as the number of medical issues, financial problems, and stressors (Matthews et al., 2019).

- Several studies examined depression and major depressive episode (MDE). In one study, 23.8 percent of women had a diagnosis of at least one MDE. African American women had the highest percentage of MDE diagnosis (33.8 percent) compared to White women (29.9 percent). In addition, the study reported that postmenopausal women had 3.86 higher odds of MDE, compared to premenopausal women (Bromberger et al., 2011). A more recent study used the Center for Epidemiologic Studies Depression Scale (CES-D) to indicate severity of depressive symptoms; a CES-D score of 16 or higher indicated high depressive symptom levels. Study results suggested postmenopausal women had higher odds of high depressive symptoms levels compared to premenopausal women (odds ratio: 1.49; 95% confidence interval: 1.09–2.04) (Kravitz et al., 2022).
- Approximately 60.0 percent of midlife women report problems with memory during late perimenopause and early menopause (Fuh et al., 2006; Greendale et al., 2009; Greendale et al., 2010; Sullivan Mitchell and Fugate Woods, 2001). Results of one study suggest that memory problems improved postmenopause, and memory returned to premenopausal levels (Greendale et al., 2009).
- During menopausal transition stages, the incidence of urinary incontinence varied. Postmenopausal women had the lowest incidence (8.2 per 100 woman-years), compared to women in late perimenopause (14.5 per 100 woman-years) or early perimenopause (17.8 per 100,000) (Waetjen et al., 2009).
- At baseline, when all women participating in the study were either pre- or early perimenopausal, 19.6 percent of women reported vaginal dryness. By the time the women were postmenopausal, or at the study's end, about 34.0 percent of all women reported vaginal dryness (Waetjen et al., 2018).
- Menopausal stage was not associated with frequency of sexual intercourse, emotional satisfaction with partner, or physical pleasure (Avis et al., 2009).[30]

SDOH and Menopause

Cross-sectional analyses have shown that race, ethnicity, and adverse social determinants of health (SDOH) appear to influence the characteristics of VMS (Avis et al., 2001; De Mello et al., 2021; Gold et al., 2000). A longitudinal analysis of VMS in a multiethnic cohort of women in SWAN evaluated possible associations with race and ethnicity and showed that regardless of racial and ethnic background, reporting of VMS increased over time during perimenopause, although the rate of change differed among the groups (Gold et al., 2006). Black women reported the highest rates of change across all stages of the transition,

whereas Asian women exhibited the lowest. Compared to White women, significantly more Black women reported VMS; insignificant decreases in reporting were noted in Hispanic and Chinese or Japanese women (Gold et al., 2006). The Penn Ovarian Aging Study cohort compared VMS in Black and White women and women who were premenopausal with follow-up assessments conducted annually (Freeman et al., 2005; Freeman et al., 2011). Follow-up data at 13 and 16 years showed that Black women experienced a longer duration of VMS, specifically moderate-to-severe hot flashes compared to White women (Freeman et al., 2011; Freeman et al., 2014).[31]

Compared to White women, Black women tended to experience persistent and increasing VMS (Kim et al., 2024). Large-scale studies support the findings that Black women are susceptible to persistent VMS (Freeman et al., 2011; Gold et al., 2006; Kim et al., 2024; Freeman et al., 2011). Recent GWAS may provide clues that explain this. For example, GWAS identified 3 SNPs located on chromosomes 3 and 11 that were associated with VMS in Black women in the SNP Health Association Resource cohort in WHI (Crandall et al., 2017). In addition, specific changes in a gene involved in thermoregulation occurred more frequently in Black women (Small et al., 2000, 2002). However, GWAS analysis of data from SWAN did not find a significant association between this genetic change and the frequency of VMS during perimenopause (Aharon et al., 2019).[32]

Key Takeaways

- There are three phases of menopause that occur as part of the aging process and occur over a period time.
- Perimenopause can begin in the mid-40s and typically continues into the early 50s.
- A female is considered to be in menopause when she has not had a period for one year.
- Post-menopause refers to the period when estrogen levels approach zero. Post-menopause varies among females but changes in skin, bone health, and more are common.
- Hormone replacement therapy (HRT) has been controversial but temporary use can help alleviate hot flashes and other hormone-related symptoms of menopause.
- Impacts of Menopause vary greatly depending on age, race, ethnicity, geography, and socioeconomic status.

Glossary Terms

androstenedione

anabolic steroid - manmade hormone that are the same as, or similar to, androgens, the male-type sex hormones in the body.

atherosclerosis

condition in which plaque builds up inside your arteries. Plaque is a sticky substance made up of cholesterol, fat, blood cells, calcium, and other substances found in the blood.

apocrine glands

large, branched, specialized sweat glands that empty into the upper portion of a HAIR FOLLICLE instead of directly onto the SKIN.

corpus luteum

transformed follicle after ovulation that secrets progesterone.

endometrium

inner lining of the uterus, part of which builds up during the secretory phase of the menstrual cycle and then sheds with menses.

estriol

hydroxylated metabolite of ESTRADIOL or ESTRONE that has a hydroxyl group at C3, 16-alpha, and 17-beta position and a major urinary estrogen.

estrogen

Class of predominantly female sex hormones important for the development and growth of the female reproductive tract, secondary sex characteristics, the female reproductive cycle, and the maintenance of pregnancy.

estrone

aromatized C18 steroid with a 3-hydroxyl group and a 17-ketone, a major mammalian estrogen.

follicle

ovarian structure of one oocyte and surrounding granulosa (and later theca) cells.

FSH

Follicle-stimulating Hormone - Anterior pituitary hormone that stimulates the production and maturation of sex cells.

HDL

high-density lipoproteins; sometimes called the "good" cholesterol because it carries cholesterol from other parts of your body back to your liver. Your liver then removes the cholesterol from your body.

hippocampus

curved elevation of GRAY MATTER extending the entire length of the floor of the TEMPORAL HORN of the LATERAL VENTRICLE (see also TEMPORAL LOBE).

hyperplasia

abnormal growth due to the production of cells.

LDL

low-density lipoproteins; sometimes called the "bad" cholesterol because a high LDL level leads to a buildup of cholesterol in your arteries.

LH

Luteinizing hormone. The anterior pituitary hormone that triggers ovulation and the production of ovarian hormones in females and the production of testosterone in males.

lipoproteins

lipid-protein complexes involved in the transportation and metabolism of lipids in the body. They are spherical particles consisting of a hydrophobic core of TRIGLYCERIDES and CHOLESTEROL ESTERS surrounded by a layer of hydrophilic free CHOLESTEROL; PHOSPHOLIPIDS; and APOLIPOPROTEINS.

menopause

cessation of the menstrual cycle; is considered complete when a woman has not menstruated in a full year.

metabolic syndrome

a group of risk factors for heart disease, diabetes, and other health problems. You can have just one risk factor, but people often have several of them together. When you have at least three of them, it is called metabolic syndrome.

osteoporosis

disease characterized by a decrease in bone mass that occurs when the rate of bone resorption exceeds the rate of bone formation.

ovulation

release of a secondary oocyte and associated granulosa cells from an ovary.

perimenopause

transitional period before and after menopause wherein the menstrual cycle is irregular and hormone levels widely fluctuate.

postmenopause

physiological period following the MENOPAUSE, the permanent cessation of the menstrual life.

progesterone

sex hormone important in regulating the reproductive cycle in those with ovaries and the maintenance of pregnancy.

sebaceous glands

small, sacculated organs found within the DERMIS. Each gland has a single duct that emerges from a cluster of oval alveoli. Each alveolus consists of a transparent BASEMENT MEMBRANE enclosing epithelial cells.

stress incontinence

stress urinary incontinence occurs when your bladder leaks urine during physical activity or exertion. It may happen when you cough, sneeze, lift something heavy, change positions, or exercise.

testosterone

Androgenic steroid and major product secreted by the LEYDIG CELLS of the TESTIS.

uterine fibroids

most common noncancerous (benign) tumors in women of childbearing age

Footnotes

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8.3: Aging Related Cancers

8.3.1 Breast Cancer

In aging women as in aging men, reproductive system cancers are common and serious disorders. A common cancer of the female reproductive system is breast cancer**.** In women, the incidence of breast cancer is exceeded only by that of lung cancer. Breast cancer occurs in 10 percent of all women at some time. The rate of new cases increases with age throughout life, with the most rapid increase occurring between ages 45 and 65. For women over age 55, breast cancer is second only to heart disease as a cause of death.

8.3.1.1 Risk Factors

A woman's chances of developing breast cancer are increased by many risk factors besides age. One of the strongest factors is having a mother or sister with breast cancer, especially if it occurred during early adulthood or in both breasts. Other risk factors include using oral contraceptives containing **estrogen**, undergoing estrogen replacement therapy, drinking alcoholic beverages, being exposed to high doses of **radiation**, having no children, and, possibly, consuming a high-fat diet.

8.3.1.2 Consequences

Though the dozen or more types of breast cancer have various effects on the breasts, the most dangerous ones are those which tend to spread easily to other parts of the body. Spreading usually occurs through **lymph** and blood vessels. The structures more frequently invaded include certain bones (skull, **vertebrae**, ribs, **pelvis**), the lungs, the liver, and the kidneys. The loss of **homeostasis** resulting from fractures or inadequate functioning of other vital organs leads to illness and death.

8.3.1.3 Prevention and Treatment

In spite of the serious threat posed by breast cancer, most of the complications, illnesses, and deaths it causes can be prevented by early detection and treatment. Knowing and routinely checking for signs of breast cancer can be helpful. These signs include (1) a thickening or lump in the breast, (2) changes on the breast skin, **areola**, or nipples (e.g., wrinkling, puckering, sores), (3) enlarged **lymph nodes** near the armpits, and (4) irregularly shaped or asymmetrical breasts. These signs can be detected by monthly breast self-examination and by having a breast examination as part of a routine physical examination. However, the most effective way to detect breast cancer in the early stages is to receive **mammograms** (x-rays of the breast). An annual mammogram is especially recommended for women over age 45 because the risk of developing breast cancer increases markedly after that age.

Another important aspect of prevention is minimizing risks from estrogen intake by limiting the amount of estrogen used for oral contraception or estrogen replacement therapy, administering estrogen on a cyclic basis rather than continuous one, and including **progesterone** along with the estrogen.

When breast cancer is suspected, the preliminary diagnosis can be confirmed or negated by examining a sample of the tissue (**biopsy**). If cancer is present, the specific type and its extent are determined. Depending on the results of these investigations, treatment plans designed to cure the cancer or reduce the effects by slowing its progress are developed. Such treatment plans may involve surgery, radiation therapy, chemotherapy, and hormone therapy.[1]

For more information

Improving outcomes for women aged 70 years or above with early breast cancer: research programme including a cluster RCT.

Source: Wyld L, Reed MWR, Collins K, et al. Improving outcomes for women aged 70 years or above with early breast cancer: research programme including a cluster RCT. Southampton (UK): National Institute for Health and Care Research; 2022 Jun. (Programme Grants for Applied Research, No. 10.6.) Available from: https://www.ncbi.nlm.nih.gov/books/NBK581776/ doi: 10.3310/XZOE2552

8.3.2 Endometrial Cancer

Endometrial cancer is cancer of the uterine lining. It has the highest incidence among cancers of the female reproductive structures, occurring in slightly more than 2 percent of all women. New cases develop most frequently between ages 50 and 64. Risk factors include eating excess calories in the diet, having a lowered glucose tolerance, having no children, having relatives with endometrial cancer, and receiving estrogen therapy.

The risk of developing endometrial cancer can be reduced by avoiding overeating and adjusting estrogen therapies in ways similar to those recommended for preventing breast cancer. Once initiated, endometrial cancer reveals its presence by causing bleeding from the vagina between menstrual periods or after menopause. This type of cancer is not as dangerous as others because it is usually detected early. The most common indicator is abnormal bleeding from the reproductive system. Because endometrial cancer is usually detected early, it is easily and effectively treated by surgery and hormone therapy.[2]

8.3.3 Ovarian Cancer

Ovarian cancer ranks fifth in occurrence among cancers in women and in older women, it ranks second among cancers of the female reproductive structures. Ovarian cancer causes more deaths than any other female reproductive system cancer and is the fifth leading cause of death for women.

Risk factors include never being pregnant, inhaling cigarette smoke, and estrogen replacement therapy. Avoiding or minimizing these factors can help reduce the incidence of this cancer. However, little can be done to prevent it from spreading and destroying other organs because it is difficult to detect before it is well established in many areas. Surgery, radiation, and chemotherapy usually can only slow its destructive progress somewhat.[3]

8.3.4 Cervical Cancer

Cervical cancer ranks third in older women among cancers of the female reproductive structures. Recall that the cervix is the lower part of the uterus and protrudes into the upper part of the vagina (Figure 7.3.1). Cervical cancer occurs in 2 to 3 percent of all women before age 80. Most new cases develop between ages 40 and 60.[4]

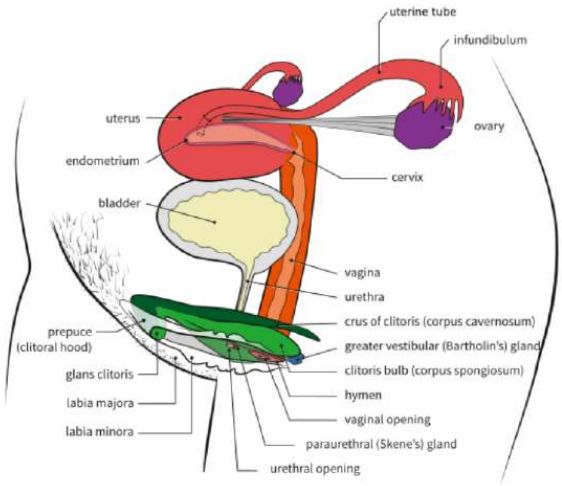


Figure 7.3.1 Structure of the female reproductive system. DiGiovanna. Augustine G. (2020). Chapter 13. "Reproductive Systems." In Age Changes in the Female System." In *Human Aging. Biological Perspectives.*. This work is distributed shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Augustine G. DiGiovanna. Available from LibreTexts.

Research over many years has confirmed that cervical cancer is most often caused by a sexually transmitted infection with **human papillomavirus (HPV**). There are over 100 related viruses in the HPV family, and the characteristics of each strain determine the outcome of the infection. In all cases, the virus enters body cells and uses its own genetic material to take over the host cell's metabolic machinery and produce more virus particles.

HPV infections are common in both men and women. Indeed, a recent study determined that 42.5 percent of females had HPV at the time of testing. These women ranged in age from 14 to 59 years and differed in race, ethnicity, and number of sexual partners. Of note, the prevalence of HPV infection was 53.8 percent among women aged 20 to 24 years, the age group with the highest infection rate.

HPV strains are classified as high or low risk according to their potential to cause cancer. Though most HPV infections do not cause disease, the disruption of normal cellular functions in the low-risk forms of HPV can cause the male or female human host to develop **genital warts**. Often, the body is able to clear an HPV infection by normal immune responses within 2 years. However, the more serious, high-risk infection by certain types of HPV can result in cancer of the **cervix**. Infection with either of the cancer-causing variants HPV 16 or HPV 18 has been linked to more than 70 percent of all cervical cancer diagnoses. Although even these high-risk HPV strains can be cleared from the body over time, infections persist in some individuals. If

this happens, the HPV infection can influence the cells of the cervix to develop precancerous changes.

Risk factors for cervical cancer include having unprotected sex; having multiple sexual partners; a first sexual experience at a younger age, when the cells of the cervix are not fully mature; failure to receive the HPV vaccine; a compromised immune system; and smoking. The risk of developing cervical cancer is doubled with cigarette smoking.

In most cases, cells infected with the HPV virus heal on their own. In some cases, however, the virus continues to spread and becomes an invasive cancer (figure 7.3.2).

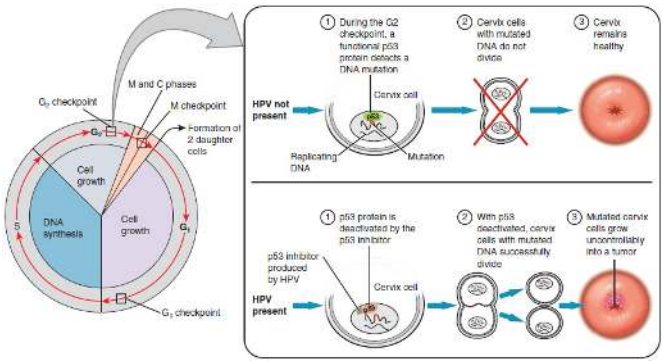


Figure 7.3.2 Source: Development of Cervical Cancer. Lumen Learning. 14.5. "Age Related Dysfunctions to the Reproductive System". In *Biology of Aging (LUMEN)*. This work is made available under a CC BY 4.0 license and was authored, remixed, and/or curated by Lumen Learning. Access from LibreTexts.

When the high-risk types of HPV enter a cell, two viral proteins are used to neutralize proteins that the host cells use as checkpoints in the cell cycle. The best studied of these proteins is **p53**. In a normal cell, p53 detects DNA damage in the cell's genome and either halts the progression of the cell cycle—allowing time for DNA repair to occur—or initiates **apoptosis**. Both of these processes prevent the accumulation of **mutations** in a cell's **genome.** High-risk HPV can neutralize p53, keeping the cell in a state in which fast growth is possible and impairing apoptosis, allowing mutations to accumulate in the cellular DNA.

The prevalence of cervical cancer in the United States is very low because of regular screening exams called pap smears. **Pap smears** sample cells of the cervix, allowing the detection of abnormal cells. If pre-cancerous cells are detected, there are several highly effective techniques that are currently in use to remove them before they pose a danger. However, women in developing countries often do not have access to regular pap smears. As a result, these women account for as many as 80 percent of the cases of cervical cancer worldwide.

In 2006, the first vaccine against the high-risk types of HPV was approved. There are now two HPV vaccines available: Gardasil® and Cervarix®. Whereas these vaccines were initially only targeted for women, because HPV is sexually transmitted, both men and women require vaccination for this approach to achieve its maximum efficacy. A recent study suggests that the HPV vaccine has cut the rates of HPV infection by the four targeted strains at least in half.

Unfortunately, the high cost of manufacturing the vaccine is currently limiting access to many women worldwide.[5]

8.3.4.1 Risk Factors

The most important risk factor for cervical cancer is having sexual intercourse soon after sexual maturation. Other risk factors include having many male sex partners; having male sex partners who have had sexual intercourse with other women with cervical cancer; inhaling cigarette smoke; using oral contraceptives; and having sexually transmitted diseases such as human papillomavirus. This virus sometimes causes genital warts and often occurs together with genital herpes and chlamydia. Hence, the incidence of cervical cancer is higher in women with these diseases.

8.3.4.2 Consequences

Once present, cervical cancer usually spreads by infiltrating nearby organs. Later, it is carried to more distant organs by the **lymphatics**. Like other reproductive system cancers, it causes illness and death by destroying the structure and functioning of any organ it invades.

8.3.4.3 Prevention and Treatment

A primary strategy in the prevention of cervical cancer is avoiding or minimizing behaviors that increase its risk factors. Once cervical cancer begins, it provides few indications of its presence, though it may cause slight bleeding or a watery discharge from the vagina between menstrual periods or after menopause. However, cervical cancer can be easily detected in the early stages by a Pap smear, which involves examining a sample of cells scraped off the cervix. It is recommended that younger women and women with abnormal cervical cells have a Pap smear as part of an annual physical examination. Older women who repeatedly have normal Pap smears may require smears at 2- to 3-year intervals rather than annually. As with most cancers, early detection and treatment can prevent the development of complications, illness, and death.

If a Pap smear reveals the presence of cervical cancer, one or a combination of treatments (e.g., surgery, radiation therapy, chemotherapy) may be used to cure it or slow its progress.[6]

Key Takeaways

- Endometrial cancer is the most common reproductive system cancer in females, occurring most frequently between 50 and 64.
- Breast cancer a common cancer associated with the female reproductive system. Familial history is a common risk factor. Regular self checks and mammograms are the best approaches to early detection.
- HPV is a significant risk factor for cervical cancer.

Glossary Terms

Footnotes

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8.4: Aging Related Abnormal and Disease Conditions

8.4.1 Introduction

Several abnormal and disease conditions affect the reproductive systems and become especially common or serious with advancing age.[1] Women experience chronic conditions differently than men; some are specifically influenced by women's biology and hormonal makeup, and others are influenced by gender differences related to how women access health services, their life roles, environmental exposures, and other factors.[2]

8.4.2 Prolapse of the Uterus

Prolapse of the uterus is a result of weakness of the ligaments supporting the organ. It is characterized by the uterus dropping through the cervical canal and protrudes into the vagina. Uterine prolapse may be corrected surgically or by the placement of a supportive instrument called a pessary in the vagina.[3]

For more information

Abdel-Fattah M, Cooper D, Davidson T, et al. **Single-incision mini-slings versus standard synthetic mid-urethral slings for surgical treatment of stress urinary incontinence in women: The SIMS RCT** [Internet]. Southampton (UK): National Institute for Health and Care Research; 2022 Dec. (Health Technology Assessment, No. 26.47.) Available from: https://www.ncbi.nlm.nih.gov/books/NBK587586/ doi: 10.3310/BTSA6148

8.4.3 Vaginal Infection

In aging women changes in the vagina increase the risk of developing vaginal infections. Perhaps the most common type of vaginal infection which results from the age-related decrease in vaginal acidity is **yeast infection**. This type of infection often causes intense itching and is usually accompanied by excessive vaginal discharge.

Wearing underwear made of cotton and avoiding clothing that fits tightly in the genital area reduce the risk of developing vaginal infections. Yeast infections can be treated effectively with antibiotic creams or suppositories.[4]

8.4.4 Uterine Fibroids

One type of growth in the female reproductive system that becomes less of a problem as age increases after menopause is ***uterine fibroids***, or **leiomyomas**. A uterine fibroid consists of a spherical mass of smooth muscle within the muscular wall of the uterus.

Uterine fibroids may begin to develop during or after puberty and may continue to grow until menopause. They occur in various sizes and sometimes become larger than a grapefruit. They usually develop in the upper part of the uterus, though they may occur anywhere in its wall. Uterine fibroids occur in 20 percent to 25 percent of women beyond age 35, and affected

women often have more than one. Since uterine fibroids do not invade neighboring regions or metastasize, they are not cancerous.

Most women with uterine fibroids suffer no adverse effects. However, some fibroids cause excessive bleeding during menstrual periods, and unusually large ones may cause problems such as constipation, frequent urination, and kidney disease by putting pressure on adjacent structures. Finally, fibroids occasionally become painful. Treatment may consist of removing the fibroids and the affected part of the uterus or removing the entire uterus (**hysterectomy**).

Women with uterine fibroids who do not experience significant problems before menopause rarely develop fibroid-related problems afterward because fibroids shrink when blood levels of estrogen and progesterone decline. However, postmenopausal women on estrogen replacement therapy may develop fibroid-related problems because this therapy can cause fibroids to enlarge.[5]

8.4.5 Sexually Transmitted Diseases

Both male and female reproductive systems are affected by sexually transmitted diseases (STDs). Commonly encountered examples include bacterial types (e.g., **gonorrhea, syphilis, chlamydia)** and viral types (e.g., **herpes type II, human papillomavirus, AIDS**). The incidence of STDs is much lower among older people than among younger adults, perhaps because older people have sexual encounters with fewer partners. However, increasing age seems to have little impact on the causes, effects, methods of prevention, and treatments for STDs.[6]

8.4.6 Pelvic Floor Disorders

Pelvic floor disorders (PFD) include urinary incontinence, fecal incontinence, and pelvic organ prolapse. Based on 2005–2010 NHANES data, the prevalence in women was 25.0 percent, with 17.1 percent of women experiencing moderate to severe urinary incontinence, 9.4 percent experiencing fecal incontinence, and 2.9 percent having pelvic organ prolapse (Wu et al., 2014). Urinary incontinence is associated with lower urinary track symptoms (LUTS) with symptoms falling in three areas: symptoms with storage of urine, voiding of urine, and after voiding (Abrams et al., 2003). One study using data from the Boston Area Community Health Survey found that 22.9 percent of women aged 30–80 years reported LUTS and LUTS interference with activities such as travel, exercise, and social activities. About 59.6 percent of women reported some LUTS and/or interference with activities, and 17.5 percent reported no LUTS or interference with activities (Sutcliffe et al., 2019). Risk factors associated with PFD include high BMI, having given birth to more children, and hysterectomy (Wu et al., 2014). The prevalence increases significantly by age, from 6.3 percent in women aged 20–29 to 52.7 percent in women 80 and older (Wu et al., 2014). In addition, racial and ethnic groups showed a significant difference: non-Hispanic White women had a higher prevalence of one or more pelvic floor disorder at 26.4 percent compared to Hispanic, Mexican American women at 24.0 percent, and other Hispanic and non-Hispanic Black women, both at 20.0 percent (Wu et al.,

2014). With respect to urinary incontinence, a more recent study based on NHANES 2015–2018 data reported 61.8 percent of women 20 years or older experienced urinary incontinence and 22.1 percent experienced moderate to severe urinary incontinence (Patel et al., 2022).[7]

8.4.7 Osteoporosis

Osteoporosis is a chronic condition that affects women more than men and is associated with bone fragility and repeated fracture risk (Weaver et al., 2017). Hip fractures account for a large proportion of the morbidity and mortality associated with osteoporotic fractures. Biological factors, prevention, diagnosis, treatment, and disparities associated with osteoporosis in women are described next.[8]

8.4.7.1 Biological Factors

Genetic factors substantially influence an individual's bone strength, microarchitectural properties, and risk of osteoporosis and fractures (Mäkitie et al., 2019). **Bone mineral density (BMD)** is highly heritable, as demonstrated by twin studies showing that one's genetic makeup determines up to 80 percent of its variance (Mäkitie et al., 2019). Studies have identified specific genes associated with osteoporosis risk, such as those involved in bone metabolism and regulation of calcium absorption. A family history of osteoporosis or fractures is known to increase fracture risk, indicating a strong genetic component. The most common genetic cause is osteogenesis imperfecta, an inherited disorder also known as "brittle bone disease" (Mäkitie et al., 2019). A meta-analysis has identified several important genes involved in osteoporosis (Hasan et al., 2021) and several genes and pathways that may be possible to target to develop new treatments for osteoporosis.[9]

8.4.7.2 Sex Chromosome Effects

Recent findings have identified a gene on the X chromosome that is associated with osteoporosis, plastin 3 (PLS3). This gene codes for a protein involved in the formation of actin bundles and also in the maintenance of bone health. This is supported by human genetic studies demonstrating that variants in this gene caused osteoporosis and osteoporotic fractures in members of 10 different families (van Dijk et al., 2013). In vivo studies using PLS3 knockout mice also led to phenotypic features of osteoporosis, and in vitro cellular experiments indicated the involvement of this gene in osteoclast formation (Neugebauer et al., 2018). More recently, research has linked PLS3 polymorphisms with early-onset osteoporosis in young individuals (Costantini et al., 2020), and mutations in this gene correlate with osteoporosis in postmenopausal women (Wolff et al., 2021).[10]

8.4.7.3 The Effects of Estrogens

Estrogens maintain bone homeostasis by regulating the metabolic activity of the two main cell types found in bone—**osteoblasts**, which release bone growth factors, and **osteoclasts**, which promote bone resorption (Biason-Lauber and Lang-Muritano, 2022). Estrogens preserve bone mass by interfering with the action of inflammatory cytokines that promote osteoclast development (D'Amelio et al., 2008; Jilka et al., 1992; Pietschmann et al., 2016; Weitzmann et

al., 2002) and inducing apoptosis, or programmed cell death, of osteoclasts (Kameda et al., 1997). The gradual decline of estrogens during menopause may therefore increase osteoclast activity, leading to higher bone turnover and breakdown and potentially osteoporosis.[11]

8.4.7.4 Other Biological Factors and Mechanisms

In addition to hormonal changes, other factors involved in osteoporosis include aging, oxidative stress, and inflammation. Evidence is increasing that oxidative stress is elevated with age, and that the decline in estrogens during menopause is often accompanied by increases in reactive oxygen species and proinflammatory **cytokines**. The production of reactive oxygen species occurs in parallel with inflammation and is thought to mediate the inflammatory process. These factors influence the functional activity of bone cells and consequently, bone **homeostasis**. Both oxidative stress and inflammation contribute to the development of osteoporosis by preventing the differentiation of bone-forming osteoblasts, inducing the differentiation and activity of bone-degrading osteoclasts, and enhancing apoptosis of osteocytes. In addition, there are bidirectional influences between certain microRNAs(miRNA) with oxidative stress and inflammation. Reactive oxygen species can alter miRNA expression, and conversely, miRNAs can regulate reactive oxygen species production and inflammatory processes (Iantomasi et al., 2023).[12]

Key Takeaways

- Chronic diseases and conditions often develop in the post-menopausal period, including but not limited to vaginal infections, uterine prolapse, uterine fibroids and STDs.

Footnotes

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8.5: Glossary

Androstenedione - An anabolic steroid - manmade hormone that are the same as, or similar to, androgens, the male-type sex hormones in the body. [1]

Apocrine glands - Large, branched, specialized sweat glands that empty into the upper portion of a HAIR FOLLICLE instead of directly onto the SKIN. [6]

Atherosclerosis - Atherosclerosis is a condition in which plaque builds up inside your arteries. Plaque is a sticky substance made up of cholesterol, fat, blood cells, calcium, and other substances found in the blood. [4]

Atresia - absence or abnormal narrowing of an opening or passage in the body

Corpus luteum - Transformed follicle after ovulation that secrets progesterone. [2]

Cystitis -Inflammation of the lining of the bladder (National Cancer Institute, n.d.) [3]

Embyro - A group of blastocyst cells that will become an embryo and thus develop into a baby.

Endometrium - The inner lining of the uterus, part of which builds up during the secretory phase of the menstrual cycle and then sheds with menses. [2]

Estriol - A hydroxylated metabolite of ESTRADIOL or ESTRONE that has a hydroxyl group at C3, 16-alpha, and 17-beta position and a major urinary estrogen.6][

Estrogen - Class of predominantly female sex hormones important for the development and growth of the female reproductive tract, secondary sex characteristics, the female reproductive cycle, and the maintenance of pregnancy. [2]

Estrone - An aromatized C18 steroid with a 3-hydroxyl group and a 17-ketone, a major mammalian estrogen. [6]

Fertility - Fertility refers to the actual production of offspring, rather than the physical capability to reproduce, which is termed fecundity.

Follicle - Ovarian structure of one oocyte and surrounding granulosa (and later theca) cells. [2]

FSH - Follicle-stimulating Hormone - Anterior pituitary hormone that stimulates the production and maturation of sex cells. [2]

Glycogen - A polysaccharide that is converted to glucose. [3]

HDL - HDL stands for high-density lipoproteins. It is sometimes called the "good" cholesterol because it carries cholesterol from other parts of your body back to your liver. Your liver then removes the cholesterol from your body. [4]

Hippocampus - A curved elevation of GRAY MATTER extending the entire length of the floor of the TEMPORAL HORN of the LATERAL VENTRICLE (see also TEMPORAL LOBE). [6]

Hyperplasia - Abnormal growth due to the production of cells. [3]

Inhibin - Hormone secreted by the gonads that inhibits FSH production by the anterior pituitary ischemia. [2]

Labia majora - (labia = “lips”; majora = “larger”), folds of hair-covered skin that begin just posterior to the mons pubis. [3]

LDL - LDL stands for low-density lipoproteins. It is sometimes called the "bad" cholesterol because a high LDL level leads to a buildup of cholesterol in your arteries. [4]

LH - Luteinizing hormone. The anterior pituitary hormone that triggers ovulation and the production of ovarian hormones in females and the production of testosterone in males. [2]

Ligaments - connective tissues that join bones to other bones. [5]

Lipoproteins - Lipid-protein complexes involved in the transportation and metabolism of lipids in the body. They are spherical particles consisting of a hydrophobic core of TRIGLYCERIDES and CHOLESTEROL ESTERS surrounded by a layer of hydrophilic free CHOLESTEROL; PHOSPHOLIPIDS; and APOLIPOPROTEINS. [6]

Menopause - cessation of the menstrual cycle; is considered complete when a woman has not menstruated in a full year. [3]

Menstrual cycle - menstrual cycle begins when you get your period or menstruate. This cycle is part of your reproductive system and prepares your body for a possible pregnancy. A typical cycle lasts between 24 and 38 days. [5]

Metabolic syndrome - Metabolic syndrome is the name for a group of risk factors for heart disease, diabetes, and other health problems. You can have just one risk factor, but people often have several of them together. When you have at least three of them, it is called metabolic syndrome. [4]

Osteoporosis - A disease characterized by a decrease in bone mass that occurs when the rate of bone resorption exceeds the rate of bone formation. [3]

Ovaries - Female gonads that produce oocytes and sex steroid hormones (notably estrogen and progesterone). [2]

Ovulation - Release of a secondary oocyte and associated granulosa cells from an ovary. [2]

Perimenopause - The physiological period following the MENOPAUSE, the permanent cessation of the menstrual life. [6]

Pituitary - bean-sized organ suspended from the hypothalamus that produces, stores, and secretes hormones in response to hypothalamic stimulation (also called hypophysis) [2]

Placenta - The organ that supplies oxygen and nutrients to the fetus, excretes waste products, and produces and secretes estrogens and progesterone. [3]

Postmenopausal - Stage of life after menopause; hormone levels are very low and menses has ceased.

Progesterone - A sex hormone important in regulating the reproductive cycle in those with ovaries and the maintenance of pregnancy. [2]

Sebaceous glands - Small, sacculated organs found within the DERMIS. Each gland has a single duct that emerges from a cluster of oval alveoli. Each alveolus consists of a transparent BASEMENT MEMBRANE enclosing epithelial cells. [6]

Stress incontinence - Stress urinary incontinence occurs when your bladder leaks urine during physical activity or exertion. It may happen when you cough, sneeze, lift something heavy, change positions, or exercise. [4]

Testosterone - Androgenic steroid and major product secreted by the LEYDIG CELLS of the TESTIS. [6]

Uterine fibroids - most common noncancerous (benign) tumors in women of childbearing age. [4]

Uterine prolapse - Uterine prolapse occurs when the womb (uterus) drops down and presses into the vaginal area. [4]

Uterus - Muscular organ that nourishes and supports the growing embryo. Its average size is approximately 5 cm wide by 7 cm long, and it has three sections. [3]

Vagina - Muscular canal (approximately 10 cm long) that is the entrance to the reproductive tract. It also serves as the exit from the uterus during menses and childbirth. The outer walls of the anterior and posterior vagina are columns with ridges. The superior fornix meets the uterine cervix. The cervix is the opening to the uterus. [3]

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CHAPTER OVERVIEW

9: Social Determinants of Health (SDOH) and Women's Health

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9.2: Case Study 1 - Forced Sterilization Programs
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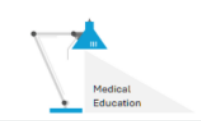
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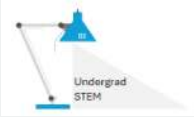
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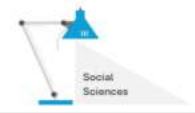
When thinking of women's reproductive health, it is important to not only examine the ways in which the social determinants of health have informed one's health outcomes but also to evaluate the broader sociomedical, sociopolitical, and historical variables that inform the perpetuation of the SDOH. Ask yourself what mechanisms or processes within society have informed the normalization and legitimization of inequitable access to goods and resources that would improve the health outcomes of entire communities. When the medical community is able to answer that question, it will be more aptly situated to holistically address the nexus of the SDOH with the health and well-being of minoritized people.

The content of this chapter is appropriate for, or easily adapted for the following audiences:









Learning Objectives

- Demonstrate an understanding of the social and structural determinants of health and their effects on the doctor-patient relationship, patient care, individual health, and community health
- Discuss factors leading to the development and perpetuation of inequities in health care to improve health outcomes and reduce health disparities
- Develop and maintain an appreciation of the underlying causes of health inequality, including how and why health disparities impact social and economically disadvantaged populations
- Demonstrate understanding of culture and how culture supports and challenges health beliefs, practices, behaviors, and cultural humility related to healthcare

- Develop and strengthen tools to support and reinforce anti-racism initiatives in healthcare systems and patient management plans for equitable healthcare outcomes
- Advocate for social justice in recognizing the common humanity of patients from all backgrounds and the unique intersectional differences that reflect the various societal groups to which they belong

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9.1: Women's Health and the History of Medicine

Chapter Author: Imanni Sheppard, PhD

As noted earlier in the text, the primary means of healthcare and healthcare-related services for women is a medical specialty called obstetrics and gynecology. These two terms, while often used in relationship to each other, are not quite the same. The word *obstetric* comes from the Latin word for midwife (*obstetrix*), used in the late 18th century. It is a medical specialty that cares for the health of a pregnant person throughout the course of their pregnancy and for the first six weeks after the child is born (postpartum). Gynecology, on the other hand, is the study of diseases, sicknesses, and functions of a person's vagina relative to their reproductive health (from the Greek words for woman, *gyne,* and the suffix for "study of," *logy*). As such, obstetrics and gynecology as a medical field focuses on an individual's vaginal and reproductive health throughout maturation.

Likewise, many aspects of Western philosophical and ideological thought, science, and medicine are heavily based on the work of Greek philosophers and alchemists--hence the use of the original Hippocratic oath as the basis of the professional identity formation, obligations, and appropriate practices of physicians. Hippocrates, for example, is considered the "father of modern medicine." He often articulated his beliefs about women's bodies relative to a lens of *Otherness* and in direct opposition to ideas about logic and rationality that he perceived as being inherent in man.[1] It is important to note, however, that the concept of "man" in the fifth century was a homograph in that it simultaneously referred to the species of *man* (referring to one's perceived humanness) and the concept of *man* as a gendered, socio-political, and medically situated *Self*. This linguistic interplay did not create the male/female or man/woman dichotomies that contemporarily exist in Western society. They did, however, facilitate their perpetuation.

Other theories, such as the notion that a woman's body was a defunct version of a man's, that a woman's uterus was a living creature that wandered around her body and caused her to be hysterical in nature, and that the womb "…pushes through a woman's trunk wreaking havoc on her physical and mental well-being, causing her to faint or become speechless," were all foundational aspects of the scientific ideas, medical practices, and epistemologies of the time.[2],[3] Thus, the belief that women were inherently unwell because of the deficient nature of their physicalities prompted the need for social and sociomedical paternalism.

Sociomedical paternalism often informs discriminatory practices, inequity, and sex-linked injustices within every **ideological state apparatus** (ISA).[4],[5] Additionally, within ISAs is an emphasis on reproduction or reproductive health care—with vulnerable populations and minoritized women being overrepresented relative to inequitable access, experimentation, and exploitation. As such, sociomedical paternalism, social injustices, and structural violences that instigate negative health outcomes also tend to disproportionately affect minoritized women.

The forced **sterilization** of minoritized women throughout the 20th century in the United States, laws that limit or control reproductive freedoms, the history of gynecological exploitation in dialogue with the maternal/infant mortality rates for African American people, and the perceived viability of one's offspring based on race, gender, class or able-bodiedness also follow the basic premises of **medical paternalism**. They are also remnants of Western philosophical and ideological thought that allowed for the direct or indirect normalization of **structural violence** in the epistemologies and practices of medicine.

Please continue to the following case studies as examples of such circumstances.

9.1.1 Case Study 1 - Forced Sterilization Programs

9.1.2 Case Study 2 - Social Darwinism and the Medical Quesiton of "Defective" Children

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[3] Jane Rowlandson, *Women and Society in Greek and Roman Egypt: A Sourcebook,* (Cambridge, Massachusetts: Cambridge University Press, 1999). We see the contemporary implications of these ideas in the use of the terms *hysterical, hysteria,* and *hysterectomy* which are all derived from the Greek word *hystera* which means womb. So, when referring to someone as "hysterical" we are essentially saying that her uterus is causing her to behave outside of social and emotional normative behavior. Likewise, within these ideologies, a hysterectomy (ectomy is removal of) was the removal of the thing (hystera/womb) that was hindering a woman's ability to be a productive or sensible member of society.

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9.2: Case Study 1 - Forced Sterilization Programs

From the early part of the 20th century into the 21st century—as recent as 2020—ISAs within the United States have forcibly sterilized more that 65,000 women. This process is an echo of the **eugenics** movement started by Francis Galton.[6] Galton, the "father of eugenics," created what was referred to as negative eugenics—programs designed to hinder particular groups from procreating and thus negatively investing in the human gene pool—in response to the work of Thomas Malthus, who wrote heavily on the notion that the planet would eventually be unable to support unlimited population growth and the allocation of resources.[7] As such, according to Galton, the sterilization of undesired populations--considered unfit for society—was important to protecting the race of *man* (the human species) and the overall public health of society.[8],[9]

More specifically, before WWII, more than sixty percent of the country and its applicable legislatures enacted compulsory sterilization laws primarily targeting poor, minoritized, or differently abled people. For example, in 1927, an eighteen-year-old girl by the name of Carrie Buck (considered to be "feebleminded" by the state of Virginia) was told by Justice Holmes of the U.S. Supreme Court, during a case against the mental institution of which she was a ward, that her desire to keep her unborn child was unsound on the basis that "three generations of imbeciles was enough." In that moment, Buck v. Bell (as the case was titled) became a landmark case of medical ethics and reproductive rights with the applicable phrasing by Justice Holmes ringing throughout the country as a dog whistle for the proliferation of reproductive paternalism on the grounds of protecting the gene pool of *man*—thereby providing a solid foundation and framework to be echoed in other states. The case was also a succinct characterization of society's perceptions of women (and young girls) deemed to be unfit or unworthy of motherhood now or in the future. As such, it was the stark application of Darwinian fitness into one's reproductive rights. After WWII, the vast majority of sterilization laws focused solely on minoritized women or women in prisons.

For example, the National Fertility Study in noted that roughly "twenty percent of all married Black women had been (unknowingly) sterilized; about the same percent of Chicana women had been sterilized; and over thirty-five percent of women of childbearing age in Puerto Rico had been sterilized."[10] Just under one hundred of such women were coerced--via a lack of informed consent--into receiving postpartum tubal ligations (also known as having one's tubes tied) immediately after giving birth by cesarean section, asked to sign documents while in labor, or forced to sign consent when being treated for labor pains at the Los Angeles County USC Medical Center. In fact, in the mid-twentieth century, California did more than twice as many sterilizations than any other state—with Virginia and North Carolina being in second and third at 8,000 at 7,600 sterilizations, respectively.

However, in the early 1970's, ten Mexican American women sued the Los Angeles County USC Medical Center on the grounds that the applicable concession documents were not in a

language that they were proficient in, that they had not been counseled on the risks or consequences of having their tubes tied, that several physicians waived consent asserting exigent circumstances, and that the federally funded medical center (supported by the California Department of Health) had racially targeted them as Mexican American women and economically targeted them under the assumption that they were on state assistance programs. The case was known as the Madrigal v. Quilligan (1973). Within one patient's testimony, a doctor is quoted as telling her that "Mexican people were very poor and that she should not have any more children because she could not support them" and later that "you better sign those papers or your baby could probably die here."[11] Nonetheless, in 1978, federal court Judge Jessie W. Curtis ruled in favor of the hospital due to cultural differences which precipitated miscommunication and language barriers.[12] However, because of the Madrigal case, the United States Department of Health, Education, and Welfare (HEW) began to require federally funded hospitals to restructure the process and procedures for developing and monitoring bilingual medical forms—this occurred on the heels of the thousands of coerced sterilizations of poor and minoritized women whose procedures were paid for by the HEW each year.[13]

In a similar case in 1973 (Relf v Weinberger)[14], teen sisters Mary Alice Relf and Minniue Lee Relf were surgically sterilized after their mother (who was poor and unable to read or write) put an X on the signature line of a document that she was told agreed to her daughters receiving birth control shots. Like the women in the Madrigal case, the sterilizations were funded by the U.S. Department of Health, Education, and Welfare (now the Department of Health and Human Services), the Public Health Service, and the Social and Rehabilitation Service. Many of the mothers approached by social workers and aids during the time were told that they would lose their welfare benefits if they did not sign the document. Also, given that the average age of **menarche** during the late 20th century was approximately twelve to thirteen years of age, the Relf sisters would have likely been sterilized shortly after starting puberty.

Nonetheless, forced sterilizations continued to be practiced throughout the United States—with specific maleficence occurring at State or Federally funded institutions. For example, in 2020, complaints were filed by the human rights organization Project South against the Irwin County Detention Center (ICDC) in Ocilla, Georgia on the grounds that the immigrant women held in custody there by the U.S. Immigration and Customs Enforcement Agency (ICE) were given hysterectomies at "alarming rates," that there was a lack of informed consent, that the women were forced to live in unsanitary living conditions, that they lacked adequate medical and mental health care,[15] and that they were subject to varied human rights violations.[16] Approximately 42% of the women were told by Dr. Mahendra Amin (a non-board certified physician) that they had benign ovarian cysts that required surgery—although this condition can generally be resolved without intervention.

According to the Staff Report of the United States Senate on the Medical Mistreatment of Women in ICE detention, Dr. Amin accounted for at least one in three obstetric and

gynecological procedures done, he received approximately half of all ICE payments for obstetric and gynecological procedures between 2018 and 2020, and he accounted for the greatest percentage of obstetric and gynecological referrals, visits, and procedures within the ICE system.[17] Since discovery of the medical abuses at the ICDC, ICE has been instructed to no longer use the facility for the custody of immigrant detainees.

Similar cases, such as one brought about by Kelli Dillon, a formerly incarcerated woman at the California Women's facility in Chowchilla, California, state that more than 150 African American and Hispanic female inmates in the California Department of Corrections had been sterilized without their consent (approximately 148 of those occurred in violation of prison rules and regulations). In addition, a 2014 prison audit conducted by the state of California found that almost 800 sterilizations had been performed throughout the state.[18]

Thus, the ideological and physical practice of eugenics continue to disproportionately impact minoritized women—particularly when they are wards in a state or federal governmental institution or when they are perceived as being impoverished monetarily or genetically. Because women in these situations have been sterilized without their consent, have not been provided adequate forms of health literacy, and have typically been denied appropriate consultations relating to the potential medical complications or risks of the surgeries performed on them, their health outcomes continue to be shaped by the normalization of health disparity, medical paternalism, and the social determinants of health.

? Ethical questions to consider:

1. What is the responsibility of the medical community to ensure the wellbeing, safety, and health literacy of their patients? How would you define "wellbeing" within the context of this case study?
2. If a physician performs a surgery that harms their patient but is approved by the state or federal government, is it medical maleficence? Does the probability of this change with different racial or ethnic groups, social classes, or educational levels?
3. What role does racialized medicine play in perpetuating the **social and structural determinants of health**?

Historically, the social determinants of health relative to women's reproductive health outcomes, have also been tethered to the exploitation and experimentation of their bodies. For example, the "father of American obstetrics and gynecology," was an American surgeon names James Marion Sims. In the early 19th century, Sims perfected the repair of the vesiocovaginal fistula, developed what is called the lateral Sims position,[19] and invented both the Sims speculum and the Sims sigmoid catheter. The former device is used to examine an individual's vagina and cervix while also allowing for the unrestricted movement of bodily fluids or secretions. The latter of the devices is a S-shaped tube that is inserted into a women's body through her urethra and into her bladder. Each of these surgical processes and their

concomitant devices were perfected through more than 100 surgeries and five years of medical experimentation on approximately twelve enslaved girls and women without the use of anesthesia.

While Sims' work created the foundation for the contemporary field of obstetrics and genecology, it also developed a normalized framework for the exploitation and medical trauma of poor, enslaved, incarcerated, and minoritized women. More specifically, his failure to use anesthetics when experimenting with fistula treatments---even though anesthesia had already been invented----and his use of enslaved women (whom could not appropriately give their consent) helped to inform contemporary practices within obstetrics and gynecology that negatively impact the health outcomes of minoritized women.

For example, the maternal mortality rates for African American women have continued to increase for the last hundred years or so. Contemporarily, according to the Center for Disease Control (CDC), the maternal deaths per 100,000 live births for African American women in the United States have increased by 56.6% in the last three years. In fact, African American women are three times as likely to die from a preventable condition within one month of giving birth compared to their European American counterparts. The CDC goes on to state that "multiple factors contribute to these disparities, such as variation in quality healthcare, underlying chronic conditions, structural racism, and implicit bias."[20] Thus, the increase in the maternal mortality rate of African American women is not only about one's socioeconomic factors such as income, amount of education, or housing. The enduring maternal mortality rates for African American women are not only due to the social determinants of health. They are, instead, the result of structural violences that hinder African American women's ability to access equitable health care—thus facilitating their negative health outcomes. A similar fate exists for minoritized children born in the United States—noting a five-fold difference in the IMR (infant mortality rate) per 1,000 live births in the last hundred years.

The health and well-being of children is largely imbricated with the health of the mother, her access to healthcare, reproductive justice, and whether or not they (mom and baby) are perceived as being "fit" for society. The notion of "fitness" is an echo of **social Darwinism** and is counterintuitive to social justice or the acknowledgement of the common humanity of all people. And yet, varied aspects of social Darwinism, adjacent forms of reproductive injustice, and the issue of paternalism versus parental rights continue to be embedded in the epistemologies and practices of medicine. The following case study elaborates on these issues.

References

[6] Eugenics is a Greek word meaning "good birth." Galton was also the cousin of Charles Darwin (who contributed the idea of natural selection to the scientific community), and was friends with Herbert Spencer (who coined the phrase "survival of the fittest" which applied the theory of natural selection to social, economic, and population-based engagement.

[7] Thomas Robert Malthus, *An Essay on the Principle of Population* (London, England: J.M. Dent, 1973). Thomas was an economist, cleric, and demographer from England.

[8] Philip R. Riley, "Eugenics and Involuntary Sterilization: 1907-2015," *Annual Review of Genomics and Human Genetics* no. 16 (2015): 351-368. Also note Philip R. Reilly, "Involuntary Sterilization in the United States: A Surgical Solution," *The Quarterly Review of Biology* vol. 62, no. 2 (1987): 153-170.

[9] Alexandra Minna Stern, Sterilized in the Name of Public Health: Race, Immigration, and Reproductive Control in Modern California," *American Journal of Public Health* vol. 95, no. 7 (2005): 1128-1138.

[10] Maya Manian, "The Story of Madrigal v. Quilligan: Coerced Sterilization of Mexican American Women," University of San Francisco School of Law (2018): 2. Virginia Espino, "Women Sterilized as They Give Birth: Forced Sterilization and the Chicana Resistance in the 1970s," In Vicki Ruiz & Chon Moriega eds, *Las Obreras: Chicana Politics of Work and Family* (2002): 65-82.

[11] Manian, "Madrigal v. Quilligan" (2018): 6.

[12] Stern, "Sterilized in the Name of Public Health" (2005).

[13] Lisa C. Ikemoto, "Infertile by Force and Federal Complicity: The Story of Relf v. Weinberger," In Elizabeth M. Schneider & Stephanie M. Wildman eds *Women and the Law Stories*, New York, New York: Foundation Press/Thomson Reuters (2011): 189-191.

[14] The case was Relf v. Weinberger because Casper Weinberger was the Secretary of the U.S. Department of Health, Education, and Welfare (HEW) at the time. This case is a landmark case because it led to hospitals being required to get informed consent before sterilization procedures. The U.S. District Court for the District of Columbia also stated that federal funds could not be used for the involuntary sterilization of certain people. HEW agreed in an appeal to change its regulations and thus the case was dismissed in 1977.

[15] More than 689 reports of delayed or deficient medical care were noted between 2018 and 2020.

[16] Ghandakly EC, Fabi R, "Sterilization in US Immigration and Customs Enforcement's (ICE's) Detention: Ethical Failures and Systemic Injustice," *Am J Public Health* vol. 111, no 5 (2021): 832-834.

[17] United States Senate Permanent Subcommittee on Investigations Committee on Homeland Security and Government Affairs, *Medical Mistreatment of Women in ICE Detention* Staff Report Released 2022: 70-77.

[18] California State Auditor, *Sterilization of Female Inmates: Some Inmates Were Sterilized Unlawfully, and Safeguards Designed to Limit Occurrences of the Procedure Failed Report 2013-120.* Sacramento, California (2014).

[19] James Marion Sims, *Silver Sutures in Surgery: The Anniversary Discourse Before the New York Academy Medicine,* New York, New York: Samuel S. William Wood Publishing (1857). https://collections.nlm.nih.gov/bookviewer?PID=nlm:nlmuid-66910990R-bk

[20] Center for Disease Control, “Working Together to Reduce Black Maternal Mortality,” *Health Equity* (Apr. 2023): https://www.cdc.gov/healthequity/features/maternal-mortality/index.html.

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9.3: Case Study 2 - Social Darwinism and the Medical Question of "Defective" Children

In 1915, Chicago, Illinois physician Dr. Harry J. Haiselden publicly committed the “passive killing[21]” of newly born “Baby Bollinger” who was considered to be defective due to the fusion of his kidneys, underdeveloped skin on his shoulders, a partially developed coccyx, and no right ear.[22] According to Haiselden and the Chicago Medical society ethics committee, he acted within his moral and ethical rights—relative to advising Bollinger’s mother to not surgically intervene and in choosing not to provide potentially lifesaving surgical care to the infant.[23] Soon after the Bollinger case, a newborn named Grace Werder was also passively killed—due to the presence of water tumors, paraplegia, and hydrocephaly. The attending physician concluded that “Baby Werder” would have not had proper moral or mental functioning because of her condition and as such was denied surgical intervention and died four days after birth.[24] In response to the overwhelming medical and public support, Haiselden developed and starred in a fictional accounting of his experiences (and decision-making processes) in the 1917 film titled “The Black Stork.” The film aimed at educating the public of the potential social, physiological, and personal harms of allowing a “defective” child to live beyond birth.[25]

The idea of passively killing children with congenital defects continued into the 1980’s with the death of “Baby Doe.” “Baby Doe” was born in 1982, with Down Syndrome and an esophagus that was separated from his stomach. Due to his condition, his inability to absorb food, and his fifty-percent survival rate, the attending physician suggested that the parents withhold surgery —thus allowing “Baby Doe” to die of natural causes.[26] Several of the hospital’s pediatricians and attorneys disagreed with this assessment and sued the parents on the basis of child neglect. However, within one week of birth and before a ruling could be made, “Baby Doe” died of pneumonia and dehydration.[27] Public interest in the ethics of the Doe case led to the development of Baby Doe Rules (and Baby Doe Squads made up of state child protective agents and officials from Health and Human Services) that were tasked with ensuring that federally funded institutions provide treatment to all babies with congenital defects or handicaps (regardless of the advice of the parents or physicians) or risk being defunded.

With the birth of “Baby Jane Doe,” in 1983, however, the question of medical neglect v. parental neglect and the reach of the government fueled public debate when the baby’s parents refused surgical treatment of their daughter’s hydrocephaly and spina bifida.[28] There were also several legal cases from non-familial members of the public and unassociated lawyers. Over time, the parents of “Baby Jane Doe” won the right to be the sole decision makers of their child’s medical treatment. Within one year, the spina bifida had healed naturally and the parents agreed to surgical treatment to treat her hydrocephaly.[29] The last known interview of “Baby Jane Doe” occurred in 2013 at her thirtieth birthday party.[30] Although she has some physical and cognitive delays, she is otherwise healthy.

Several other court cases, including the *American Academy of Pediatrics v Heckler*, *Weber v. Stony Brook Hospital*,[31] *The United States v. University Hospital*, and *Bowen, Secretary of Health and Human Services v. American Hospital Association* were all in response to the "Doe" cases, the governmental response to the parents' and physicians decision, whether or not the government should be allowed to make medical decisions for someone, and the amount of access non-hospital based institutions should have to one's medical records. The overarching question, however, remained whether or not children with congenital sickness or diseases were perceived as being fit (in the sense of Darwinian fitness) for society—and thus whether or not they represented reproductive success— and who should be allowed to make that decision. Medical resource allocation, perceived health and wellbeing, and the child's presumed quality of life were all tied into that general idea—a set of ideas that have continued from the 19th century into the 21st century.[32] Thus, the notion of customary medical care, the medical rights of children, the question of reproductive success, and the role of the government in discerning the reproductive, fundamental, and/or familial rights of the parents vs that of the child (in this case, "Baby Doe and "Baby Jane Doe") continue to be debated.

? Ethical Questions to consider:

1. What is the difference between the right to life and the right to quality of life? Who should decide the parameters of those rights and why? What role does one's race, gender, and class play into those decisions?
2. What is the intersection between reproductive rights, the rights of the biological parents, and the rights of a child? Who should decide the parameters of those rights and why?
3. Imagine that you are either the child or the parents in one of the "Doe" cases. What specific medical, governmental, or personal rights or access would you want for yourself? How would that be shaped by your social environment, education, or economic standing?

[21] Passive killing was a term used to reference infanticide through conscious neglect or disregard of medical care for children considered to be defective and thus unfit for society. Passive killings were thusly discussed as mercy killing or euthanasia in many circles.

[22] "Another Baby Dies as Did Bollinger Boy" The Chicago Tribune (Chicago, Illinois) December 8, 1915. https://www.disabilitymuseum.org/dhm...d=1237&&page=1

[23] "Judge Clears, Yet Condemns, Dr. Haiselden" The Chicago Daily Tribune (Chicago, Illinois), November 20, 1915. https://www.disabilitymuseum.org/dhm/lib/detail.html?id=1236&page=all also see: The Day Book. Chicago Illinois 1911-1917, November 29, 1915. https://chroniclingamerica.loc.gov/l...9/ed-1/seq-30/

[24] Another Baby Dies as Did Bollinger Boy" (1915)

[25] Martin S. Pernick, *The Black Stork: Eugenics and the Death of "Defective" Babies in American Medicine and Motion Pictures in America Since 1915*, Oxford University Press, 1996.

[26] “Congenital Birth Defects and the Medical Rights of Children: The "Baby Doe" Controversy,” *The National Library of Medicine* (Bethesda, MD). https://profiles.nlm.nih.gov/spotlight/qq/feature/babydoe

[27] Ibid.

[28] Dennis J. Horan and Burke J. Balch, "Infant Doe and Baby Jane Doe: Medical Treatment of the Handicapped Newborn," *The Linacre Quarterly* Vol. 52, No. 1, Article 9 (1985): 45-72.

[29] Ibid.

[30] Nicole Fuller, "Baby Jane Doe, center of debate in '80s, now 30," *Newsday* (2013).

[31] Jack Resnik, "Weber v. Stony Brook Hospital (1983)". Embryo Project Encyclopedia (2011).

[32] Jennifer C. Kett, “Who Is the Next "Baby Doe?" From Trisomy 21 to Trisomy 13 and 18 and Beyond,” *Pediatrics*. 2020 vol. 146, Suppl 1 (2020): S9-S12.

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9.4: Film Recommendations

No más bebés (2016) directed by Renee Tajima-Peña. This film is a documentary discussing the Madrigal V. Quilligan case of forced sterilization of Mexican women in the 1960's and 1970's. (runtime: 1 hour, 19 minutes). Additional info: https://www.pbs.org/independentlens/documentaries/no-mas-bebes/

Belly of the beasts (2020) directed by Erika Cohn. This film is a documentary discussing the unauthorized hysterectomy of incarcerated African American women in Central California's Women's Facility. (runtime: 1 hour, 22 minutes) Additional info: https://www.pbs.org/independentlens/documentaries/belly-of-the-beast/

Marion rose white (1982) directed by Garry Rusoff. This film is a fictional depiction of the true story of Marion Rose White—a young girl who was committed to an institution for the feebleminded at age nine, forcibly sterilized, and released from the psychiatric institution at age thirty-two. (runtime: 1 hour, 20 minutes) Additional info: https://cnpa.com/cja2021/Print/2021_California_Journalism_Awards___Print_Division/General/19_Feature_Story_(DB)/Third_Place_The_Press_Democrat_3/Attachment_02.pdf

Predestination (2014) directed by the Spierig Brothers. This is a fictional film with an underlining them discussing gendered identity and the effects of medical paternalism. (runtime: 1 hour, 37 minutes) Additional info: https://www.rogerebert.com/reviews/predestination-2015

The black stork (1917) directed by Leopold Wharton and Theodore Wharton. This film (also referred to as "Are You Fit to Marry?") is a fictional retelling of Dr. Harry J. Haiselden's interaction with Anna Bollinger following the birth of her son, "Baby Bollinger" who was born with paralysis on the left side of his body, brain damage (which was discovered later), and a severely curved spine (which was the potential cause of his right ear being connected or fused with his right shoulder).

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9.5: Glossary

Eugenics

the act of editing the human gene pool through genocide, segregation, scientific racism, social exclusion, planned or selective breeding of certain races, or the sterilization of individuals perceived as being unfit for society.

For more information on eugenics: https://www.genome.gov/about-genomics/fact-sheets/Eugenics-and-Scientific-Racism

Euthanasia

the act of killing a patient or permitting their death to reduce their suffering. E.g. merci killing. This practice is considered illegal in most countries.

For more information on euthanasia: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4311376/

Hysterectomy

surgical process in which all or part of the uterus is removed. When a total hysterectomy is performed, the cervix is removed in addition to the uterus. When a radical hysterectomy is performed, the fallopian tubes, ovaries, cervix, uterus, lymph nodes, and upper vagina are removed.

For more information: https://pubmed.ncbi.nlm.nih.gov/15985249/

Ideological State Apparatus

concept coined by French philosopher, Louis Pierre Althusser in which social institutions (such as schools, churches, and mass media) socialize individuals to identify with the needs and ideologies of the state or larger governmental body..

For more information: https://mforbes.sites.gettysburg.edu/cims226/wp-content/uploads/2018/09/Week-3b-Louis-Althusser.pdf

Medical Paternalism

occurs when the state, hospital, physician, or other medical practitioner determines every aspect of a patient's medical care without accounting for the patient's autonomy, comprehension, or desire for shared decision making.

For more information on medical paternalism: https://medicine.missouri.edu/centers-institutes-labs/health-ethics/faq/provider-patient-

relationship#:~:text=In%20a%20healthcare%20context%20“paternalism,in%20the%20patient%27s%20best%20interests.

Menarche

the period at which an individual begins to menstruate (when blood and tissue are shed through the vagina).

For more information on Menarche: https://www.unfpa.org/menstruationfaq

Social Darwinism

term coined by Herbert Spencer in the 19th century that wrongfully applied the laws of natural selection to determine the success of individuals based on their race, able-bodiedness, wealth, health, and perceived genetic predisposition. The term “survival of the fittest” comes out of the practice of social Darwinism.

For more information: https://www.history.com/topics/early-20th-century-us/social-darwinism

Social and Structural Determinants of Health

aspects of one’s built or social environment, educational access, economic access, and access to healthcare that affect their health outcomes.

For more information: https://health.gov/healthypeople/priority-areas/social-determinants-health

Sterilization

surgical procedure designed to prevent an individual from reproducing. The most common procedure for women is the tubal ligation in which a section of the fallopian tubes (or the entire fallopian tube) is removed through a small cut made under the belly button. It is a permanent procedure. For men, a small cut is made in the scrotum to access the vas deferens. A piece of the vas deferens is then removed to prevent sperm from reaching semen. A vasectomy is not permanent and can be reversed with a surgical procedure to reconnect the vas deferens.

For more information: https://www.uchicagomedicine.org/conditions-services/obgyn/minimally-invasive-gynecologic-surgery/female-sterilization-tubal-ligation-tubal-removal

Structural Violence

social or institutional processes within society that directly or indirectly cause harm by preventing an individual’s ability to access their basic needs.

For more information: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1621099/

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10: Models for 3D Printing

Introduction

The material found in this chapter will help those of you who are interested in printing your own 3D anatomical models. In this chapter you will find videos to introduce you to the 3D printing process, and images and STL files for a number of models that relate to the content of this text.

10.1: Sample Printer Settings

10.2: Model of Normal Female Pelvis

10.3: Pathological Models

About 3D Printing Videos

Video 10.1 Overview of 3D Printing

Video 10.2 About STL Files

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10.1: Sample printer settings

In this section you will find examples of, and documentation of printer settings for three different material types.

10.1.1 Sample Printer Settings - PLA

PLA - Polylactic acid - a material used in desktop 3D printing; it is the default filament of choice for most extrusion-based 3D printers because it can be printed at a low temperature and does not require a heated bed)

10.1.2 Sample Printer Settings - TPU

TPU - Thermoplastic polyurethane - a type of flexible and elastic 3D printing filament; it is suitable for uses requiring impact-absorption and a soft-touch surface

10.1.3 Sample Printer Settings - Multicolor PLA

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10.1.1: Sample Printer Settings - PLA

Below you will find sample settings for printing a model of the normal anatomy of the Left Pelvis on a Bambu Labs Carbon X1C printer.

If you prefer, you can download this file as a spreadsheet.

You can also download printer settings for both sides of the pelvis model as word documents:

- Specification Sheet Left Pelvis (PLA)
- Specification Sheet Right Pelvis (PLA)

10.2.1.1 Model Information

- Model Name: Pelvis_Left_NormalAnatomy_CARLI
- Designer/Creator: Janet Sinn-Hanlon
- Purpose/Intended Use: The left portion of the pelvic model

10.2.1.2 Printer Details

- Printer Model: Bambu Labs Carbon X1C
- Printer Settings:
  - Print Duration: 8 hrs, 45 min (includes supports)
  - Print Scale: 1:1
  - Estimated Material Used: 297.45 g (includes supports)
  - Layer Height: 0.2 mm
  - Infill Density: 15%
  - Top Shell Layers: 3
  - Top Shell Thickness: 0.6 mm
  - Bottom Shell Layers: 4
  - Bottom Shell Thickness: 0 mm
  - Walls/Perimeter: 2 layers
  - Print Speed: 500 mm/s (10000 mm/s2 acceleration)
  - Nozzle Temperature: 220oc
  - Bed Temperature: 35oc
  - Printing Material: PLA
  - Nozzle Diameter: 0.2 mm

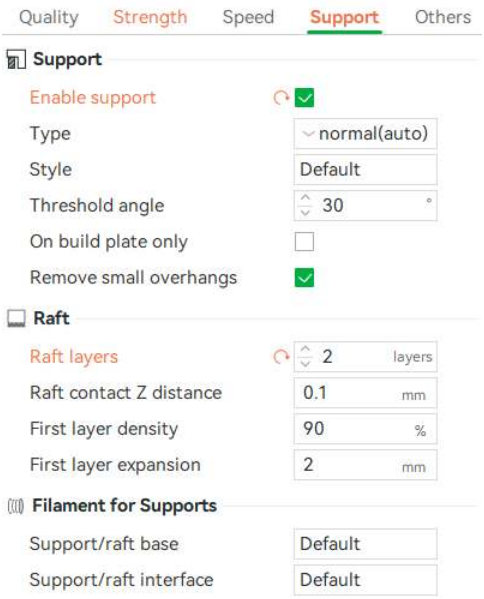
10.2.1.3 File Details

- File Format: .stl
- Software Used: Bambu Studios
- Slicing Software Settings:
  - Brim/Skirt: No skirt used and “Auto” Brim type used in Bambu software
  - Supports:
    - Normal supports that were auto-generated (linear supports)
    - Small overhangs removed

- Top Z-distance: 0.25 mm
- Bottom Z-distance: 0.20 mm
- Rafts: 2 layers of raft with a density of 90%
- Top interface layers: 2 layers

- Further support settings

SUPPORT



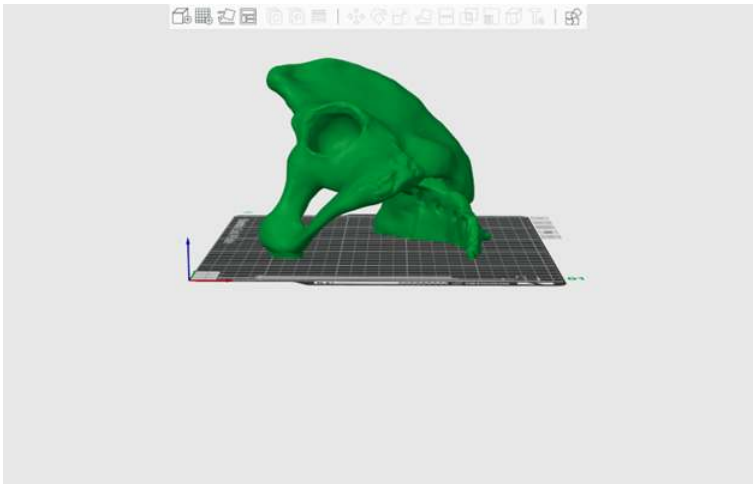
ADVANCED

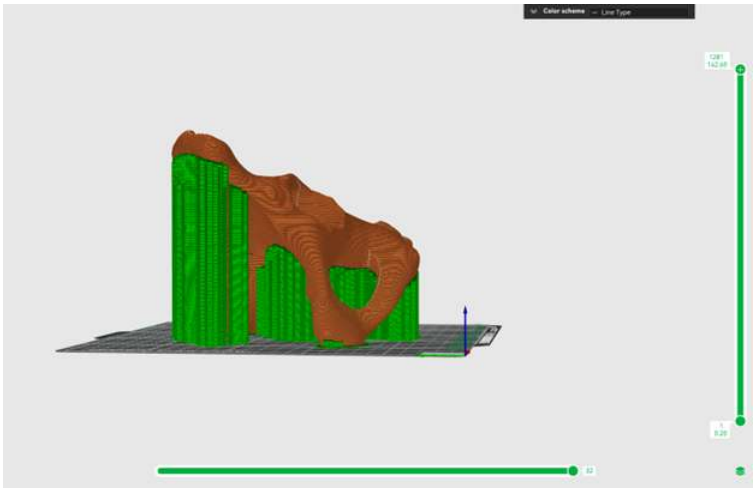


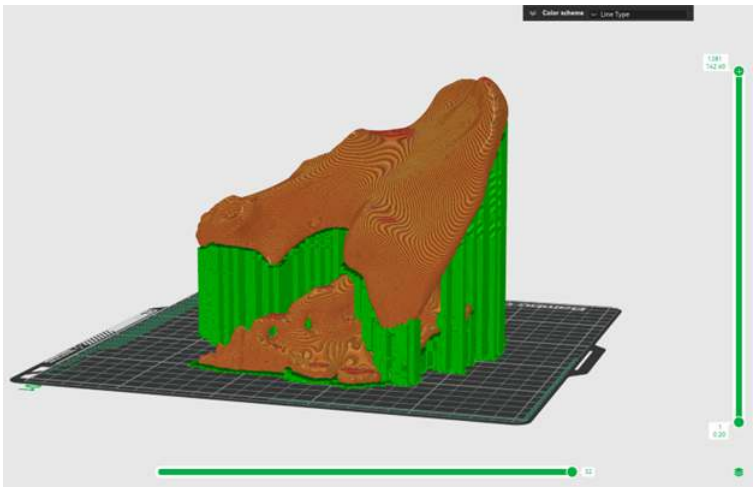
10.2.1.4 Materials Details

- Material Type: PLA
- Brand:
  - Bambu Lab PLA Basic [Beige]
  - Hatchbox PLA [Beige]
  - Prusament PLA [Vanilla White]

10.2.1.5 Slicer Images







10.2.1.6 Slicer Settings

QUALITY

Quality | Strength | Speed | Support | Others

Layer height

Layer height	0.2 mm
First layer height	0.2 mm

Line width

Default	0.42 mm
First layer	0.5 mm
Outer wall	0.42 mm
Inner wall	0.45 mm
Top surface	0.42 mm
Sparse infill	0.45 mm
Internal solid infill	0.42 mm
Support	0.42 mm

Seam

Seam position	Aligned

PRECISION

Precision

Slice gap closing radius	0.049 mm
Resolution	0.012 mm
Arc fitting	☑
X-Y hole compensation	0 mm
X-Y contour compensation	0 mm
Elephant foot compensation	0.15 mm

Ironing

Ironing type	No ironing

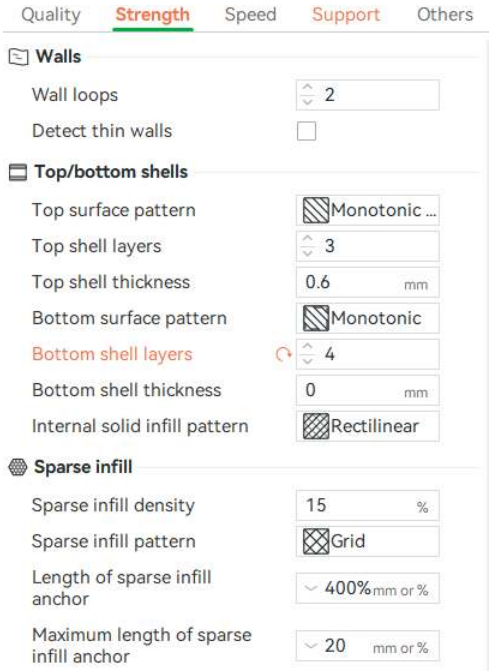
Wall generator

Wall generator	Classic

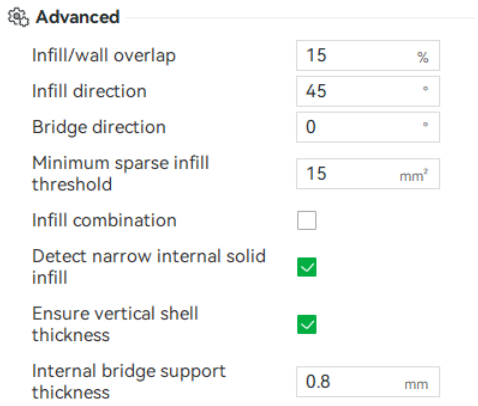
Advanced

Order of inner wall/outer wall/infill	inner/outer/i...
Bridge flow	1
Thick bridges	☐
Only one wall on top surfaces	All top surfa...
Only one wall on first layer	☐
Avoid crossing walls	☐

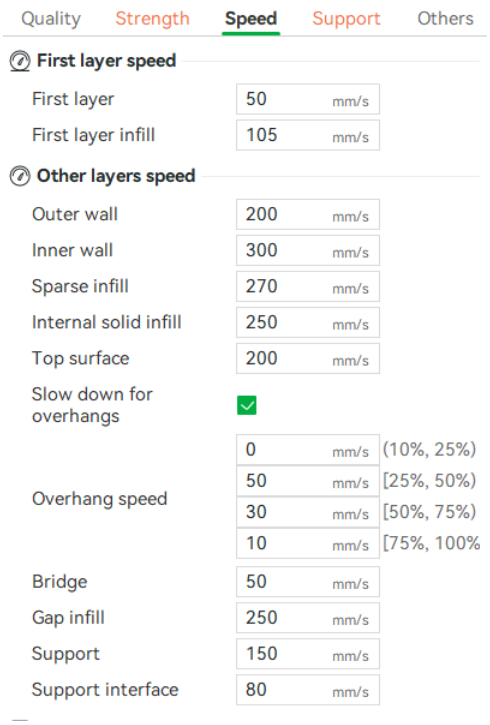
STRENGTH



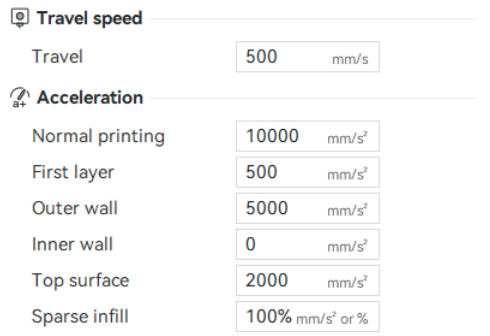
ADVANCED



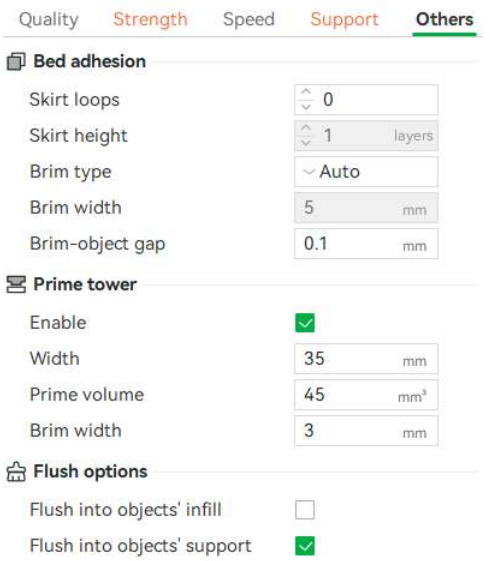
SPEED



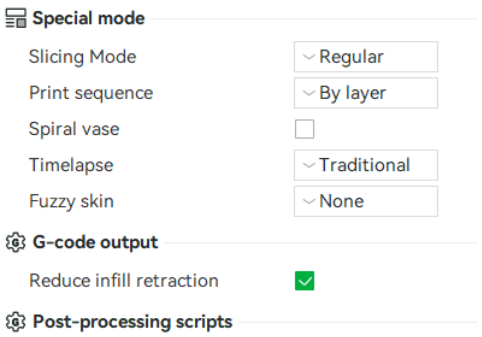
TRAVEL SPEED



OTHER



SPECIAL MODE



10.1.1: Sample Printer Settings - PLA is shared under a CC BY 4.0 license and was authored, remixed, and/or curated by LibreTexts.

10.1.2: Sample Printer Settings - TPU

> **Note**
>
> Below you will see sample documentation for printing a model of the Left Uterus on a Bambu Labas Carbon X1C printer.
>
> If you prefer, you can download this information as a spreadsheet.
>
> You can also download printer settings for the following models as word documents:
>
> - Left Uterus TPU
> - Right Uterus TPU
> - Left Bladder TPU
> - Right Bladder TPU
> - Colon TPU
> - Combined Floor TPU

10.1.2.1 Model Information

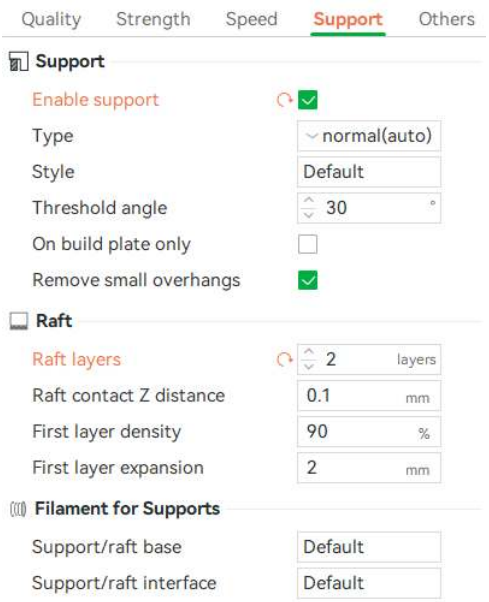
- Model Name: Uterus_Left_NormalAnatomy_CARLI
- Designer/Creator: Janet Sinn-Hanlon
- Purpose/Intended Use: The left portion of the uterus model

10.2.1.2 Printer Details

- Printer Model: Bambu Labs Carbon X1C
- Printer Settings:
  - Print Duration: 3 hrs. 54 min (includes supports)
    - Print Duration increased to 7 hrs 14 minutes when printed with the other half
    - Print Scale: 1:1
    - Estimated Material Used: 47.24 g (includes supports)
    - Layer Height: 0.2 mm
    - Infill Density: 15%
    - Top Shell Layers: 3
    - Top Shell Thickness: 0.6 mm
    - Bottom Shell Layers: 3
    - Bottom Shell Thickness: 0 mm
    - Walls/Perimeter: 2 layers
    - Print Speed: 500 mm/s (10000 mm/s2 acceleration)
    - Nozzle Temperature: 230^{oc}
    - Bed Temperature: 30^{oc}
    - Printing Material: TPU
    - Nozzle Diameter: 0.2 mm

10.2.1.3 File Details

- File Format: .stl
- Software Used: Bambu Studios
- Slicing Software Settings:
  - Brim/Skirt: No skirt used and “Auto” Brim type used in Bambu software.
  - Supports:
    - Normal supports that were auto-generated (linear supports)
    - Small overhangs removed
    - Threshold angle: 30°
    - Top Z-distance: 0.15 mm
    - Bottom Z-distance: 0.10 mm
    - Base Pattern: Rectilinear
    - Base pattern spacing: 1.5 mm
    - Rafts: 2 layers of raft with a density of 90%
    - Top interface layers: 2 layers
    - Interface pattern: Concentric
  - Further support settings
- SUPPORT



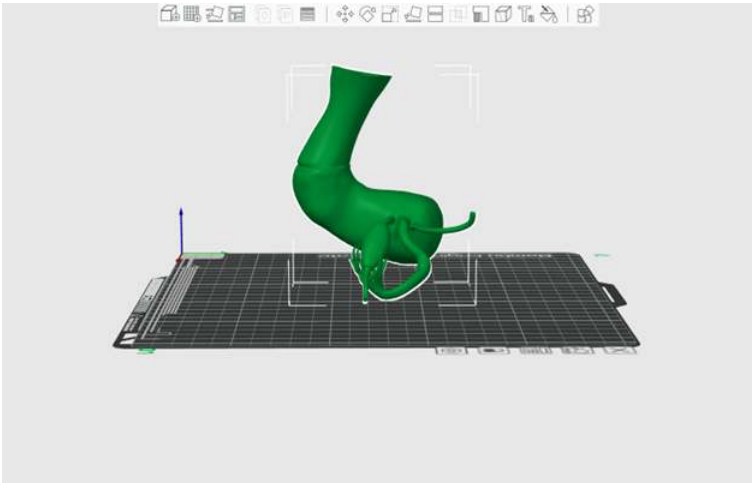
- ADVANCED

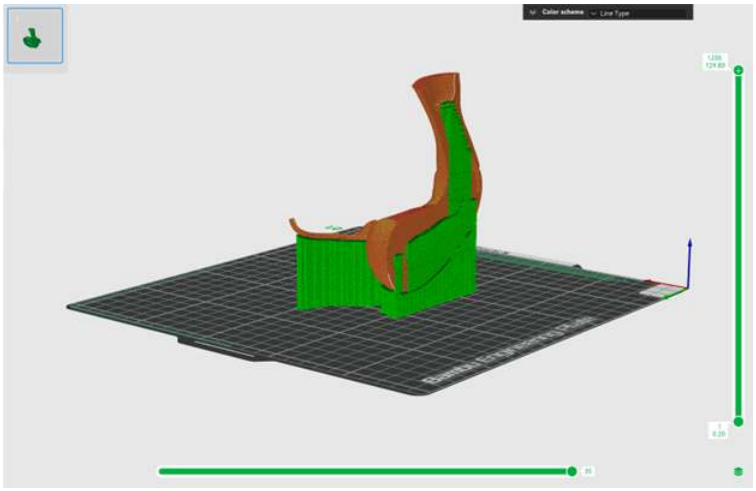


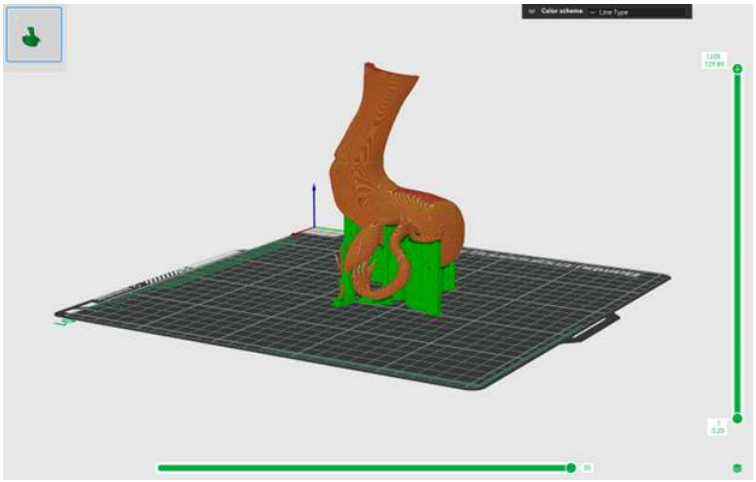
10.2.1.5 Material Details

- Material Type: TPU
- Brand:
  - Hatchbox TPU [Pink]
  - Hatchbox TPU [Purple]
- Diameter: 1.75 mm

10.2.1.6 Slicer Images







10.2.1.7 Slicer Settings

- QUALITY

Quality | Strength | Speed | Support | Others

Layer height

Layer height	0.2	mm
First layer height	0.2	mm

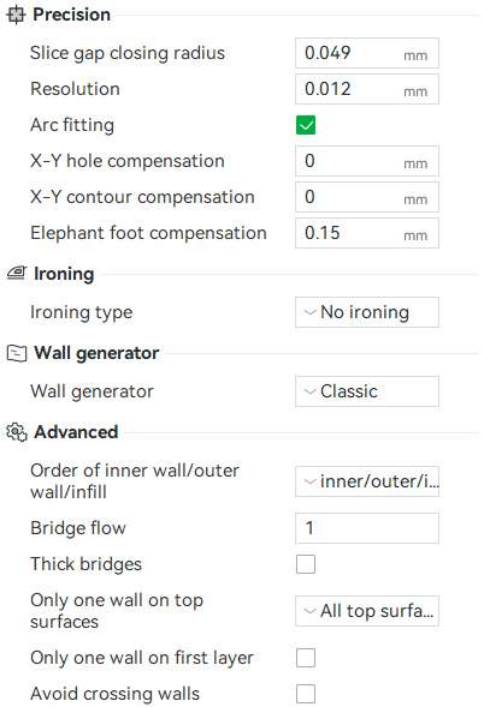
Line width

Default	0.42	mm
First layer	0.5	mm
Outer wall	0.42	mm
Inner wall	0.45	mm
Top surface	0.42	mm
Sparse infill	0.45	mm
Internal solid infill	0.42	mm
Support	0.42	mm

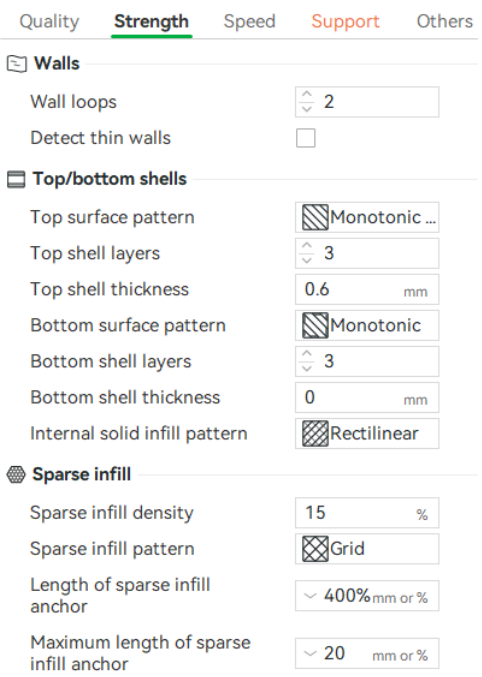
Seam

Seam position	Aligned

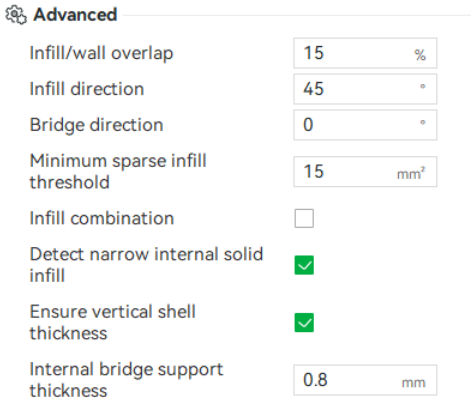
- PRECISION



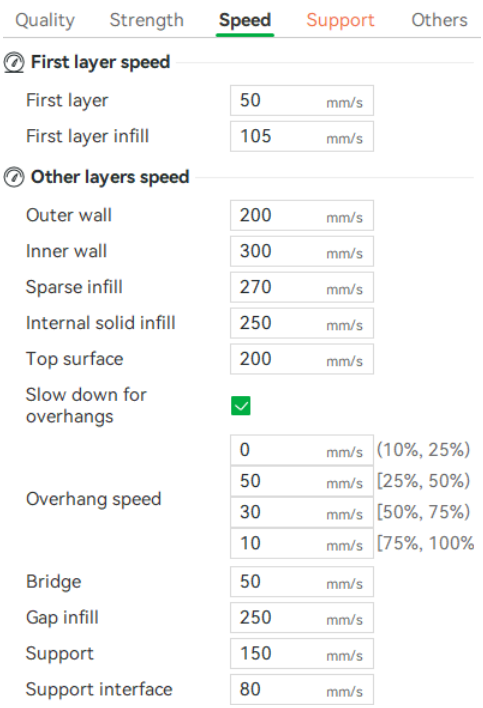
- STRENGTH



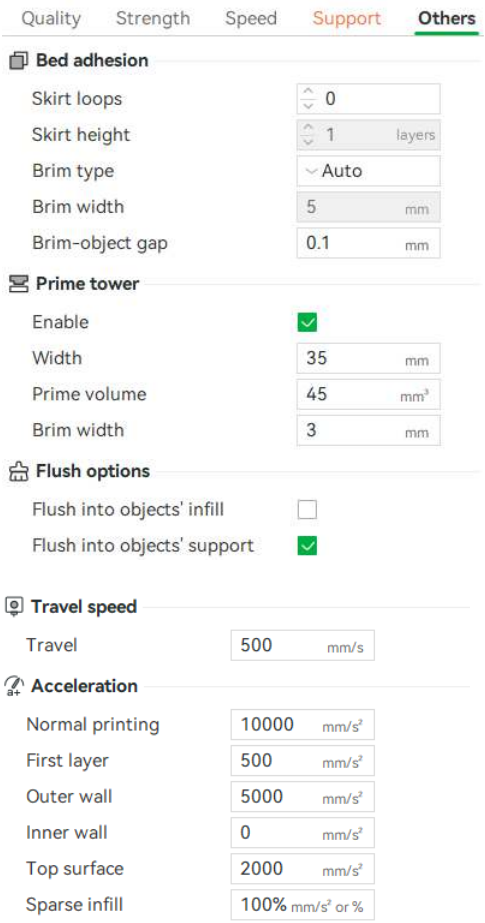
- ADVANCED



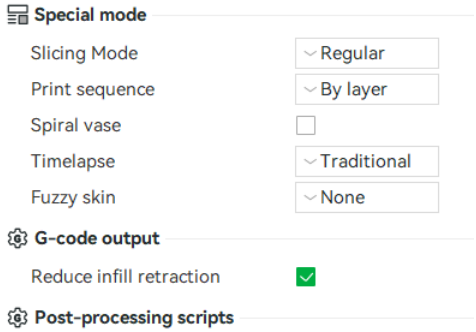
- SPEED



- OTHERS



- SPECIAL MODE



10.1.2: Sample Printer Settings - TPU is shared under a CC BY 4.0 license and was authored, remixed, and/or curated by LibreTexts.

10.1.3: Sample Printer Settings - Multicolor PLA

Note

Below you will find sample documentation for printing a model of the Endodermal Fibroid pathological model on a Bambu Labs Carbon X1C printer.

If you prefer, you can download the settings in a spreadsheet file.

You can also download printer settings for both sides of the pelvis model as word documents:

- Uterus Unicornuate PLA Multi
- Uterus Bicornuate PLA Multi
- Uterus Didelphys PLA Multi
- Intramural Subserosal PLA Multi
- Endodermal Fibroid PLA Multi
- Uterine Polyps PLA Multi

10.1.3.1 Model Information

- Model Name: EndodermalFibroid_Pathologocial_CARLI
- Designer/Creator: Janet Sinn-Hanlon
- Purpose/Intended Use: Uterus model with an endodermal fibroid

10.1.3.2 Printer Details

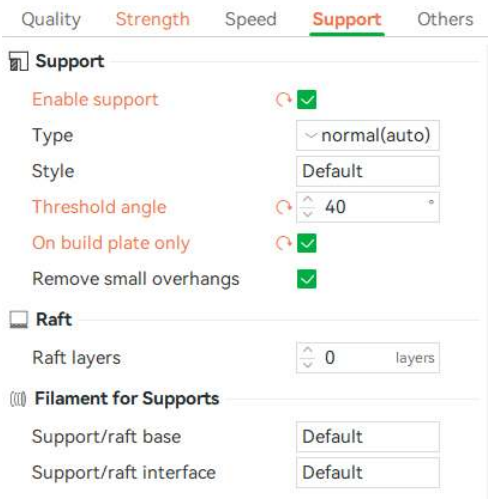
- Printer Model: Bambu Labs Carbon X1C
- Printer Settings:
  - Print Duration: 17 hrs, 57 min (includes supports and purged material)
  - Print Scale: 1:1
  - Estimated Total Material Used: 324.3 g (includes supports and purged material)
    - Fibroid (Beige): 56.03 g (includes purged material)
    - Endometrium (Pink): 80.59 g (includes purged material)
    - Rest of Model (Clay): 187.67 g (includes purged material)
  - Layer Height: 0.2 mm
  - Infill Density: 15%
  - Top Shell Layers: 3
  - Top Shell Thickness: 0.6 mm
  - Bottom Shell Layers: 4
  - Bottom Shell Thickness: 0 mm
  - Walls/Perimeter: 2 layers
  - Print Speed: 500 mm/s (10000 mm/s2 acceleration)
  - Nozzle Temperature: 220^{oc}
  - Bed Temperature: 35^{oc}

- Printing Material: PLA
- Nozzle Diameter: 0.2 mm

10.1.3.3 File Details

- File Format: .stl
- Software Used: Bambu Studios
- Slicing Software Settings:
  - Brim/Skirt: No skirt used and “Auto” Brim type used in Bambu software
  - Supports:
    - Normal supports that were auto-generated (linear supports)
    - Small overhangs removed
    - Threshold angle: 40°
    - Top Z-distance: 0.23 mm
    - Bottom Z-distance: 0.20 mm
    - Rafts: 2 layers of raft with a density of 90%
    - Top Interface Layers: 2 layers
    - Top Interface Spacing: 0.4 mm
    - Supports Only On Build Plate Enabled
  - Further support settings

- SUPPORT



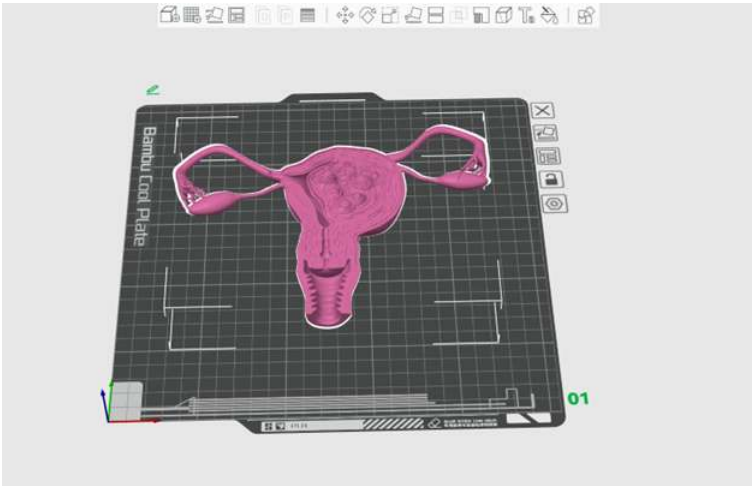
- ADVANCED

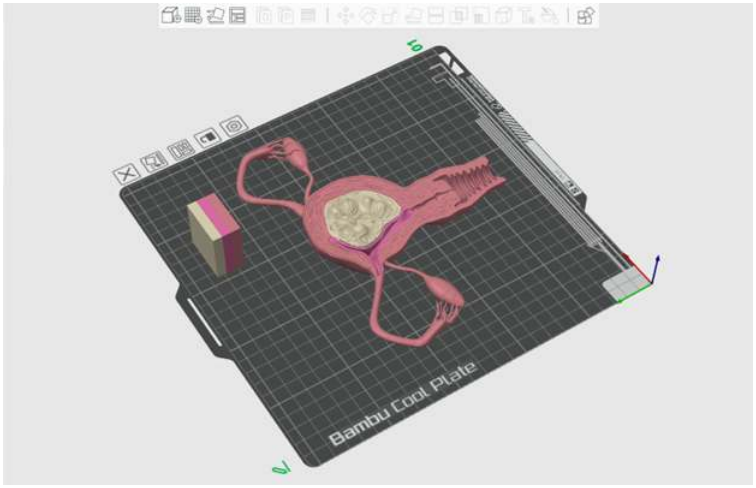


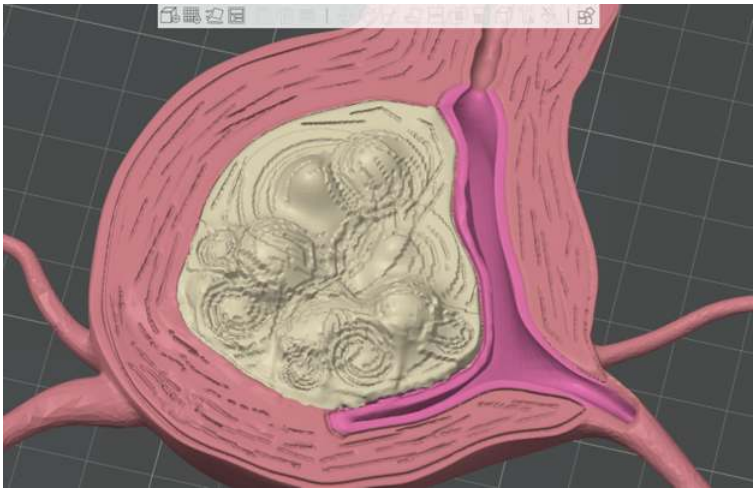
10.1.3.4 Materials Details

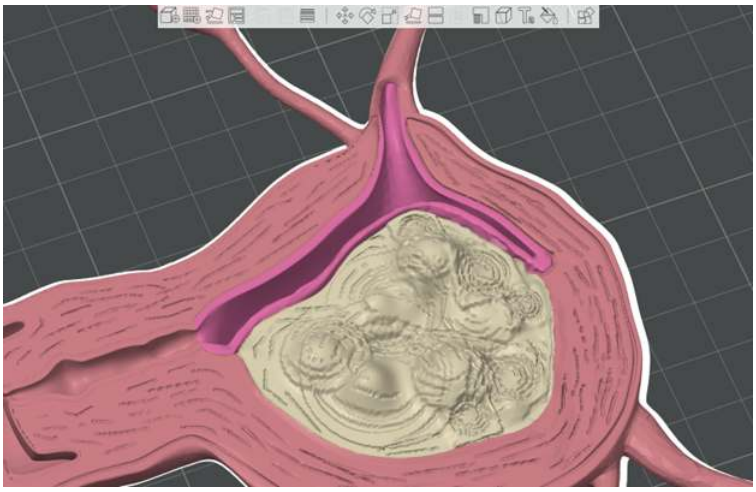
- Material Type: PLA
- Brand:
  - Endometrium: Hatchbox Silk PLA [Pink]
  - Fibroid: Hatchbox PLA [Beige]
  - Rest of Model: Hatchbox Matte PLA [Terracotta]
- Diameter: 1.75 mm

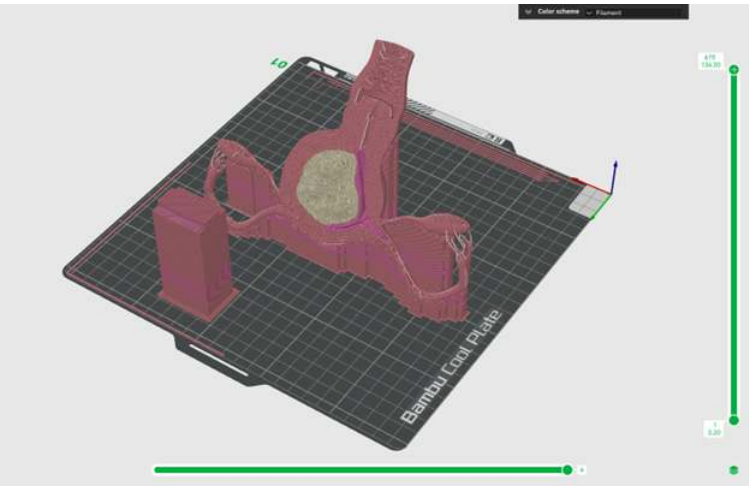
10.1.3.5 Slicer Images

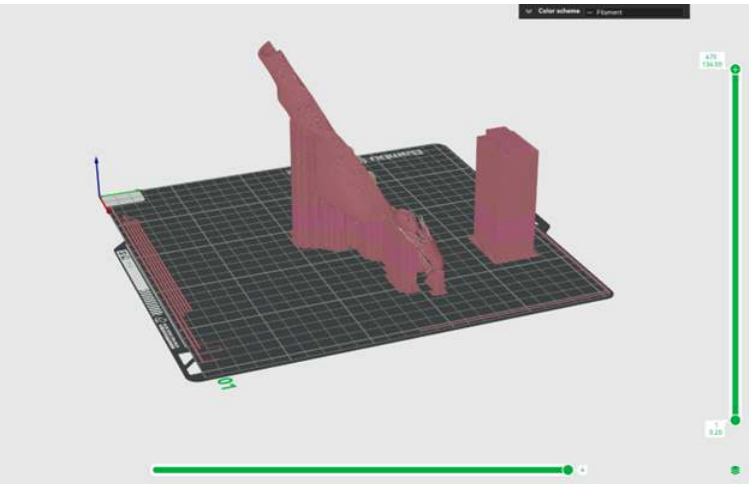



Bambu Cool Plate









10.1.3.6 Slicer Settings

- QUALITY

Quality | Strength | Speed | Support | Others

Layer height

Layer height	0.2	mm
First layer height	0.2	mm

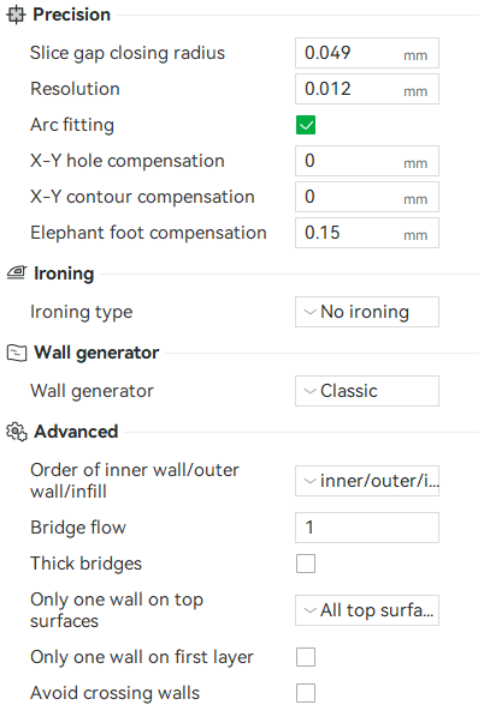
Line width

Default	0.42	mm
First layer	0.5	mm
Outer wall	0.42	mm
Inner wall	0.45	mm
Top surface	0.42	mm
Sparse infill	0.45	mm
Internal solid infill	0.42	mm
Support	0.42	mm

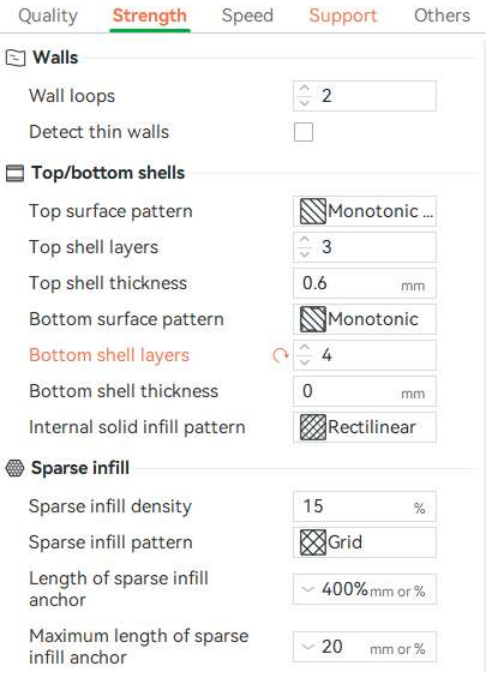
Seam

Seam position	Aligned

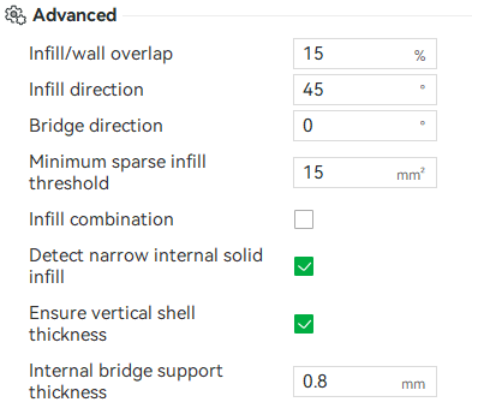
- PRECISION



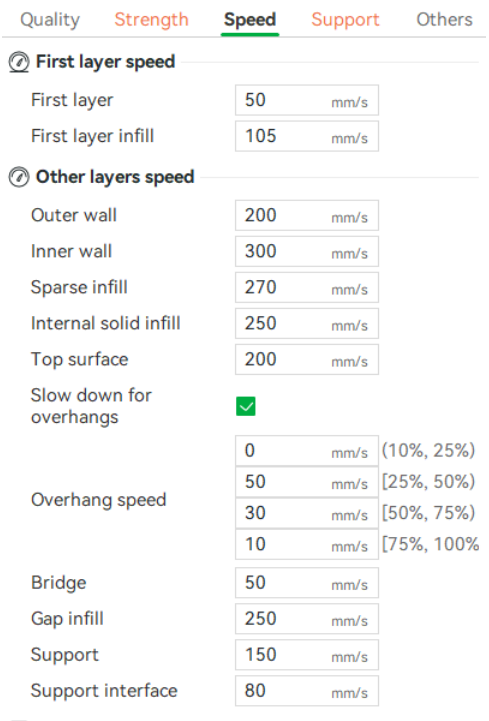
- STRENGTH



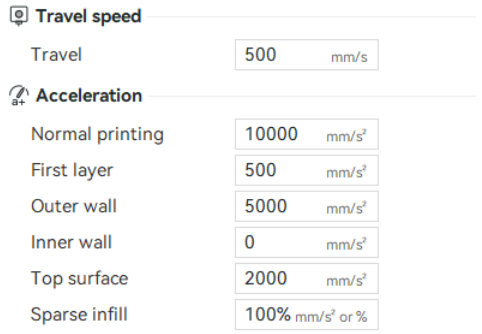
- ADVANCED



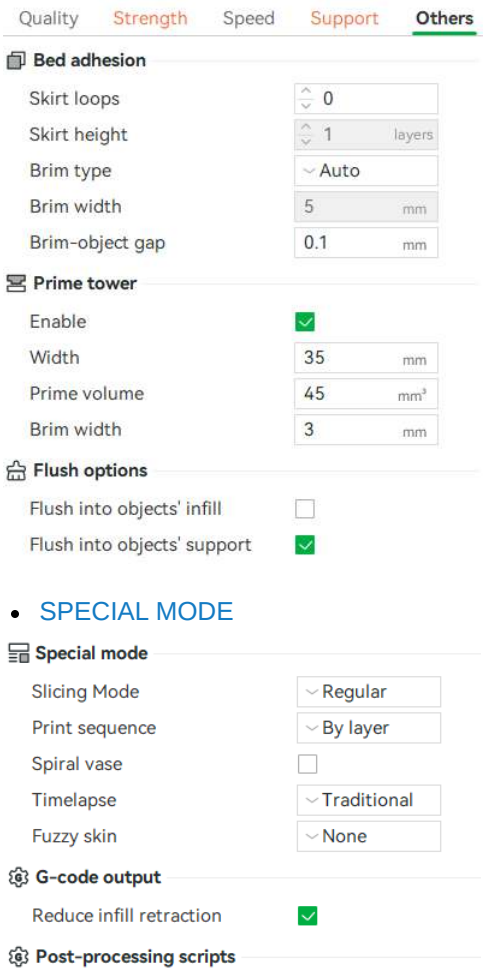
- SPEED



- TRAVEL SPEED



- OTHER



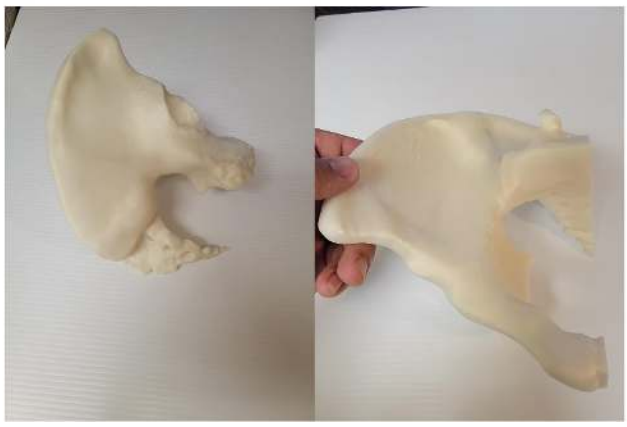
- SPECIAL MODE

10.1.3: Sample Printer Settings - Multicolor PLA is shared under a CC BY 4.0 license and was authored, remixed, and/or curated by LibreTexts.

10.2: Normal Pelvis Model

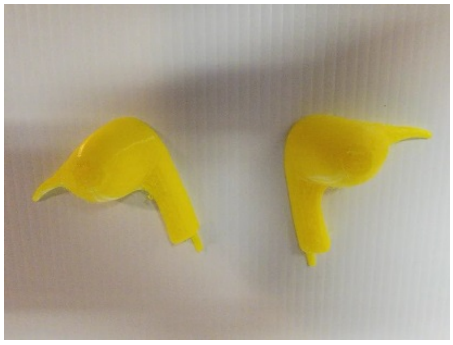
10.2.1 Components of the Normal Pelvis

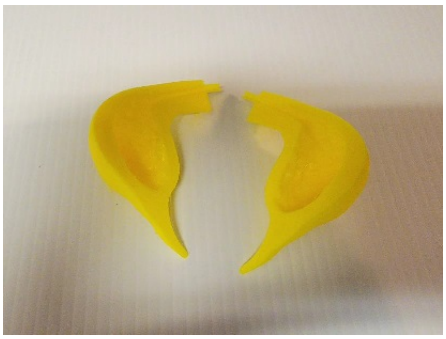
The following models were printed on a Bambu 3D Printer.

PRINTED MODEL IMAGES	FILES FOR PRINTING
Left Pelvis 	10.2.1.1 Left Pelvis Pelvis_Left_NormalAnatomy.stl Pelvis_Left_NormalAnatomy_specs
Right Pelvis 	10.2.1.2 Right Pelvis Pelvis_Right_NormalAnaromy.stl Pelvis_Right_NormalAnatomy_specs
Pelvic Floor 	10.2.1.3 Pelvic Floor Pelvic_Floor_NormalAnatomy.stl Pelvic_Floor_NormalAnatomy_specs



Left and Right Bladder





10.2.1.4 Left and Right Bladder

- Bladder_Left_NormalAnatomy.stl
- Bladder_Right_NormalAnatomy.stl
- Bladder_Left_NormalAnatomy_specs
- Bladder_Right_NormalAnatomy_specs

Left and Right Uterus



10.2.1.5 Left and Right Uterus

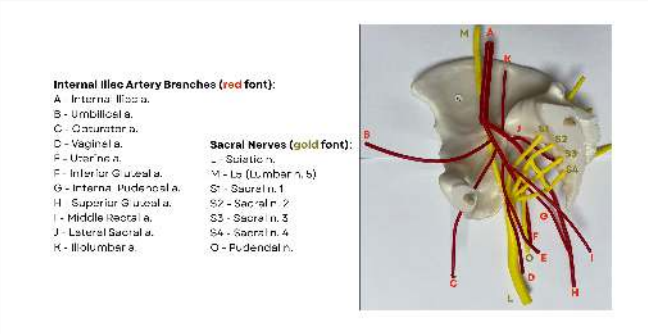
- Uterus_Left_NormalAnatomy.stl
- Uterus_Right_NormalAnatomy.stl
- Uterus_Left_NormalAnatomy_specs
- Uterus_Right_NormalAnatomy_specs





10.2.1.6 Colon

- Colon_NormalAnatomy.stl
- Colon_NormalAnatomy_specs

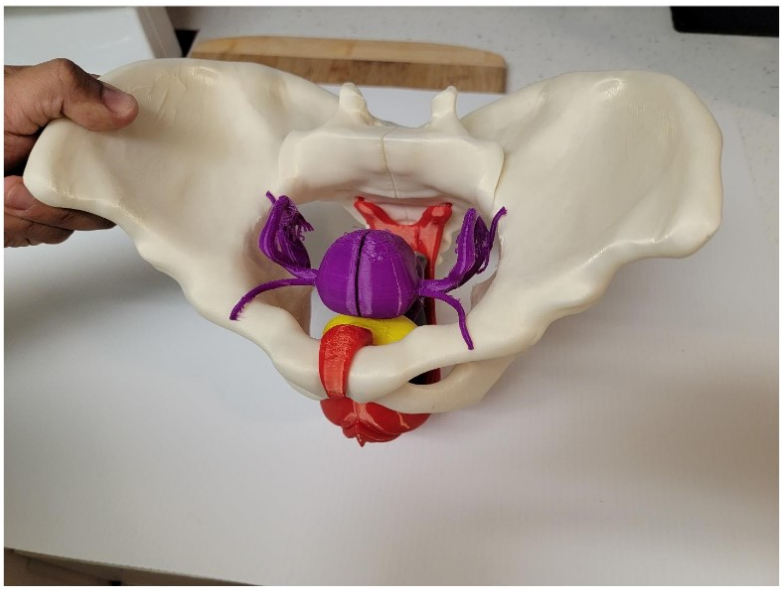


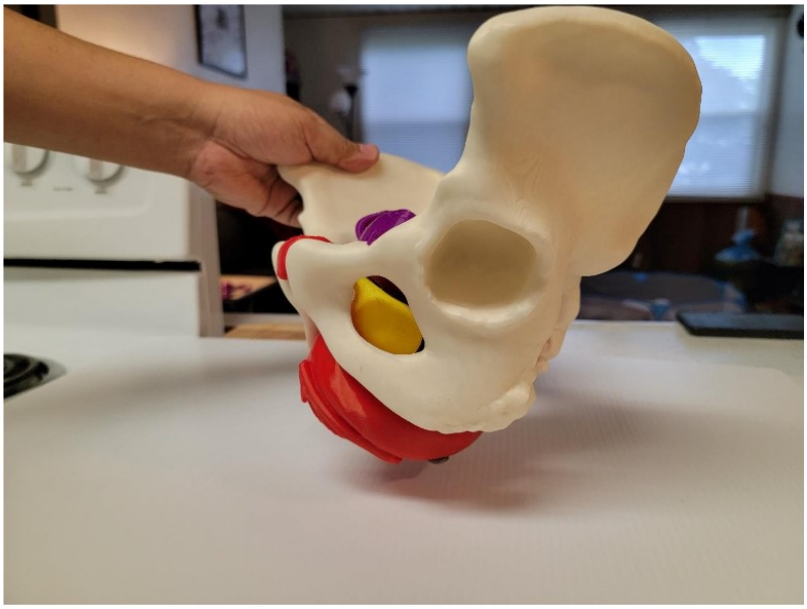
10.2.1.7 Artery Branches & Sacral Nerves

- InternalliacBranches.stl
- InternalliacBranches.3mf
- SciaticNerves.stl
- Sciatic Nerves.3mf

10.2.2 Normal Pelvis Fully Assembled

Full Assembly





10.2: Normal Pelvis Model is shared under a CC BY 4.0 license and was authored, remixed, and/or curated by LibreTexts.

10.3: Pathological Models for 3D Printing

10.3.1 Model Images with STL Files and printing specs for Bambu Printer



10.3.1.1 Submucous Fibroid

Submucous_Fibroid.stl

Submucous_Fibroid_specs



10.3.1.2 Uterine Polyps

- Uterine_Polyps.stl
- Uterine_Polyps_specs



10.3.1.3 Intramural and Subserosal Fibroid

- Intramural_Subserosal_Fibroid.stl
- Intramural_Subserosal_Firboid_specs



10.3.1.4 Unicornuate Uterus

- Uterus_Unicornuate.stl
- Uterus_Unicornuate_specs



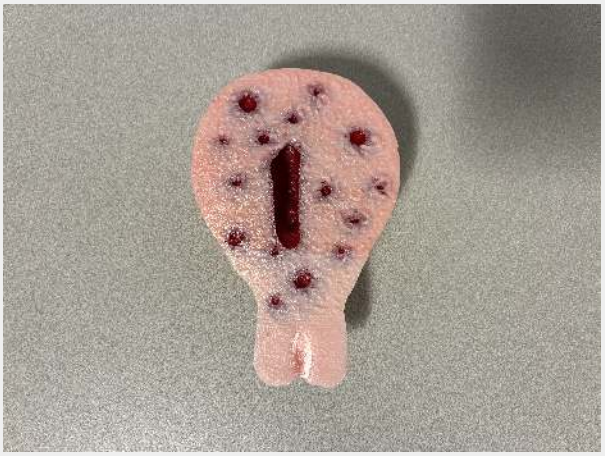
10.3.1.5 Uterus Didelphys

- Uterus_Didelphys.stl
- Uterus_Didelphys_specs



10.3.1.6 Bicornuate Uterus

- Uterus_Bicornuate.stl
- Uterus_Bicornuate_specs



10.3.1.7 Adenomyosis

- Adenomyosis.stl



10.3.1.8 Cervical Cancer

Cervical Cancer.stl



10.3.1.9 Endometrial Cancer

Endometrial Cancer.stl

10.3: Pathological Models for 3D Printing is shared under a CC BY 4.0 license and was authored, remixed, and/or curated by LibreTexts.

10.4: Embryo Models

10.4.1 3D Printed Plates for Embryonic Development

Embryo plates created and printed from the NIH Carnegie Stages of Embryonic Development. Corresponding STL files are listed below the image.

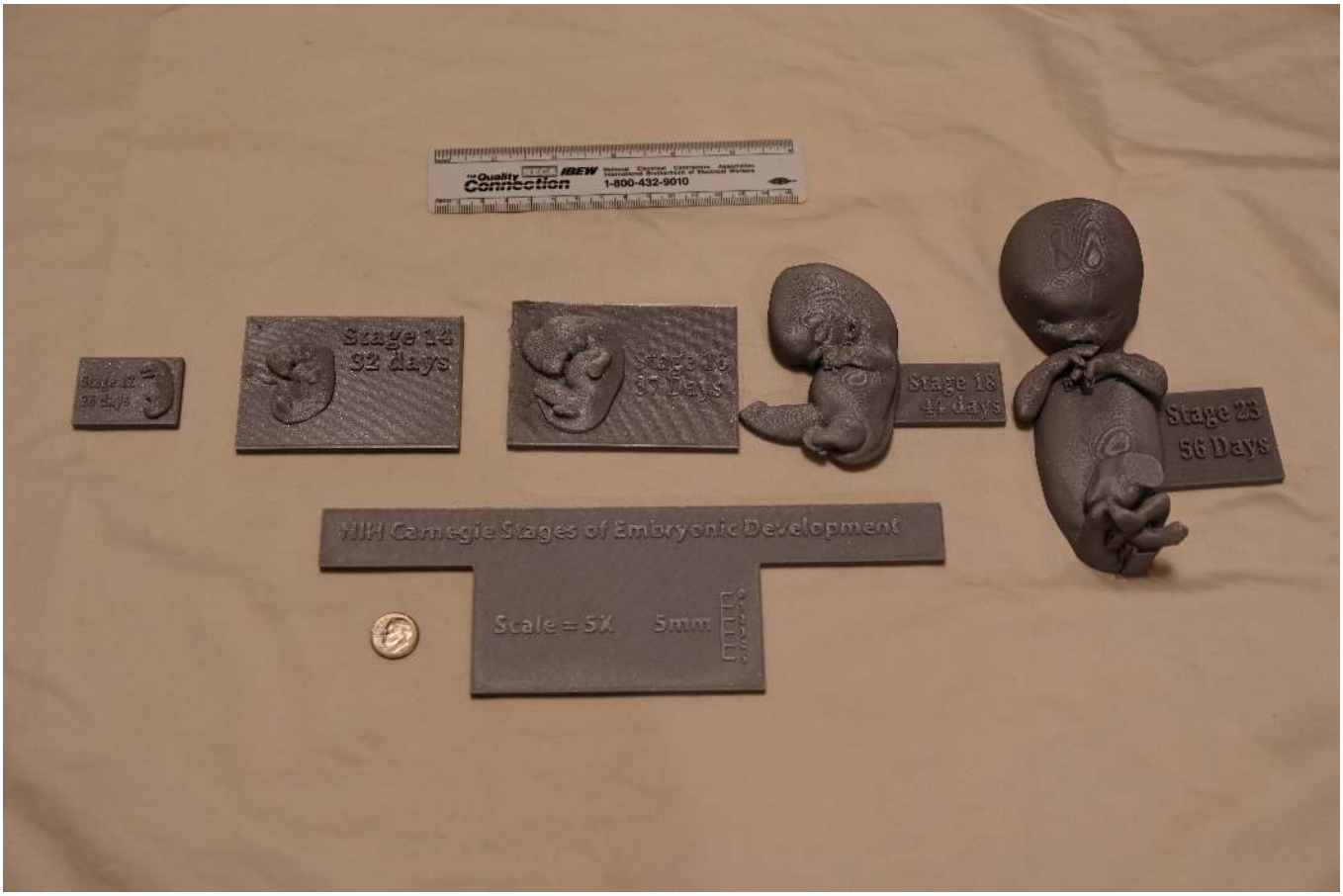


Image Source: KNOX College.

10.4.2 STL Files for Embryo Models

- **Carnegie Human Embryo Stage 12** **Stage 12 EmbryoPlate.stl**
- **Carnegie Human Embryo Stage 14** **Stage 14 EmbryoPlate.stl**
- **Carnegie Human Embryo Stage 14** **Stage 14 EmbryoPlate.stl**
- **Carnegie Human Embryo Stage 18** **Stage 18 EmbryoPlate.stl**
- **Carnegie Human Embryo Stage 23** **Stage 23 EmbryoPlate.stl**

10.4: Embryo Models is shared under a CC BY 4.0 license and was authored, remixed, and/or curated by LibreTexts.

CHAPTER OVERVIEW

11: Learning and Assessment - Tools, Strategies, Cases

11.1: Self-Assessment for Learners

11.2: Assessment for Educators

11.3: Concept Mapping

11.4: Student Contributions

Bibliography

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11.1: Self-Assessment for Learners

11.1.1 Concept Maps/Mind Maps

Concept mapping is an activity invites participants to see a concept within its context. It prompts collaborators to share important components around a concept and find the connections. It places a concept against the backdrop of a larger ecosystem or landscape. Creating this big picture facilitates more expansive group thinking, problem framing, and solution making.[1]

Concept mapping has the potential to expand the problem space that students explore through the attention given to the relationship between concepts. It helps integrate existing knowledge in new ways.[2]

Please see Concept Mapping for more information.

11.1.2 Summarization

Content forthcoming

11.1.3 Flashcards

Flashcards help promote recall through visual and textual cues. Cards include question and answer sides. Creating one's own cards helps promote learning and both sides of the cards should be used for study.

Flashcards should be engaging enough to promote critical thinking and not just memorization. Manually writing out cards provides you with the resources best suited to your own learning needs.[3]

11.1.4 Portfolios

Portfolios provide a consolidated collection of learning outputs that can be built over time to showcase achievement. An example of an openly licensed portfolio template can be found at *My Learning Journey* (Trent University/eCampusOntario). This resource helps students creat a customized portfolio using Pressbooks, an open access publishing platform.

Footnotes

1. Digital.gov. Design Operations Guide. Available from: https://digital.gov/guides/hcd/desig...tions/thinking.

2. Green, Amy E., Fettes, Danielle L. and Gregory A. Aarons. J Behav Health Serv Res. 2012 Oct;39(4):10.1007/s11414-012-9291-1. doi: 10.1007/s11414-012-9291-1. publisher's version of this article is available at J Behav Health Serv Res. Publicly available from: https://par.nsf.gov/biblio/10397720-...s-minds-brains.

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11.2: Assessment for Educators

11.2.1 Concept Maps/Mind Maps

Concept mapping is an activity invites participants to see a concept within its context. It prompts collaborators to share important components around a concept and find the connections. It places a concept against the backdrop of a larger ecosystem or landscape. Creating this big picture facilitates more expansive group thinking, problem framing, and solution making.[1]

Concept mapping has the potential to expand the problem space that students explore through the attention given to the relationship between concepts. It helps integrate existing knowledge in new ways.[2]

Please see Concept Mapping for more information.

11.2.2 Case-based Inquiry

What is case-based inquiry?

Using a case-based approach engages students in discussion of specific scenarios that resemble or typically are real-world examples. This method is learner-centered with intense interaction between participants as they build their knowledge and work together as a group to examine the case. The instructor's role is that of a facilitator while the students collaboratively analyze and address problems and resolve questions that have no single right answer.[3]

Clyde Freeman Herreid provides eleven basic rules for case-based learning.[4]

1. Tells a story.
2. Focuses on an interest-arousing issue.
3. Set in the past five years
4. Creates empathy with the central characters.
5. Includes quotations. There is no better way to understand a situation and to gain empathy for the characters
6. Relevant to the reader.
7. Must have pedagogic utility.
8. Conflict provoking.
9. Decision forcing.
10. Has generality.
11. Is short.

When is Case-based Inquiry most useful?

Case-based learning allows students to

- put theory into practice. Real world or authentic contexts expose students to viewpoints from multiple sources and see why people may want different outcomes. Students can also see how a decision will impact different participants, both positively and negatively.[5]
- analyze data in order to reach a conclusion. Since many assignments are open-ended, students can practice choosing appropriate analytic techniques as well. Instructors who use case-based learning say that their students are more engaged, interested, and involved in the class. [6]
- develop analytic, communicative and collaborative skills along with current knowledge. In their effort to find solutions and reach decisions through discussion, students sort out factual data, apply analytic tools, articulate issues, reflect on their relevant experiences, and draw conclusions they can relate to new situations. In the process, they acquire substantive knowledge and develop analytic, collaborative, and communication skills.[7]

Formats for Cases[8]

- **“Finished” cases based on facts:** for analysis only, since the solution is indicated or alternate solutions are suggested.
- **“Unfinished” open-ended cases:** the results are not yet clear (either because the case has not come to a factual conclusion in real life, or because the instructor has eliminated the final facts.) Students must predict, make choices and offer suggestions that will affect the outcome.

- **Fictional cases:** entirely written by the instructor—can be open-ended or finished. Cautionary note: the case must be both complex enough to mimic reality, yet not have so many "red herrings" as to obscure the goal of the exercise.
- **Original documents:** news articles, reports with data and statistics, summaries, excerpts from historical writings, artifacts, literary passages, video and audio recordings, ethnographies, etc. With the right questions, these can become problem-solving opportunities. Comparison between two original documents related to the same topic or theme is a strong strategy for encouraging both analysis and synthesis. This gives the opportunity for presenting more than one side of an argument, making the conflicts more complex.

Case Design[9]

Cases can be more or less "directed" by the kinds of questions asked. These kinds of questions can be appended to any case, or could be a handout for participants unfamiliar with case studies on how to approach one.

- What is the situation—what do you actually know about it from reading the case? (Distinguishes between fact and assumptions under critical understanding)
- What issues are at stake? (Opportunity for linking to theoretical readings)
- What questions do you have—what information do you still need? Where/how could you find it?
- What problem(s) need to be solved? (Opportunity to discuss communication versus conflict, gaps between assumptions, sides of the argument)
- What are all the possible options? What are the pros/cons of each option?
- What are the underlying assumptions for [person X] in the case—where do you see them?
- What criteria should you use when choosing an option? What does that mean about your assumptions?

11.2.3 Gaming

Diagnostic Board Game

An example of a gaming approach to learning can be found at *Diagnosis* (University of Newcastle/CAUL OER Collective). Using Pressbooks' as a resource hub, the authors built an interactive, case-based game where students move through scenarios, make decisions, and get real-time feedback. For more information, see *Diagnosis: A Medical Education Game*.

11.2.3 H5P Assessments

Fertilization & Embryo Development [Chapter 4]

Pregnancy & Birth [Chapter 5]

Footnotes

1. Digital.gov. Design Operations Guide. Available from: https://digital.gov/guides/hcd/desig...tions/thinking.
2. Green, Amy E., Fettes, Danielle L. and Gregory A. Aarons. J Behav Health Serv Res. 2012 Oct;39(4):10.1007/s11414-012-9291-1. doi: 10.1007/s11414-012-9291-1. publisher's version of this article is available at J Behav Health Serv Res. Publicly available from: https://par.nsf.gov/biblio/10397720-...s-minds-brains.
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11.3: Concept Mapping

11.3.1 What is Concept Mapping?

Concept mapping is an activity invites participants to see a concept within its context. It prompts collaborators to share important components around a concept and find the connections. It places a concept against the backdrop of a larger ecosystem or landscape. Creating this big picture facilitates more expansive group thinking, problem framing, and solution making.[1]

Concept mapping has the potential to expand the problem space that students explore through the attention given to the relationship between concepts. It helps integrate existing knowledge in new ways.[2]

When is Concept Mapping most useful?

Concept maps can help learners in various ways:[3]

- Individual or group study
- Note-taking
- Brainstorming
- Creating presentations
- Collaborating

Concept maps provide opportunities to:

- Drill down on a broad topic
- Organize concepts & ideas
- Enhance recall through visual learning
- Understand relationships between concepts & ideas

In science courses, the primary use of student-generated concept maps is to improve content knowledge. The two primary research questions explored in the literature are: 1) Are concept map activities associated with improved learning outcomes? 2) Do students' concept maps—more specifically, structural aspects of students' concept maps—correspond to learning outcomes? In response to the first question, many studies show that students' creation of maps that represent their understanding is associated with improved learning (Novak *et al*., 1983; Canas *et al*., 2003; Nesbit and Adesope, 2006; Wu *et al*., 2012; Lee *et al*., 2013; Bramwell-Lalor and Rainford, 2014). In response to the second question, although there is no consensus about how to "best" assess concept maps, the prevailing message in the literature is that *structural complexity increases with expertise* (Novak *et al*., 1983; Wallace and Mintzes, 1990; Markham *et al*., 1994; McClure *et al*., 1999; Mintzes and Quinn, 2006; Srinivasan *et al*., 2008). Markham *et al*. (1994) show that more senior students use more sophisticated concepts in their maps, suggesting that complexity and sophistication in understanding may be related.[4]

11.3.2 Types of Concept Maps

There are various kinds of concepts depending on what you are trying to do.[5]

- Spider Map - Core idea is in the center and sub-topics branch out from there, like a spider web. This format is good when you have one simple overarching idea that you want to branch out from.
- Flowchart - Using a starting point, your ideas are built based on prompts; think *decision tree* or *choose your own adventure*. This format is good for processes or decision making.
- Hierarchy Map - Start with the very top level (usually at the top) and branch out from there; think *org chart*. This format works well for visualizing hiearchical systems.
- Systems Map - This is a complex map that represents both positive and negative correlations.

11.3.3 Concept Mapping Steps

Concept maps have three basic elements - concepts (shapes) and relationships (lines and arrows).[6]

- Focus question: specific question to be addressed
- Nodes: circles or boxes that house concepts or keywords

- Linking lines: connecting lines that represent relationships between concepts

Patricia Williamson outlines seven steps for concept mapping.[7]

Step One - Brainstorm

- Identify the main topic
- Brainstorm everything you know about the topic
- Use relevant content from course, lectures, textbooks, and course material

Sticky notes can be a great way of jotting down ideas – you can move the notes around as you begin to identify similarities and differences. You can also ask questions and include reminders of work that you need to do.

Step Two - Identify Main Points

- Organize information into main points

After noting down what I know about my topic and identifying key questions that I'll need to research, I can focus on a few things that will be important to describe and analyze.

Step Three - Start Mapping

- Start creating map beginning with main or broader points at the top
- Branch out to supporting details or more specific concepts
- Cyclical depictions may be useful for more dynamic processes

You can use a piece of paper, or concept mapping software, to make notes of ideas and start to connect them.

Step Four - Identify Connections

- Use lines to describe relationship between two concepts (Proposal)
- Use lines to link various regions of the map (Cross-links)
- Review map and look for more connections
- Use arrows, symbols, and colours, to show relationships between ideas
- Build layers of connections and relationships

Step Five - Add Details

- Include details
- Provide examples that may help to clarify a concept

This is where you can provide more information about each point.

Step Six - Analyze & Improve

- Analyze and improve map by asking questions
- How do ideas fit together?
- Have all necessary connections been made?

Step back and review the map keeping the purpose or goal in mind. Follow up on questions as needed. Talk through ideas with collaborators and continue to develop and refine ideas.

Step Seven - Update

- Update concept map as you learn more
- Ask key questions about connections between ideas

For more information

Try the *Miro* Concept Map Maker - create a concept map with Miro to visualize key concepts and get a big-picture overview. With AI-powered workflows, your team can brainstorm, ideate, and bring concepts to life from start to finish. *Free to try.*

11.3.4 Assessment of Concept Maps

Hierarchical concept maps—maps in which concepts tend to subsume or constitute related concepts—are often assessed based on the accuracy of the content, the structural characteristics (such as the number of concepts, linkages or propositions, and branches), and the quality of each specific connection (Novak *et al*., 1983; Markham *et al*., 1994; McClure *et al*., 1999; Canas *et al*., 2003). However, not all concept maps are hierarchical (Ruiz-Primo and Shavelson, 1996; Derbentseva *et al*., 2007), particularly when generated for writing. Therefore, as we cannot identify hierarchies or crossovers (links between hierarchies) in students' maps, we focus our structural assessment on the number of concepts, the number of propositions (relationships involving two concepts and the link between them), and the number of branching points (concepts with at least three links connected to them) in each map.[8]

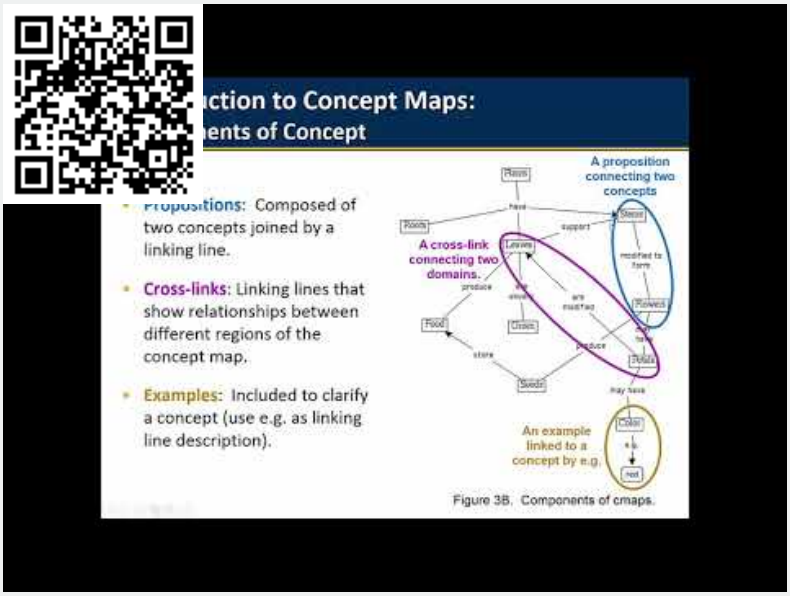
For more information...

Library Guides

- Cornell University - The Learning Strategies Center. Concept Mapping.
- Georgia Tech SCoRE - Introduction to Concept Mapping. [YouTube Tutorial]
- The Learning Center - University of North Carolina at Chapel Hill. Concept Maps.
- Stanford - Center for Teaching and Learning. Concept Mapping.

Tutorials

Georgia Tech SCoRE - Introduction to Concept Mapping.



Handout

Concept Mapping Handouts excerpted from the video above.

Introduction to Concept Mapping Handout.doc

Introduction to Concept Mapping Handout.pdf

Footnotes

1. Digital.gov. Design Operations Guide. Available from: https://digital.gov/guides/hcd/desig...tions/thinking.

2. Green, Amy E., Fettes, Danielle L. and Gregory A. Aarons. J Behav Health Serv Res. 2012 Oct;39(4):10.1007/s11414-012-9291-1. doi: 10.1007/s11414-012-9291-1. publisher's version of this article is available at J Behav Health Serv Res. Publicly available from: https://par.nsf.gov/biblio/10397720-...s-minds-brains.

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5. Boogaard, Kat. What is a Concept Map? Blog post for Miro.com, Oct. 31, 2019. https://miro.com/blog/what-is-concept-map/.

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8. Dowd et al. 2015

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11.4: Student Contributions

Chapter 4

Transplanted and Artificial Uterus: A deep dive into development, health and ethics

S Alvarez, P Flores, N Phulwar and J Thorn

Summary embedded in Chapter 4:3 Infertility and Assisted Reproduction

Male Birth Control: Current Methods

Amira, Isabel, Caroline

Summary embedded in Chapter 4:4 Testicular Reproductive System

Chapter 6

Melanocyte Development: How the Fetus Acquires Skin Color and Fetal Model Representation

Ava Vaccarella, Kailyn Storer, Sonia Lopez and Judith Thorn

Embedded in Chapter 6:3 Week 3 Gastrulation

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Glossary

Glossary Entries

Word(s)	Definition	Source
Ablation	The removal or destruction of a body part or tissue or its function. Ablation may be performed by surgery, hormones, drugs, radiofrequency, heat, or other methods.	Menefee, Whitney, Julie Jenks, Chiara Mazzasette, and Kim-Lelioni Nguyen. 2024. Anatomy and Physiology Glossary. Shared under a CC BY. Available from https://med.libretexts.org/Workbench/Anatomy_and_Physiology_Glossary/01%3A_Introduction_to_Anatomical_Terminology.
Abortion	The removal or destruction of a body part or tissue or its function.	Nelson, Andrea and Katherine Greene. 2022. Glossary. In *Medical Terminology for Healthcare Professions.* Shared under a CC BY 4.0 license. Available from https://med.libretexts.org/Bookshelves/Medicine/Medical_Terminology_for_Healthcare_Professions_(Nelson_and_Greene)/zz%3A_Back_Matter/20%3A_Glossary.
Acetabulum	Large, cup-shaped cavity located on the lateral side of the hip bone; formed by the junction of the ilium, pubis, and ischium portions of the hip bone.	Menefee et al, 2024
Acidosis	A pathologic condition of acid accumulation or depletion of base in the body. The two main types are RESPIRATORY **ACIDOSIS** and metabolic **acidosis**, due to metabolic acid build up.	National Library of Medicine(NLM). Medical Subject Headings (MeSH) thesaurus. https://www.ncbi.nlm.nih.gov/mesh?Db...BMeSH+Terms%5D.
Adenocarcinoma	A malignant epithelial tumor with a glandular organization.	MeSH
Adenomyosis	The extension of endometrial tissue (ENDOMETRIUM) into the MYOMETRIUM. It usually occurs in women in their reproductive years and may result in a diffusely enlarged	MeSH

Word(s)	Definition	Source
	uterus with ectopic and benign endometrial glands and stroma	
Adenosquamous (Carcinoma, Adenosquamous)	A mixed adenocarcinoma and squamous cell or epidermoid carcinoma.	MeSH
Adhesions	Adhesions are bands of scar-like tissue. Normally, internal tissues and organs have slippery surfaces so they can shift easily as the body moves. Adhesions cause tissues and organs to stick together. They might connect the loops of the intestines to each other, to nearby organs, or to the wall of the abdomen. They can pull sections of the intestines out of place. This may block food from passing through the intestine.	National Library of Medicine. MedlinePlus. Public Domain. Available from: https://medlineplus.gov/.
Adipose tissue	Specialized areolar tissue rich in stored fat.	Menefee, Whitney, Julie Jenks, Chiara Mazzasette, and Kim-Lelioni Nguyen. 2021. Human Anatomy (OERI). Shared under a CC BY. Available from https://med.libretexts.org/Bookshelves/Anatomy_and_Physiology/Human_Anatomy_(OERI).
Adjuvant	Supplement, augment, stimulate, activate, potentiate or modulate action or response of medical treatment.	MeSH
Adnexal	Of the uterine appendages (ADNEXA UTERI) including diseases involving the OVARY, the FALLOPIAN TUBES, and ligaments of the uterus (BROAD LIGAMENT; ROUND LIGAMENT)	MeSH
Adrenal glands	Endocrine glands located at the top of each kidney that are important for the regulation of the stress response, blood pressure and blood volume, water homeostasis, and electrolyte levels.	Menefee et al, 2021
Adrenocorticotropic	An anterior pituitary hormone that stimulates the ADRENAL CORTEX and its production of CORTICOSTEROIDS. ACTH is a 39-amino acid polypeptide of which the N-terminal 24-amino acid segment is identical in all species and contains the adrenocorticotrophic activity. Upon further tissue-specific processing, ACTH can yield ALPHA-MSH and corticotrophin-like intermediate lobe peptide (CLIP).	MeSH
Afterbirth	Third stage of childbirth in which the	Lange, Jennifer et al. 2023 General

Word(s)	Definition	Source
	placenta and associated fetal membranes are expelled.	Human Anatomy. LibreTexts, https://med.libretexts.org/Bookshelv...ic_Development. Shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Jennifer Lange et al.
Alveoli (of the breast)	Milk-secreting cells in the mammary gland.	Menefee et al, 2021
Allantois	An extra-embryonic membranous sac derived from the YOLK SAC of REPTILES; BIRDS; and MAMMALS. It lies between two other extra-embryonic membranes, the AMNION and the CHORION. The allantois serves to store urinary wastes and mediate exchange of gas and nutrients for the developing embryo.	MeSH
Amenorrhea	Absence of menstruation.	Nelson & Greene, 2022
Amniocentesis	A procedure for obtaining amniotic fluid.	Nelson & Greene, 2022
Amnion	The innermost membranous sac that surrounds and protects the developing embryo which is bathed in the AMNIOTIC FLUID. Amnion cells are secretory EPITHELIAL CELLS and contribute to the amniotic fluid.	MeSH
Ampulla	A sac-like enlargement of a canal or duct.	Menefee et al, 2024
Androgens	Male sex hormones; for example, testosterone.	Nelson & Greene, 2022
Androstenedione	A delta-4 C19 steroid that is produced not only in the TESTIS, but also in the OVARY and the ADRENAL CORTEX. Depending on the tissue type, androstenedione can serve as a precursor to TESTOSTERONE as well as ESTRONE and ESTRADIOL.	MeSH

Word(s)	Definition	Source
Anemia	A condition in which the number of red blood cells or hemoglobin is deficient.	Nelson & Greene, 2022
Angiogenesis	Development of new blood vessels from existing vessel.	Menefee et al, 2021
Anti-Müllerian hormone (AMH)	A glycoprotein that causes regression of Müllerian ducts. It is produced by Sertoli cells of the testes. In the absence of this hormone, the Müllerian ducts develop into structures of the female reproductive tract. In males, defects of this hormone result in persistent Müllerian duct, a form of male pseudohermaphroditism.	MeSH
Anticoagulants	Agents that prevent BLOOD CLOTTING.	National Library of Medicine(NLM). Medical Subject Headings (MeSH) thesaurus. https://www.ncbi.nlm.nih.gov/mesh?Db...BMeSH+Terms%5D
Antidiuretic hormone (ADH)	A hormone that helps blood vessels constrict and helps the kidneys control the amount of water and salt in the body. This helps control blood pressure and the amount of urine that is made. Antidiuretic hormone is made by a part of the brain called the hypothalamus and is secreted into the blood by the pituitary gland. Certain types of tumors may release high amounts of antidiuretic hormone, which can cause low levels of sodium in the blood and the body to retain water. Also called arginine vasopressin and vasopressin.	National Cancer Institute (NCI) Dictionary of Cancer Terms. Public Domain. Available from: https://www.cancer.gov/publications/dictionaries/cancer-terms.
Antiemetic	Male sex hormones; for example, testosterone.	MeSH
Antrum	Fluid-filled chamber that characterizes a mature tertiary (antral) follicle.	Menefee et al 2021
Apgar Score	A technique used to assess the general wellbeing of a newborn. The newborn is assessed one minute after birth and again five minutes after birth.	Nelson & Greene, 2022
Apocrine glands	Large, branched, specialized sweat glands that empty into the upper portion of a HAIR FOLLICLE instead of directly onto the SKIN.	MeSH
Apoptosis	Programmed cell death.	Nelson & Greene, 2022
Areola	Highly pigmented, circular area surrounding the raised nipple and containing areolar glands that secrete fluid important for lubrication during suckling.	Menefee et al 2021
Aromatase	An enzyme that catalyzes the desaturation	MeSH

Word(s)	Definition	Source
	(aromatization) of the ring A of C19 androgens and converts them to C18 estrogens. In this process, the 19-methyl is removed. This enzyme is membrane-bound, located in the endoplasmic reticulum of estrogen-producing cells of ovaries, placenta, testes, adipose, and brain tissues.	
Arteries	The vessels carrying blood away from the heart.	MeSH
Aspirate	To withdraw fluid, tissue, or other substances from a body cavity, cyst, or tumor	Nelson & Greene, 2022
Atherosclerosis	A hardening of the arteries that involves the accumulation of plaque	Nelson & Greene, 2022
Atresia	Absence or abnormal narrowing of an opening or passage in the body.	
Atrophy	Loss of mass and function.	Menefee et al, 2021
Atypia	Abnormality in cells in tissue.	NCI Dictionary
Autoimmune	Disorders in which the immune system overreacts and begins to attack itself.	Nelson & Greene, 2022
Barbiturates	A class of chemicals derived from barbituric acid or thiobarbituric acid. Many of these are GABA MODULATORS used as HYPNOTICS AND SEDATIVES, as ANESTHETICS, or as ANTICONVULSANTS.	MesH
Bartholin's glands (also, greater vestibular glands)	Glands that produce a thick mucus that maintains moisture in the vulva area; also referred to as the greater vestibular glands	Nelson & Greene, 2022
Basalis	The basal part of the endometrium that is not shed during menstruation.	
Behcet syndrome	Rare chronic inflammatory disease involving the small blood vessels. It is of unknown etiology and characterized by mucocutaneous ulceration in the mouth and genital region and uveitis with hypopyon. The neuro-ocular form may cause blindness and death. SYNOVITIS; THROMBOPHLEBITIS; gastrointestinal ulcerations; RETINAL VASCULITIS; and OPTIC ATROPHY may occur as well.	MeSH
Benign	Non-cancerous.	Nelson & Greene, 2022
Bile	A fluid made by the liver and stored in the gallbladder. Bile is excreted into	NCI Dictionary

Word(s)	Definition	Source
	the small intestine, where it helps digest fat.	
Bilirubin	Substance formed when red blood cells are broken down. Bilirubin is part of the bile, which is made in the liver and is stored in the gallbladder. The abnormal buildup of bilirubin causes jaundice.	NCI Dictionary
Blastocyst	A post-morula preimplantation mammalian embryo that develops from a 32-cell stage into a fluid-filled hollow ball of over a hundred cells. A blastocyst has two distinctive tissues. The outer layer of trophoblasts gives rise to extra-embryonic tissues. The inner cell mass gives rise to the embryonic disc and	MeSH
	eventual embryo proper.	
Bone mineral density (BMD)	A bone mineral density (BMD) test measures how much calcium and other types of minerals are in an area of your bone.	MedlinePlus
Braxton Hicks	Weak and irregular peristaltic contractions that can occur in the second and third trimesters; they do not indicate that childbirth is imminent.	Lange et al, 2023
Broad Ligament	Wide ligament that supports the uterus by attaching laterally to both sides of the uterus and pelvic wall.	Menefee et al, 2021
Brown adipose tissue	Highly vascularized fat tissue that is packed with mitochondria; these properties confer the ability to oxidize fatty acids to generate heat.	Lange et al, 2023
Calcification	Process by	MeSH
	which organic tissue becomes hardened by the physiologic deposit of calcium salts.	
Canalization (defect)	The process of making a channel in part of the body, either naturally or using a medical procedure.	Cambridge Dictionary. English.
Cannula	Short, hollow cylinders or tubes for insertion into a canal, vessel, or body cavity.	MeSH
Capillary	The smallest type of blood vessel. A capillary connects an arteriole (small artery) to a venule (small vein) to form a network of blood vessels in almost all parts of the body.	Nelson & Greene, 2022
Carcinogenesis	The process by which normal cells are transformed into cancer cells.	NCI Dictionary
Carcinoma	Condition in which abnormal cells that look like cancer cells under a	NCI Dictionary

Word(s)	Definition	Source	Word(s)	Definition	Source	Word(s)	Definition	Source
	microscope are found only in the place where they first formed and haven't spread to nearby tissue.				tives 4.0 International (CC BY-NC-ND 4.0) (http://creativecommons.org/licenses/by-nc-nd/4.0/) Available from: https://www.ncbi.nlm.nih.gov/books/NBK499970/.		eyes, impairing vision or causing blindness. The many kinds of cataract are classified by their morphology (size, shape, location) or etiology.	Db...BMeSH+Terms%5D
Cardinal ligament	Cardinal ligament, otherwise known as the transverse cervical ligament, is attached from the lateral aspect of the cervix to the respective pelvic wall. It forms the inferior border of the broad ligament and houses the uterine artery and uterine veins.	Chaudhry SR, Chaudhry K. Anatomy, Abdomen and Pelvis: Uterus Round Ligament. [Updated 2023 Jul 24]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Creative Commons Attribution-NonCommercial-NoDeriva	**Carotid arteries**	Two principal arteries on both sides of the neck that supply blood to the head and neck; each divides into two branches, the internal carotid artery and the external carotid artery.	MeSH	**Celiac Disease**	A malabsorption syndrome that is precipitated by the ingestion of foods containing GLUTEN, such as wheat, rye, and barley. It is characterized by INFLAMMATION of the SMALL	MeSH
			Cataract	Partial or complete opacity on or in the lens or capsule of one or both	National Library of Medicine(NLM). Medical Subject Headings (MeSH) thesaurus. https://www.ncbi.nlm.nih.gov/mesh?			

Word(s)	Definition	Source
	INTESTINE, loss of MICROVILLI structure, failed INTESTINAL ABSORPTION, and MALNUTRITION.	
Cell proliferation	All of the processes involved in increasing CELL NUMBER including CELL DIVISION.	MeSHMeSH
Cervical os (cervix uteri)	Neck portion of the UTERUS between the lower isthmus and the VAGINA forming the cervical canal.	National Library of Medicine(NLM). Medical Subject Headings (MeSH) thesaurus. https://www.ncbi.nlm.nih.gov/mesh?Db...BMeSH+Terms%5D
Cervix	Narrow inferior portion of the uterus that projects into the vagina.	Nelson & Greene, 2022
Chlamydia	A genus of the family CHLAMYDIACEAE whose species cause a variety of diseases in vertebrates including humans, mice, and swine. Chlamydia species are gram-negative and produce glycogen.	
Chloasma		
Choriocarcinoma	A malignant, fast growing tumor that develops from trophoblastic cells (cells that help an embryo attach to the uterus and help form the placenta)	Nelson & Greene, 2022
Chorion	The outermost extra-embryonic membrane surrounding the developing embryo. In REPTILES and BIRDS, it adheres to the shell and allows exchange of gases between the egg and its environment. In MAMMALS, the chorion evolves into the fetal contribution of the PLACENTA.	MeSH
Chorionic villi	Projections of the chorionic membrane that burrow into the endometrium and develop into the placenta.	Lange et al, 2023
Chromatin	Substance consisting of DNA and associated proteins.	Menefee et al 2021
Cilia	Small appendages on certain cells formed by microtubules and modified for movement of materials across the cellular surface.	Menefee et al 2021
Clitoris (glans clitoris)	An organ that originates from the same cells as the glans penis and has abundant nerves that make it important in sexual sensation and orgasm.	Nelson & Greene, 2022
Coagulopathy	Bleeding disorder	MedlinePlu

Word(s)	Definition	Source
Coagulation	The process of the interaction of BLOOD COAGULATION FACTORS that results in an insoluble FIBRIN clot.	MeSH
Coccyx (tailbone)	The small bone at the bottom of the spine. It is made up of 3-5 fused bones. Also called tailbone.	NCI Dictionary
Coccygeus	see Ischiococcygeus	
Collagen	Flexible fibrous proteins that give connective tissue tensile strength.	Menefee et al, 2021
Columnar	Having a tall or long, narrow shape, like a column, as in columnar cells.	NCI Dictionary
Common iliac vein	One of a pair of veins that flows into the inferior vena cava at the level of L5; the left common iliac vein drains the sacral region; divides into external and internal iliac veins near the inferior	Menefee et al, 2021
	portion of the sacroiliac joint.	
Comorbid	The condition of having two or more diseases at the same time.	NCI Dictionary
Confluent	Two things, such as areas of skin or cells that join or come together without any space between them, or flow together in the same direction.	NCI Dictionary
Contraception	The use of drugs, devices, or surgery to prevent pregnancy.	Nelson & Greene, 2022
Contractile myoepithelial cells		
Contraindication	Anything (including a symptom or medical condition) that is a reason for a person to not receive a particular treatment or procedure because it may be harmful. For example, having a bleeding disorder is a contraindicati	NCI Dictionary
	on for taking aspirin because treatment with aspirin may cause excess bleeding.	
Corpus albicans	Nonfunctional structure remaining in the ovarian stroma following structural and functional regression of the corpus luteum.	Menefee et al 2021
Corpus luteum	Transformed follicle after ovulation that secretes progesterone.	Menefee et al 2021
Coxal bones (pelvic bones)	Hip bones.	Menefee et al 2021
Cremaster muscles	Muscles forming the ABDOMINAL WALL including RECTUS ABDOMINIS; ABDOMINAL OBLIQUE MUSCLES,	MeSH

Word(s)	Definition	Source
	transversus abdominis, pyramidalis muscles and quadratus abdominis.	
Curettage	A scraping, usually of the interior of a cavity or tract, for removal of new growth or other abnormal tissue, or to obtain material for tissue diagnosis. It is performed with a curet (curette), a spoon-shaped instrument designed for that purpose	MeSH
Cyst	A closed, sac-like pocket of tissue that can form anywhere in the body. It may be filled with fluid, air, pus, or other material. Most cysts are benign (not cancer).	NCI Dictionary
Cystitis	Inflammation of the lining of the bladder (National Cancer Institute, n.d.)	Nelson & Greene, 2022
Cytokine	A signaling molecule that allows cells to communicate with each other over short distances	Nelson & Greene, 2022
Cytological	Methods used to study CELLS.	MeSH
Cytoplasm	A water-based cellular fluid	Menefee et al, 2024
Cytotrophoblast	Cells lining the outside of the BLASTOCYST. After binding to the ENDOMETRIUM, trophoblasts develop into two distinct layers, an inner layer of mononuclear cytotrophoblasts and an outer layer of continuous multinuclear cytoplasm, the syncytiotrophoblasts, which form the early fetal-maternal interface (PLACENTA).	MeSH
Dartos muscle		
De Novo	The first occurrence of cancer in the body.	MeSH
Decidual cells	Hyperplastic endometrial stromal cells	
Desmoplastic	Causing or forming adhesions or fibrous connective tissue within a tumor.	NCI Dictionary
Detrusor	A muscle which forms a layer of the wall of the bladder	Menefee et al 2024
Diabetes Mellitus	A disease in which the body does not control the amount of glucose (a type of sugar) in the blood and the kidneys make a	Nelson & Green, 2022

Word(s)	Definition	Source
	large amount of urine. This disease occurs when the body does not make enough insulin or does not use it the way it should.	
Diaphragm	A sheet of skeletal muscle separation the thoracic and abdominal cavities that has to contract and relax for you to breathe	Nelson & Green, 2022
Differential diagnosis	Determination of which one of two or more diseases or conditions a patient is suffering from by systematically comparing and contrasting results of diagnostic measures.	MeSH
Diffusion	The movement of a substance from an area of higher concentration to one of lower concentration.	Menefee et al, 2021
Dilapan		

Word(s)	Definition	Source
Dilation	The act of dilating.	MeSH
Dilation and curettage (D&C)	A procedure to scrape and remove tissue from the inner lining of the uterus. The cervix is dilated (made larger) and a curette (spoon-shaped instrument) is inserted into the uterus to remove tissue. The procedure is used to test tissue for signs of disease, after a miscarriage, or to treat certain conditions.	Nelson & Green, 2022
Diploid	A cell containing two matched sets of chromosomes.	Nelson & Green, 2022
Dopamine	One of the catecholamine neurotransmitters in the brain. It is derived from tyrosine and is the precursor to norepinephrine and epinephrine. Dopamine is a major transmitter in the	MeSH

Word(s)	Definition	Source
	extrapyramidal system of the brain, and important in regulating movement.	
Ductus Arteriosus	A temporary connection between pulmonary trunk and aorta in the fetal heart	Menefee et al 2024.
Dysmenorrhea	Painful menstruation.	Nelson & Green, 2022
Dyspareunia	Genital pain before, during, or after intercourse.	Nelson & Green, 2022
Dysplasia	A term used to describe the presence of abnormal cells within a tissue or organ. Dysplasia is not cancer, but it may sometimes become cancer. Dysplasia can be mild, moderate, or severe, depending on how abnormal the cells look under a microscope and how much of the tissue or organ is affected.	NCI Dictionary
Dyspnea	Difficult or labored breathing.	MeSH
Dysregulation	Abnormality	MeSH

Word(s)	Definition	Source
	or impairment in the regulation of a metabolic, physiological, or psychological process.	
Dysuria	Painful urination.	Nelson & Green, 2022
Eclampsia	A very serious condition in pregnant women with hypertension ; patients are at high risk of coma, convulsions, and even death	Nelson & Green, 2022
Ectocervix	he outer part of the neck portion of the UTERUS between the lower isthmus and the VAGINA forming the cervical canal.	MeSH
Ectopic pregnancy	A potentially life-threatening condition in which EMBRYO IMPLANTATION occurs outside the cavity of the UTERUS. Most ectopic pregnancies (>96%) occur in the FALLOPIAN TUBES, known as TUBAL PREGNANCY. They can be in other locations, such as UTERINE CERVIX; OVARY; and abdominal cavity (PREGNANCY, ABDOMINAL).	MeSH
Edema	Swelling caused by excess fluid in body tissues.	NCI Dictionary
Edematous	Relating to or affected with edema **:** abnormally swollen with fluid.	
Ejaculation	The emission of SEMEN to the exterior, resulting from the contraction of muscles surrounding the male internal urogenital ducts.	MeSH
Embolization	A procedure that uses particles, such as tiny gelatin sponges or beads, to block a blood vessel. Embolization may be used to stop bleeding or to block the flow of blood to a tumor or abnormal area of tissue. It may be used to treat some types of liver cancer, kidney cancer, and neuroendocrine tumors. It may also be used to treat uterine fibroids, aneurysms, and other conditions. Types of embolization are arterial embolization, chemoembolization, and radioembolization.	NCI Dictionary
Embyro	A group of blastocyst cells that will become an embryo and thus develop into a baby.	MedlinePlus
Embryogenesis	Human embryogenesis is a complicated process by which a fertilized egg develops into an embryo.	Menefee et al 2021

Word(s)	Definition	Source
Endocervical	The inner part of the neck portion of the UTERUS between the lower isthmus and the VAGINA forming the cervical canal.	MeSH
Endocrine	Cells, tissues, and organs that secrete hormones as a primary or secondary function and play an integral role in normal bodily processes	Nelson & Green, 2022
Endometritis	Inflammation of the ENDOMETRIUM, usually caused by intrauterine infections. Endometritis is the most common cause of postpartum fever.	MeSH
Endometrium	The innermost layer of the uterus. It provides the site of implantation for a fertilized egg and sheds during menstruation if no egg is fertilized.	Menefee et al, 2024
Endothelium	A layer of epithelium that lines the heart, blood vessels (ENDOTHELIUM, VASCULAR), lymph vessels (ENDOTHELIUM, LYMPHATIC), and the serous cavities of the body.	MeSH
Eosinophils	Granular leukocytes with a nucleus that usually has two lobes connected by a slender thread of chromatin, and cytoplasm containing coarse, round granules that are uniform in size and stainable by eosin.	MeSH
Episiotomy	Incision made in the posterior vaginal wall and perineum that facilitates vaginal birth.	Nelson & Green, 2022
Epithelium	Sheets of cells that cover the exterior surfaces of the body, line internal cavities and passageways, and form certain glands; also known as epithelial tissue	Menefee et al, 2024
Erythrocyte	Red blood cell. Mature erythrocytes are non-nucleated, biconcave disks containing HEMOGLOBIN whose function is to transport OXYGEN.	MeSH
Estradiol	The 17-beta-isomer of estradiol, an aromatized C18 steroid with hydroxyl group at 3-beta- and 17-beta-position. Estradiol-17-beta is the most potent form of mammalian estrogenic steroids.	MeSH
Estriol	A hydroxylated metabolite of ESTRADIOL or ESTRONE that has a hydroxyl group at C3, 16-alpha, and 17-beta position and a major urinary estrogen	MeSH
Estrogen	Class of predominantly female sex hormones	Menefee et al 2021

Word(s)	Definition	Source
	important for the development and growth of the female reproductive tract, secondary sex characteristics, the female reproductive cycle, and the maintenance of pregnancy.	
Estrone	An aromatized C18 steroid with a 3-hydroxyl group and a 17-ketone, a major mammalian estrogen.	MeSH
Eversion	Foot movement involving the intertarsal joints of the foot in which the bottom of the foot is turned laterally, away from the midline.	Nelson & Green, 2022
Exocrine	A gland whose secretions leave through a duct that opens directly, or indirectly, to the external environment .	Menefee et al, 2024
Exogenous	Describes substance made outside of the human body.	
Expulsion	Second stage of childbirth, during which the mother bears down with contractions; this stage ends in birth.	Lange, Jennifer et al. 2023 General Human Anatomy. LibreTexts, https://med.libretexts.org/Bookshelv...ic_Development. Page titled 24.4: Maternal Changes During Pregnancy, Labor, and Birth is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Jennifer Lange et al .
External iliac vein	Formed when the femoral vein passes into the body cavity; drains the legs and leads to the common iliac vein.	Menefee et al, 2021
External os	The neck portion of the UTERUS between the lower isthmus and the VAGINA forming the cervical canal.	MeSH
Extrauterine	Existing, formed, or occurring outside the uterus.	
Facilitated diffusion	Diffusion of a substance with the aid of a membrane protein.	Menefee et al, 2021
Fallopian tubes	Ducts that facilitate transport of an ovulated oocyte to the uterus.	Menefee et al 2021
Fascicular	Of, related to, or consisting of fasciculi (slender bundle of anatomical fibers, nerve fibers).	
Fertility	The capacity to conceive or to induce conception. It may refer to either the male or female.	MeSH
Fertilization	Fertilization occurs when sperm and an oocyte combine. Because each of these reproductive cells is a haploid cell containing half of the genetic material needed to form a human being, their combination forms a diploid cell. This new single cell is	Nelson & Green, 2022

Word(s)	Definition	Source
	called a zygote.	
Fibroblasts	Most abundant cell type in connective tissue, secretes protein fibers and matrix into the extracellular space.	Menefee et al, 2021
Fibroid	Benign tumor derived from smooth muscle tissue.	MeSH
Fibrosis	A process in which muscle fibers are replaced by scar tissue.	Nelson & Green, 2022
Fimbriae	Fingerlike projections on the distal uterine tube.	Menefee et al, 2021
Flagella/ Flagellum	A whiplike motility appendage present on the surface cells. Prokaryote flagella are composed of a protein called FLAGELLIN. Bacteria can have a single flagellum, a tuft at one pole, or multiple flagella covering the entire surface. In eukaryotes, flagella are threadlike protoplasmic extensions used to propel flagellates and sperm. Flagella have the same basic structure as CILIA but are longer in proportion to the cell bearing them and present in much smaller numbers.	MeSH
Follicle (ovarian)	Ovarian structure of one oocyte and surrounding granulosa (and later theca) cells.	Menefee et al 2021
Follicle-stimulating Hormone (FSH)	A major gonadotropin secreted by the human adenohypophysis (PITUITARY GLAND, ANTERIOR). Follicle-stimulating hormone stimulates GAMETOGENESIS and the supporting cells such as the ovarian GRANULOSA CELLS, the testicular SERTOLI CELLS, and the LEYDIG CELLS. FSH consists of two noncovalently linked subunits, alpha and beta. The alpha subunit is common in the three human pituitary glycoprotein hormones (TSH, LH, and FSH), but the beta	MeSH

Word(s)	Definition	Source
	subunit is unique and confers its biological specificity.	
Follicular phase	Period of the menstrual cycle representing follicular growth, increase in ovarian estrogen (estrogens) production, and epithelial proliferation of the endometrium. Follicular phase begins with the onset of menstruation and ends with ovulation	MeSH
Folliculogenesis	Development of ovarian follicles from primordial to tertiary under the stimulation of gonadotropins	Menefee et al, 2021
Foley catheter	A urinary catheter is a tube placed in the body to drain and collect urine from the bladder.	MedlinePlus
Foramen Ovale	An opening between right and left atria, which is normal in the fetal heart	Nelson & Green, 2022
Foremilk	The thin,	MeSH
(colostrum)	yellow, serous fluid secreted by the mammary glands during pregnancy and immediately postpartum before lactation begins. It consists of immunologically active substances, white blood cells, water, protein, fat, and carbohydrates.	
Fornix	Superior portion of the vagina.	Nelson & Green, 2022
Fundus	.The part of a hollow organ that is across from, or farthest away from, the organ's opening	Nelson & Green, 2022
Gamete	A specialized sex cell carrying 23 chromosomes.	Nelson & Green, 2022
Genome	The genome is the entire set of DNA instructions found in a cell. In humans, the genome consists of 23 pairs of chromosomes located in the cell's nucleus, as well as a small chromosome	National Human Genome Research Institute. *Talking Glossary of Genomic and Genetic Terms.* Public
	in the cell's mitochondria. A genome contains all the information needed for an individual to develop and function.	Domain. Available from: https://www.genome.gov/genetics-glossary.
Genital wart	Genital warts are soft growths on the skin and mucous membranes of the genitals. They may be found on the penis, vulva, urethra, vagina, cervix, and around and in the anus.	MedlinePlus
Germ-line mutation	Detectable and heritable alteration in the lineage of germ cell.	MeSH
Gestation	The period required for embryonic andfetal development in utero; pregnancy	Nelson & Green, 2022
Gestational trophoblastic neoplasia	A group of diseases arising from pregnancy that are commonly associate	MeSH

Word(s)	Definition	Source
	d with hyperplasia of trophoblasts (TROPHOBLAST) and markedly elevated human CHORIONIC GONADOTROPIN. They include HYDATIDIFORM MOLE, invasive mole (HYDATIDIFORM MOLE, INVASIVE), placental-site trophoblastic tumor (TROPHOBLASTIC TUMOR, PLACENTAL SITE), and CHORIO	
	CARCINOMA. These neoplasms have varying propensities for invasion and spread.	
Gland	An organ that makes one or more substances, such as hormones, digestive juices, sweat, tears, saliva, or milk. Endocrine glands release the substances directly into the bloodstream. Exocrine glands release the substances into a duct or opening to the inside or outside of the body.	NCI Dictionary
Glans penis	Bulbous end of the penis that contains a large number of nerve endings.	Nelson & Green, 2022
Glycogen	A polysaccharide that is converted to glucose.	Nelson & Green, 2022
Gonadotropin-releasing hormone (GnRH)	Homonre released by the hypothalamus that regulates the production of follicle-stimulating hormone and luteinizing hormone frfom the pituitary gland.	Nelson & Green, 2022
Gonorrhea	Acute infectious disease characterized by primary invasion of the urogenital tract.	MeSH
Granulomatous endometritis	defect of leukocyte function in which phagocytic cells ingest but fail to digest bacteria, resulting in recurring bacterial infections with granuloma formation. When chronic granulomatous disease is caused by mutations in the CYBB gene, the condition is inherited in an X-linked	MeSH

Word(s)	Definition	Source
	recessive pattern. When chronic granulomatous disease is caused by CYBA, NCF1, NCF2, or NCF4 gene mutations, the condition is inherited in an autosomal recessive pattern.	
Granulosa	Supportive cells in the ovarian follicle that produce estrogen	Menefee et al, 2021
Haploid	The presence of a single set of chromosomes in an organism's cells. Sexually reproducing organisms are diploid (having two sets of chromosomes, one from each parent). In humans, only the egg and sperm cells are haploid.	National Human Genome Research Institute
Haploid ovum	A mature haploid female germ cell extruded from the OVARY at OVULATION.	MeSH
HDL	HDL stands for high-density lipoproteins. It is sometimes called the "good" cholesterol because it carries cholesterol from other parts of your body back to your liver. Your liver then removes the cholesterol from your body	MedlinePlus
Hematocrit	A lab test which measures the percentage red blood cells in a sample of whole blood	Nelson & Green, 2022
Hematometra	Blood-filled UTERUS.	MeSH
Hemodynamics	The movement and the forces involved in the movement of the blood through the CARDIOVASCULAR SYSTEM.	
Hemoglobin	A protein inside red blood cells that carries oxygen from the lungs to tissues and organs in the body and carries carbon dioxide back to the lungs. Testing for the amount of hemoglobin in the blood is usually part of a complete blood cell (CBC) test.	NCI Dictionary
Hemolytic disease	A condition in which the mother's Rhantibodies cross the placenta inot the fetal bloodstream and destroy the fetal RBC.	Nelson & Green, 2022
Hemorrhage	Excessive bleeding.	Nelson & Green, 2022
Hemorrhagic degeneration	Hemorrhagic infarction of leiomyomas that often occurs during pregnancy.	
Hemosiderin	A type of protein that	MeSH

Word(s)	Definition	Source
	have one or more tightly bound metal ions forming part of their structure.	
Herpes	A group of acute infections caused by herpes simplex virus type 1 or type 2 that is characterized by the development of one or more small fluid-filled vesicles with a raised erythematous base on the skin or mucous membrane. It occurs as a primary infection or recurs due to a reactivation of a latent infection.	MeSH
Hindmilk	opaque, creamy breast milk delivered toward the end of a feeding; rich in fat; satisfies the infant's appetite.	Lange et al, 2023
Hippocampus	A curved elevation of GRAY MATTER extending the entire length of the floor	MeSH
	of the TEMPORAL HORN of the LATERAL VENTRICLE (see also TEMPORAL LOBE).	
Histocompatabilty	The degree of antigenic similarity between the tissues of different individuals, which determines the acceptance or rejection of allografts.	MeSH
Histology	The study of tissues.	Nelson & Green, 2022
Homeostasis	The state of steady internal conditions maintained by living thing.	Nelson & Green, 2022
Human chorionic gonadotropin (HCG)	A gonadotropic glycoprotein hormone produced primarily by the placenta. Similar to the pituitary luteinizing hormone in structure and function, chorionic gonadotropin is involved in maintaining the corpus luteum during	MeSH
	pregnancy. CG consists of two noncovalently linked subunits, alpha and beta.	
Human papilloma virus (HPV)	A group of more than 200 common viruses. Some HPVs, called cutaneous HPVs, are transmitted by casual contact and can infect the skin and cause common skin warts. Other HPVs, known as mucosal HPVs, can infect the moist surfaces or inner lining of some organs and body cavities, such as the cervix, vagina, vulva, penis, anus, mouth, and throat. Infection with some mucosal HPVs (collectively known as low-risk HPVs) can cause warts in or around the genitals, anus, mouth,	NCI Dictionary

Word(s)	Definition	Source
	and respiratory tract but rarely cause cancer. Long-lasting infection with other mucosal HPVs (collectively known as high-risk HPVs) can cause cell changes that become cancer over time if not found and removed. HPV-related cancers include cancers of the cervix, anus, oropharynx, vagina, vulva, and penis. Mucosal HPVs are transmitted through intimate skin-to-skin contact, most often during vaginal, anal, or oral sex. Also called human papillomavirus.	
Hydatidiform mole	Trophoblastic hyperplasia associated with normal gestation, or molar pregnancy. It is characterized by the swelling of the CHORIONIC VILLI and elevated human CHORIONIC GONADOTROPIN. Hydatidiform moles or molar pregnancy may be categorized as complete or partial based on their gross morphology, histopathology, and karyotype.	MeSH
Hydrops	Abnormal	MeSH
fetalis	accumulation of serous fluid in two or more fetal compartments, such as SKIN; PLEURA; PERICARDIUM; PLACENTA; PERITONEUM; AMNIOTIC FLUID. General fetal EDEMA may be of non-immunologic origin, or of immunologic origin as in the case of ERYTHROBLASTOSIS FETALIS.	
Hymen	Thin membrane that sometimes partially covers the entrance to the vagina.	Nelso & Greene, 2022
Hyperandrogenic	When you have an excess amount of androgens (a group of sex hormones) in your body.	MeSH
Hyperbilirubinemia	A condition characterized by an abnormal increase of BILIRUBIN in the blood, which may result in JAUNDICE.	MeSH

Word(s)	Definition	Source
	Bilirubin, a breakdown product of HEME, is normally excreted in the BILE or further catabolized before excretion in the urine.	
Hyperechogenic	A PRENATAL ULTRASONOGRAPHY finding of excessively dense fetal bowel due to MECONIUM buildup.	MeSH
Hyperplasia	Abnormal growth due to the production of cells.	Nelson & Green, 2022
Hypertension	Blood pressure goes below the homeostatic set point when standing.	Nelson & Green, 2022
Hypertrophy	The enlargement of muscles.	Nelson & Green, 2022
Hypothalamus	A region of the forebrain below thethalamus; has function in both the autonomic and endocrine systems and regulates homostatsis.	Nelson & Green, 2022
Hysterectomy	Surgery to remove the uterus and, sometimes, the cervix.	Nelson & Green, 2022
Hysteroscopy	Endoscopic examination of the uterus.	Nelson & Green, 2022
Iatrogenic	Adverse condition in a patient occurring as the result of treatment by a physician, surgeon, or other health professional, especially infections acquired by a patient during the course of treatment.	MeSH
Idiopathic	Something that is unknown.	Nelson & Green, 2022
Iliococcygeus	Muscle that makes up the levator ani along with the pubococcygeus.	Menefee et al, 2021
Iliolumbar		
Iliac artery	Either of two large arteries originating from the abdominal aorta; they supply blood to the pelvis, abdominal wall and legs.	MeSH
Ilium	Superior portion of the hip bone.	Menefee et al, 2021
Immunochemistry	Field of chemistry that pertains to immunological phenomena and the study of chemical reactions related to antigen stimulation of tissues. It includes physicochemical interactions between antigens and antibodies.	MeSH
Immunocompromised	Human or animal whose immunologic mechanism is deficient because of an immunodeficiency disorder or other disease or as the result of the administration of immunosuppressive drugs or radiation.	MeSH
Immunoglobulins	Multi-subunit proteins which function in IMMUNITY. They are produced by B LYMPHOCYTES from the IMMUNOGLOBULIN GENES. They are comprised of two heavy (IMMUNOGLOBULIN HEAVY CHAINS) and two light chains (IMMUNOG	MeSH

Word(s)	Definition	Source
	LOBULIN LIGHT CHAINS) with additional ancillary polypeptide chains depending on their isoforms. The variety of isoforms include monomeric or polymeric forms, and transmembrane forms (B-CELL ANTIGEN RECEPTORS) or secreted forms (ANTIBODIES). They are divided by the amino acid sequence of their heavy chains into five classes (IMMUNOGLOBULIN A; IMMUNOGLOBULIN D; IMMUNOGLOBULIN E; IMMUNOGLOBULIN G; IMMUNOGLOBULIN M) and various subclasses	
Implantation	Process by which a blastocyst embeds itself in the uterine endometrium.	Lange et al, 2023
In utero	In the uterus (womb). *In utero* also refers to the length of time that a fetus is in the uterus of the pregnant female.	Clinical Info.HIV.gov. HIV/AIDS Glossary. https://clinicalinfo.hiv.gov/en/glossary/
In vitro fertilization	A process where the ova is fertilized outside the body and then implanted into the uterus.	Nelson & Green, 2022
Incidence	The number of new cases of a disease diagnosed each year.	NCI Dictionary
Incontinence	Urinary - loss of ability to control micturition.	Nelson & Green, 2022
Infectious	Transmission of infectious disease or pathogens. When transmission is within the same species, the mode can be horizontal or vertical (INFECTIOUS DISEASE TRANSMISSION, VERTICAL).	MeSH
Inflammation	Basic innate immune response characterized by heat, redness, pain, and swelling.	Nelson & Green, 2022
Infundibulum of the uterine tube	Wide, distal portion of the uterine tube terminating in fimbriae.	Menefee et al 2021
Inhibin	Hormone secreted by the gonads that inhibits FSH production by the anterior pituitary ischemia.	Menefee et al 2021
Internal iliac vein	Vein on either side of the body which is formed by the union of the external and internal iliac veins and passes upward to join with its fellow of the opposite side to form the inferior vena cava.	MeSH
Intracytoplasmic sperm injection	An assisted fertilization technique consisting of the	MeSH

Word(s)	Definition	Source
	microinjection of a single viable sperm into an extracted ovum. It is used principally to overcome low sperm count, low sperm motility, inability of sperm to penetrate the egg, or other conditions related to male infertility (INFERTILITY, MALE).	
Intraepithelial	Within the layer of cells that form the surface or lining of an organ.	NCI Dictionary
Intraepithelial neoplasia	Term used to describe the presence of abnormal cells on the surface of or in the tissue that lines an organ, such as the cervix, breast, prostate, anus, vagina, vulva, penis, and mouth.	NCI Dictionary
Intrauterine device (IUD)	A small, plastic T-shaped device that is placed inside the uterus (the small, hollow, pear-shaped organ in a woman's pelvis in which a fetus develops) to prevent pregnancy. IUDs prevent sperm from fertilizing an egg, and prevent fertilized eggs from implanting in the uterus. The use of IUDs is also being studied in the prevention and treatment of endometrial cancer and other conditions. Also called intrauterine device.	NCI Dictionary
Intrauterine insemination	Infertility treatment that is sometimes referred to as "artificial insemination." During this procedure, specially prepared sperm are inserted into the woman's uterus. This treatment may be recommended for couples in which the male has close to normal sperm count and motility (movement) and the ability to produce a semen sample in the office (or, under some circumstances, at home) and the woman has open, functioning fallopian tubes.	Centers for Disease Control and Prevention. "Infertility: Frequently Asked Questions." *Reproductive Health.* (May 2024). Available from: https://www.cdc.gov/reproductive-health/infertility-faq/.
Intravenous	Into or within	Nelson &

Word(s)	Definition	Source
	the vein.	Green, 2022
Involution	Postpartum shrinkage of the uterus back to its pre-pregnancy volume.	Lange et al, 2023
Ischiococcygeus	Muscle that assists the levator ani and pulls the coccyx anteriorly.	Menefee et al, 2021
Ischemia	Insufficient blood flow to the tissues.	Menefee et al, 2021
Ischium	One of three bones that make up the coxal bone of the pelvic girdle. In tetrapods, it is the part of the pelvis that projects backward on the ventral side, and in primates, it bears the weight of the sitting animal.	MeSH
Isthmus	Narrow, medial portion of the uterine tube that joins the uterus.	Menefee et al, 2021
Keratin pearls	Formed by local squamous epithelium accumulation which is easily recognized under a microscope	
	and is considered a marker of well-differentiated squamous cell carcinoma.	
Koilocytosis	The presence of koilocytes (vacuolated pyknotic epithelial cell that has either a clear cytoplasm or a perinuclear halo and that tends to be associated with certain human papillomavirus infections) usually in the anogenital region or the uterine cervix.	Encyclopedia Brtiannica. *Merriam Webster Dictionary.*
Labia	Lips; can refer to the lips of the mouth or the folds of hair-covered skin that begin just posterior to the mons pubis.	Menefee et al, 2021
Labia majora	Outer lips of the vagina.	MedlinePlus
Labia minora	Inner vagina lips.	MedlinePlus
Lactation	The processes of milk secretion by the maternal MAMMARY GLANDS after PARTURITION. The	MeSH
	proliferation of the mammary glandular tissue, milk synthesis, and milk expulsion or let down are regulated by the interactions of several hormones including ESTRADIOL; PROGESTERONE; PROLACTIN; and OXYTOCIN.	
Lactiferous ducts	Ducts that connect the mammary glands to the nipple and allow for the transport of milk.	Menefee et al 2021
Lactiferous sinus	Area of milk collection between alveoli and lactiferous duct.	Menefee et al 2021
Lactocytes		
Lactogen	A polypeptide hormone of approximately 25 kDa that is produced by the SYNCYTIOTROPHOBLASTS of the PLACENTA, also known as chorionic somatomammotropin. It	MeSH

Word(s)	Definition	Source
	has both GROWTH HORMONE and PROLACTIN activities on growth, lactation, and luteal steroid production. In women, placental lactogen secretion begins soon after implantation and increases to 1 g or more a day in late pregnancy. Placental lactogen is also an insulin antagonist.	
Lamina propria	A type of connective tissue found under the thin layer of tissues covering a mucous membrane.	NCI Dictionary
Laminaria	A genus of BROWN ALGAE in the family Laminariaceae. Dried pencil-like pieces may be inserted in the cervix where they swell as they absorb moisture, serving as osmotic dilators.	MeSH
Lanugo		
Laparoscopy	Procedure that uses a laparoscope, inserted through the abdominal wall, to examine the inside of the abdomen.	Nelson & Green, 2022
Laparotomy	A surgical incision made in the wall of the abdomen.	Nelson & Green, 2022
LDL Low density lipoproteins	A class of lipoproteins of small size (18-25 nm) and light (1.019-1.063 g/ml) particles with a core composed mainly of CHOLESTEROL ESTERS and smaller amounts of TRIGLYCERIDES. The surface monolayer consists mostly of PHOSPHOLIPIDS, a single copy of APOLIPOPROTEIN B-100, and free cholesterol molecules. The main **LDL** function is to transport cholesterol and cholesterol esters to extrahepatic tissues.	MeSH
Leiomyoma	A benign tumor derived from smooth muscle tissue, also known as a fibroid tumor. They rarely occur outside of the UTERUS and the GASTROINTESTINAL TRACT but can occur in the SKIN and SUBCUTANEOUS TISSUE, probably arising from the smooth muscle of small blood vessels in these tissues.	MeSH
Lesions	Areas of abnormal tissue.	Nelson & Green, 2022
Let-down reflex	release of milk from the alveoli triggered by infant suckling.	Lange et al, 2023
Leukocyte	White blood cell. These include granular leukocytes (BASOPHILS; EOSINOPHILS; and NEUTROPHILS) as well as non-	MeSH

Word(s)	Definition	Source
	granular leukocytes (LYMPHOCYTES and MONOCYTES).	
Leukorrhea	A clear or white discharge from the VAGINA, consisting mainly of MUCUS.	MeSH
Levator ani	Muscle that makes up the levator ani along with the iliococcygeus.	Menefee et al, 2021
Lichen planus	An inflammatory, pruritic disease of the skin and mucous membranes, which can be either generalized or localized. It is characterized by distinctive purplish, flat-topped papules having a predilection for the trunk and flexor surfaces.	MeSH
Ligaments	Shiny, flexible bands of fibrous tissue connecting together articular extremities of bones. They	MeSH
	are pliant, tough, and inextensile.	
Lightening	Descent of the fetus lower into the pelvis in late pregnancy; also called “dropping”.	Lange et al, 2023
Linea Nigra	Linea Nigra is a dark vertical line that appears on the midline of the belly during pregnancy.	MedlinePlus
Lipid-soluble		
Lipoproteins	Lipid-protein complexes involved in the transportation and metabolism of lipids in the body. They are spherical particles consisting of a hydrophobic core of TRIGLYCERIDES and CHOLESTEROL ESTERS surrounded by a layer of hydrophilic free CHOLESTEROL; PHOSPHOLIPIDS; and	MeSH
	APOLIPOPROTEINS.	
Lobules	Ducts in the breast.	MedlinePlus
Localized	In medicine, describes disease that is limited to a certain part of the body. For example, localized cancer is usually found only in the tissue or organ where it began, and has not spread to nearby lymph nodes or to other parts of the body. Some localized cancers can be completely removed by surgery.	NCI Dictionary
Lociha	Postpartum vaginal discharge that begins as blood and ends as a whitish discharge; the end of lochia signals that the site of placental attachment has healed.	
Lumbosacral	Region of the back including the LUMBAR VERTEBRAE, SACRUM,	MeSH

Word(s)	Definition	Source
	and nearby structures.	
Lumen	A hollow passageway through which blood flows.	Menefee et al, 2024
Luteal phase	The period in the menstrual cycle that follows ovulation, characterized by the development of the corpus luteum, an increase in progesterone production by the ovary, and secretion by the glandular epithelium of the endometrium. The luteal phase begins with ovulation and ends with the onset of menstruation.	MeSH
Luteinization	Formation of the corpus luteum. This process includes capillary invasion of the ruptured ovarian follicle, hypertrophy of the granulosa cells and the theca cells, and the production of progesterone. Luteinization	MeSH
	is regulated by luteinizing hormone.	
Luteinizing hormone (LH)	The anterior pituitary hormone that triggers ovulation and the production of ovarian hormones in females and the production of testosterone in males.	Menefee et al, 2021
Lymph	The term used to describe interstitial fluid once it has entered the lymphatic system	Nelson & Greene, 2022
Lymph nodes	One of the bean-shaped organs found associated with the lymphatic vessels	Nelson & Greene, 2022
Lymphatic system	Network of lymphatic vessels, lymph nodes, and ducts that carries lymph from the tissues and back to the bloodstream	Menefee et al, 2024
Lymphocytes	The second most common type of leukocyte and are essential for the immune response.	Nelson & Greene, 2022
Lymph-vascular	Of, relating to, or containing	Encyclopedia Brtiannica. *Merriam*
	lymphatic vessels.	*Webster Dictionary.*
Macroscopic	Observable by the naked eye.	Encyclopedia Brtiannica. *Merriam Webster Dictionary.*
Malignancy	Cancerous.	Nelson & Greene, 2022
Mammary glands	Modified sweat glands that produce breast milk.	Nelson & Greene, 2022
Mammogram	Radiographic image of the breast.	Nelson & Greene, 2022
Meconium	Fetal wastes consisting of ingested amniotic fluid, cellular debris, mucus, and bile.	Nelson & Greene, 2022
Medical abortion (MAB)	*see Abortion*	
Meiosis	Shedding of the inner portion of the endometrium out through the vagina; also referred to as menstruation.	Menefee et al 2021
Melanocyte-stimulating hormone	Peptides with the ability to stimulate pigmented cells MELANOCYTES in mammals and MELANOPHORES in	MeSH

Word(s)	Definition	Source
	lower vertebrates. By stimulating the synthesis and distribution of MELANIN in these pigmented cells, they increase coloration of skin and other tissue.	
Menarche	First menstruation in a pubertal female.	Nelson & Greene, 2022
Menopause	Cessation of the menstrual cycle; is considered complete when a woman has not menstruated in a full year.	Nelson & Greene, 2022
Menses	shedding of the inner portion of the endometrium out though the vagina; also referred to as menstruation.	Menefee et al, 2021
Menstrual cycle	A sequence of events in the uterus that repeats itself and that involves thickening, deterioration, and shedding of the endometrium; uterine cycle	DiGiovanna, 2023
Mesenchymal	Refers to cells that develop into connective tissue, blood vessels, and lymphatic tissue.	NCI Dictionary
Mesoderm	The middle germ layer in the embryo.	Nelson & Greene, 2022
Mesothelium	Simple squamous epithelial portion of serous membranes, such as the superficial portion of the epicardium (the visceral pericardium) and the deepest portion of the pericardium (the parietal pericardium).	Menefee et al, 2021
Metabolic syndrome	Metabolic syndrome is the name for a group of risk factors for heart disease, diabetes, and other health problems. You can have just one risk factor, but people often have several of them together. When you have at least three of them, it is called metabolic syndrome.	MedlinePlus
Methotrexate	An antineoplastic antimetabolite with immunosuppressant properties. It is an inhibitor of TETRAHYDROFOLATE DEHYDROGENASE and prevents the formation of tetrahydrofolate, necessary for synthesis of thymidylate, an essential component of DNA.	MeSH
Mesovarium	An extension of the peritoneum that connects the ovaries to the broad ligament.	Menefee et al 2021
Metaplasia	A condition in which there is a change of one adult cell type to another similar adult cell type.	MeSH
Metastasis	The process in	Nelson &

Word(s)	Definition	Source
	which cancer spreads from one part of the body to another.	Greene, 2022
Methotrexate	An antineoplastic antimetabolite with immunosuppressant properties. It is an inhibitor of TETRAHYDROFOLATE DEHYDROGENASE and prevents the formation of tetrahydrofolate, necessary for synthesis of thymidylate, an essential component of DNA.	MeSH
Metrorrhagia	Excessive bleeding from	Nelson & Greene, 2022
	the uterus not related to menstruation.	
Mifepristone	A derivative of the synthetic progestin norethindrone with antiprogesterone activity. Mifepristone competitively binds to the progesterone receptor, resulting in inhibition of the effects of endogenous or exogenous progesterone. This agent also exhibits antiglucocorticoid and weak antiandrogenic activities.	National Cancer Institute. NCI Drug Dictionary. Public Domain. Available from: https://www.cancer.gov/publications/dictionaries/cancer-drug
Misoprostol	A drug used to end early pregnancies. It is also being studied in the treatment of some types of cancer and other conditions. Mifepristone blocks the action of progesterone, a hormone that helps some cancers grow. It is a type of antiprogesterone. Also called	NCI Dictionary
	Mifeprex and RU 486.	
Mitochondria	A membranous, bean-shaped organelle that is the “energy transformer” of the cell.	Menefee et al 2024
Mitosis	Type of CELL NUCLEUS division by means of which the two daughter nuclei normally receive identical complements of the number of CHROMOSOMES of the somatic cells of the species.	MeSH
Mitotic	Having to do with the presence of dividing (proliferating) cells.	NCI Dictionary
Molar pregnancy (Hydatiform mole)	Results from abnormal fertilization of the oocyte (egg). It results in an abnormal fetus. The placenta grows normally with little or no growth of the fetal tissue. The placental tissue forms a mass in the uterus. On	MedlinePlus

Word(s)	Definition	Source
	ultrasound, this mass often has a grape-like appearance, as it contains many small cysts.	
Monoclonal	Produce by a single clone of cells.	MeSH
Mons pubis	A pad of fat that is located at the anterior, over the pubic bone. After puberty, it becomes covered in pubic hair.	Nelson & Greene, 2022
Montgomery glands		
Morphology	The science of the form and structure of organisms (plants, animals, and other forms of life).	NCI Dictionary
Motility	The movement of cells from one location to another. Distinguish from CYTOKINESIS which is the process of	MeSH
	dividing the CYTOPLASM of a cell.	
Mucoid	Resembling mucus.	Encyclopedia Brtiannica. *Merriam Webster Dictionary*
Mucopolysaccharides	Long chains of sugar molecules that are found throughout the body, often in mucus and in fluid around the joints. They are more commonly called glycosaminoglycans.	MedlinePlus
Mucopurulent	Containing both mucus and pus.	Encyclopedia Brtiannica. *Merriam Webster Dictionary*
Mullerian ducts	A pair of ducts near the WOLFFIAN DUCTS in a developing	MeSH
	embryo. In the male embryo, they degenerate with the appearance of testicular ANTI-MULLERIAN HORMONE. In the absence of anti-Mullerian hormone, Mullerian ducts give rise to the female reproductive tract, including the OVIDUCTS; UTERUS; CERVIX; and VAGINA.	
Multigravida	A woman who has been pregnant more than once.	Encyclopedia Brtiannica. *Merriam Webster Dictionary*
Mutation	Any change in the DNA sequence of a cell. Mutations may be caused by mistakes during cell division, or they may be caused by exposure to DNA-damaging agents in the environment. Mutations can be harmful,	NCI Dictionary

Word(s)	Definition	Source
	beneficial, or have no effect. If they occur in cells that make eggs or sperm, they can be inherited; if mutations occur in other types of cells, they are not inherited. Certain mutations may lead to cancer or other diseases. A mutation is sometimes called a variant.	
Myomectomy	Surgical removal of a LEIOMYOMA of the UTERUS.	MeSH
Myometrium	The smooth muscle layer of uterus that allows for uterine contractions during labor and expulsion of menstrual blood.	Menefee et al, 2021
Necrosis	Accidental death of cells and tissues.	Menefee et al, 2021
Neoplasia	New abnormal growth of tissue. Malignant neoplasms show a greater degree of anaplasia and have the properties of invasion and metastasis, compared to benign neoplasms.	MeSH
Neoplasm	New abnormal growth of tissue. Malignant neoplasms show a greater degree of anaplasia and have the properties of invasion and metastasis, compared to benign neoplasms.	MeSH
Neuroendocrine	Having to do with the interactions between the nervous system and the endocrine system. Neuroendocrine describes certain cells that release hormones into the blood in response to stimulation of the nervous system.	NCI Dictionary
Neurogenesis	Formation of NEURONS which involves the differentiation and division of STEM CELLS in which one or both of the daughter cells become neurons.	MeSH
Neutrophilic	Related to granulocytes that stain with a neutral dye and are the most numerous of the leukocytes; especially active against bacteria.	Menefee et al 2021
Nodule	Growth or lump that may be malignant or benign.	Nelson & Greene, 2022
Nonshivering thermogenesis	Process of breaking down brown adipose tissue to produce heat in the absence of a shivering response.	Lange et al, 2023
Nuchal Translucency Measurement	A prenatal ultrasonography measure	MeSH

Word(s)	Definition	Source
	ment of the soft tissue behind the fetal neck. Either the translucent area below the skin in the back of the fetal neck (nuchal translucency) or the distance between occipital bone to the outer skin line (nuchal fold) is measured.	
Obstetric conjugate	Narrowest fixed distance through which a baby's head must pass during vaginal delivery (10 com).	
Obstetrician	Qualified medical professionals who specialize in OBSTETRICS - a medical-surgical specialty concerned with management and care of women during pregnancy, parturition, and the puerperium.	MeSH
Obturator internus	muscle deep to the gluteus maximus on the lateral surface of the thigh that laterally rotates the femur at the hip.	Menefee et al, 2021
Occiput	Prominence on the back of the head.	MedlinePlus
Oncogene	Gene that is a mutated form of a gene involved in normal cell growth and may cause the growth of cancer cells.	Menefee et al, 2021
Oncoprotein (Oncogene proteins)	Proteins coded by oncogenes. They include proteins resulting from the fusion of an oncogene and another gene (ONCOGENE PROTEINS, FUSION).	MeSH
Ontogenesis	Development of course of development of an organism.	
Oocyte	A cell that results from the division of the oogonium and undergoes meiosis I at the LH surge and meiosis II at fertilization to become a haploid ovum.	Menefee et al 2021
Oogenesis	Process by which oogonia divide by mitosis to primary oocytes, which undergo meiosis to produce the secondary oocyte and, upon fertilization, the ovum.	Menefee et al 2021
Oogonia	Ovarian stem cells that undergo mitosis during female fetal development to form primary oocytes.	Menefee et al 2021
Opiates	A substance used to treat pain or cause	NCI Dictionary

Word(s)	Definition	Source
	sleep. Opiates are made from opium or have opium in them. Opiates bind to opioid receptors in the central nervous system. Examples of opiates are codeine, heroin, and morphine. An opiate is a type of analgesic agent.	
Oropharynx	Part of the pharynx continuous with the oral cavity that functions in respiration and digestion.	Menefee et al, 2021
Osmotic	Having to do with osmosis (the passage of a liquid through a membrane from a less concentrated solution to a more concentrated one). This causes the more concentrated solution to become diluted, and makes the concentrations in both solutions more equal. Osmotic also refers to a	NCI Dictionary
	type of laxative that increases the amount of water in the large intestine, which softens the stool to help it pass more easily.	
Osteoblast	The cell responsible for forming new bone	Nelson & Greene, 2022
Osteoclast	A large multinuclear cell associated with the BONE RESORPTION. An odontoclast, also called cementoclast, is cytomorphologically the same as an **osteoclast** and is involved in CEMENTUM resorption.	MeSH
Osteoporosis	A disease characterized by a decrease in bone mass that occurs when the rate of bone resorption exceeds the rate of bone formation.	Nelson & Greene, 2022
Ovalis		
Ovary/Ovaries	Female gonads that produce	Menefee et al, 2021
	oocytes and sex steroid hormones (notably estrogen and progesterone).	
Ovarian ligament	A fibrous ligament that connects the ovary to the lateral surface of the uterus	Nelson & Greene, 2022
Ovulation	Release of a secondary oocyte and associated granulosa cells from an ovary.	Menefee et al 2021
Ovum	Haploid female gamete resulting from completion of meiosis II at fertilization.	Menefee et al 2021
Oxytocin	Hypothalamic hormone stored in the posteriorpituitary gland and important in stimulating uterine contractions in labor, milk ejection during breastfeeding, and feelings of attachment (also produced in males).	Nelson & Greene, 2022
Pap smear Papanicolaou smear	A procedure in which a small brush is used to gently remove cells from the surface of the	Menefee et al 2024

Word(s)	Definition	Source
	cervix and the area around it so they can be checked under a microscope for cervical cancer or cell changes that may lead to cervical cancer.	
Papillary	Of, relating to, being, or resembling a papilla or nipple-shaped projection, mass or structure; marked by the presence of papillae.	Encyclopedia Brtiannica. *Merriam Webster Dictionary.*
Paracervical block		
Paracrine	Cellular signaling in which a factor secreted by a cell affects other cells in the local environment.	Nelson & Greene, 2022
Paraventricular nucleus (PVN)	Nucleus in the anterior part of the hypothalamus.	MeSH
Parietal branches	Group of arterial branches of the thoracic aorta; includes those that supply blood to the thoracic cavity, vertebral column, and the superior	Menefee et al, 2021
	surface of the diaphragm.	
Parturition	Childbirth.	Nelson & Greene, 2022
Pathogen	An organism that causes a disease.	Menefee et al, 2024
Pedunculated	Having, growing on, or being attached by a peduncle (narrow stalk by which a tumor or polyp is attached).	Encyclopedia Brtiannica. *Merriam Webster Dictionary.*
Pelvic	Pertaining to the pelvis.	Nelson & Greene, 2022
Pelvic diaphragm	Muscular sheet that comprises the levator ani and the ischiococcygeus.	Menefee et al, 2021
Pelvic girdle	Hip girdle; consists of a single hip bone, which attaches a lower limb to the sacrum of the axial skeleton.	Menefee et al, 2021
Pelvic inflammatory disease (PID)	A condition in which the female reproductive organs are inflamed. It may affect the uterus, fallopian tubes, ovaries, and certain ligaments. PID is usually caused by a	NCI Dictionary
	bacterial infection. It may cause infertility and an increased risk of an ectopic pregnancy (pregnancy in the fallopian tubes). Also called pelvic inflammatory disease.	
Pelvis	The space or compartment surrounded by the pelvic girdle (bony pelvis). It is subdivided into the greater pelvis and LESSER PELVIS. The pelvic girdle is formed by the PELVIC BONES and SACRUM.	MeSH
Perimenopause	The transitional period before and after menopause wherein the menstrual cycle is irregular and hormone levels widely fluctuate.	Nelson & Greene, 2022
Perimetrium	The outer epithelial layer of the uterine wall.	Menefee et al 2021
Perineal tear	Tearing of your vagina and the surrounding tissues.	MedlinePlus
Perineum	Diamond-	Menefee et al

Word(s)	Definition	Source
	shaped region between the pubic symphysis, coccyx, and ischial tuberosities.	2021
Peristalsis	The rippling motion of muscles in the intestine or other tubular organs characterized by the alternate contraction and relaxation of the muscles that propel the contents onward.	NCI Dictionary
Peritoneal cavity	The space enclosed by the peritoneum, divided into two portions, the greater sac and the lesser sac or omental bursa, which lies behind the stomach. The foramen of Winslow, or epiploic foramen, connects the two sacs.	MeSH
Peritoneum	Serous membrane that lines the abdominopelvic cavity and covers the organs found there.	Menefee et al, 2021
Peritonitis	INFLAMMATION of the PERITONEUM lining the ABDOMINAL CAVITY as the result of infectious, autoimmune, or chemical processes. Primary peritonitis is due to infection of the PERITONEAL CAVITY via hematogenous or lymphatic spread and without intra-abdominal source. Secondary peritonitis arises from the ABDOMINAL CAVITY itself through RUPTURE or ABSCESS of intra-abdominal organs.	MeSH
Periumbilical	Region of the body that immediately surrounds the umbilicus.	
Phagocytes	Cells that can carry out the process of PHAGOCYTOSIS.	MeSH
Physiological	Area around the belly button.	MedlinePlus
Pituitary gland (neurohypophysis)	A bean-sized organ suspended from the hypothalamus that produces, stores, and secretes hormones in response to hypothalamic stimulation (also called hypophysis).	Menefee et al 2021
Placenta	A highly vascularized mammalian fetal-maternal organ and major site of transport of oxygen, nutrients, and fetal waste products. It includes a fetal portion (CHORIONIC VILLI) derived from TROPHOBLASTS and a maternal portion (DECIDUA) derived from the uterine ENDOMETRIUM. The placenta produces an array of steroid, protein and peptide hormones (PLACENTAL	MeSH

Word(s)	Definition	Source
	HORMONES).	
Placenta previa	Abnormal placentation in which the PLACENTA implants in the lower segment of the UTERUS (the zone of dilation) and may cover part or all of the opening of the CERVIX. It is often associated with serious antepartum bleeding and PREMATURE LABOR	MeSH
Placental abruptio	Premature separation of the normally implanted PLACENTA from the UTERUS. Signs of varying degree of severity include UTERINE BLEEDING, uterine MUSCLE HYPERTONIA, and FETAL DISTRESS or FETAL DEATH.	MeSH
Placental retention	placenta that fails to be expelled after BIRTH of the FETUS. A PLACENTA is retained when the UTERUS fails to contract after the delivery of content, or when the placenta is abnormally attached to the MYOMETRIUM.	MeSH
Plasma cells	A type of B lymphocyte that produces antibodies, which bind to specific foreign or abnormal antigens in order to destroy them.	Nelson & Greene, 2022
Plasminogen activators	A heterogeneous group of proteolytic enzymes that convert plasminogen to fibrinolysin. They are concentrated in the lysosomes of most cells and in the vascular endothelium, particularly in the vessels of the microcirculation.	MeSH
Pleomorphic	Occurring in various distinct forms. In terms of cells, having variation in the size and shape of cells or their nuclei.	NCI Dictionary
Pluripotent	Able to mature or develop in any of several ways.	NCI Dictionary.
POC		
Polymenorrhea	Variations of MENSTRUATION which may be indicative of disease.	MeSH
Polyp	A growth that protrudes from a mucous membrane (National Cancer Institute).	Nelson & Greene, 2022
Polypoid	Organism whose genomes consist of more than two complete sets of chromosomes.	
Pouch of Douglas Douglas Pouch	A sac or recess formed by a fold of the peritoneum.	Menefee et al 2021
Preeclampsia	The abnormal condition in pregnancy where the patient experiences hypertension, edema and protinuria.	Nelson & Greene, 2022
Prenatal	Having to	Nelson & Greene, 2022

Word(s)	Definition	Source
	do with the time a female is pregnant, before birth occurs; also called antenatal.	
Presacral	Presacral space is the area between the rectum and lowest part of your the spine, which is called the sacrum. The presacral space is inside the pelvis, behind the rectum and in front of the coccyx and sacrum.	
Prevalence	The total number of cases of a given disease in a specified population at a designated time. It is differentiated from INCIDENCE, which refers to the number of new cases in the population at a given time.	MeSH
Primordial follicles	Least developed ovarian follicles that consist of a	Menefee et al, 2021
	single oocyte and a single layer of flat (squamous) granulosa cells.	
Progesterone	A principal sex hormone, most of which is produced by the ovaries.	DiGiovanna, 2023
Progestins	Compounds that interact with PROGESTERONE RECEPTORS in target tissues to bring about the effects similar to those of PROGESTERONE.	MeSH
Proinflammatory	Promoting inflammation: capable of causing inflammation.	Encyclopedia Brtiannica. *Merriam Webster Dictionary.*
Prolactin	Pituitary hormone that establishes and maintains the supply of breast milk; also important for the mobilization of maternal micronutrients for breast milk.	Lange et al 2023
Proliferative phase	Phase of the menstrual cycle in which the endometrium proliferates.	Menefee et al, 2021
Prolapse	The protrusion of an organ or part of an organ into a natural or artificial orifice. *see also Uterine prolapse*	Nelson & Greene, 2022
Pronuclei		
Prophylactic	In medicine, something that prevents or protects.	NCI Dictionary
Prophyria	Porphyrias are a group of genetic disorders caused by problems with how your body makes a substance called heme. Heme is found throughout the body, especially in your blood and bone marrow, where it carries oxygen.	MedlinePlus
Prostaglandins	A group of compounds derived from unsaturated 20-carbon fatty acids, primarily arachidonic acid, via the cyclooxygenase pathway. They are extremely potent mediators of	MeSH

Word(s)	Definition	Source
	a diverse group of physiological processes.	
Pubic symphysis	Joint formed by the articulation between the pubic bodies of the right and left hip bones. joint formed by the articulation between the pubic bodies of the right and left hip bones.	Menefee et al, 2021
Pubis	Anterior portion of the hip bone.	Menefee et al, 2021
Pubocervical ligament	Ligament attached to the cervix and extends to the posterior surface of the pubic symphysis.	Chaudhry et al, 2023
Pubococcygeus	muscle that makes up the levator ani along with the iliococcygeus.	Menefee et al, 2021
Puboprostaticum		
Puborectalis		
Pubovaginalis		
Pudendal nerve	A nerve which originates in the sacral spinal cord (S2 to S4) and innervates the PERINEUM, the external GENITALIA, the external ANAL SPHINCTER and the external urethral sphincter. It has three major branches: the perineal nerve, inferior anal nerves, and the dorsal nerve of penis or clitoris.	MeSH
Pulmonary alveoli	Small polyhedral outpouchings along the walls of the alveolar sacs, alveolar ducts and terminal bronchioles through the walls of which gas exchange between alveolar air and pulmonary capillary blood takes place.	MeSH
Pulmonary trunk	The very large artery referred to as a trunk, a term indicating that the vessel gives rise to several smaller arteries.	Menefee et al, 2024
Pyogenic	Pus-producing.	MedlinePlus
Quickening	Fetal movements that are strong enough to be felt by the mother.	Lange et a;. 2023
Radiation	Energy released in the form of particle or electromagnetic waves. Common sources of radiation include radon gas, cosmic rays from outer space, medical x-rays, and energy given off by a radioisotope (unstable form of a chemical element that releases radiation as it breaks down and becomes more stable). Radiation can damage cells. It is used to diagnose and treat some types of cancer.	NCI Dictionary
Raphae		
Retrograde	A backward movement or a movement that is opposite to the usual	Cambridge Dictionary

Word(s)	Definition	Source
	direction of flow.	
RH status	When blood typing is done to see if you have Rh factor on the surface of your red blood cells, the results will be one of these: • Rh+ (positive), if you have this cell surface protein • Rh- (negative), if you do not have this cell surface protein.	MedlinePlus
Round ligament	Cord-like fibrous tissue structure that connects two articular extremities of bones, ligaments and /or cartilages.	MeSH
Rugae (vagina)	Folds of skin in the vagina that allow it to stretch during intercourse and childbirth.	Menefee et al, 2023
Saccular	Outward protrusion.	MeSH
Sacral plexus	Nerve plexus associated with the lower lumbar and sacral spinal nerves.	Menefee et al, 2021
Sacrococcygeal	The body region between (and flanking) the SACRUM and COCCYX.	MeSH
Sacroiliac	The immovable joint formed by the lateral surfaces of the SACRUM and ILIUM.	MeSH
Sacrospinous ligament	Ligament that spans the sacrum to the ischial spine of the hip bone.	Menefee et al, 2021
Sacrotuberous ligament	Ligament that spans the sacrum to the ischial tuberosity of the hip bone.	Menefee et al, 2021
Sacrum	Single bone located near the inferior end of the adult vertebral column that is formed by the fusion of five sacral vertebrae; forms the posterior portion of the pelvis.	Menefee et al, 2021
Scrotal septum		
Scrotum	External pouch of skin and muscle that houses the testes.	Nelson & GrGreene, 2022
Sebaceous glands	Small, sacculated organs found within the DERMIS. Each gland has a single duct that emerges from a cluster of oval alveoli. Each alveolus consists of a transparent BASEMENT MEMBRANE enclosing epithelial cells.	MeSH
Serous membrane	One of the thin membranes that cover the walls and organs in the thoracic and abdominopelvic cavities.	Menefee et al 2024
Serous space	The very thin, fluid-filled space between the parietal and visceral layers.	Menefee et al 2024
Sessile	Attached permanently or established.	Encyclopedia Brtiannica. *Merriam Webster Dictionary.*
Shunt	Circulatory shortcut that diverts the flow of blood from one region to another.	Lange et al, 2023

Word(s)	Definition	Source
Somatic	Having to do with the body.	NCI Dictionary
Somatotrophs (Growth Hormone (GH)	Anterior pituitary cells which produce GROWTH HORMONE.	MeSH
Sperm	The male gamete.	Menefee et al, 2021
Sphincter	A ring-shaped muscle that relaxes or tightens to open or close a passage or opening in the body. Examples are the anal sphincter (around the opening of the anus) and the pyloric sphincter (at the lower opening of the stomach).	NCI Dictionary
Squamocolumnar junction	The area around the opening of the cervix where the endocervix (inner part) and ectocervix (outer part) come together. This area contains both glandular cells (cells that make mucus) from the endocervix and squamous cells (thin, skin-like cells) from the ectocervix. Most abnormal cell changes and most cervical cancers begin in the squamous cells of the squamocolumnar junction. Also called transformation zone.	NCI Dictionary
Squamous	Flat cell that looks like a fish scale under a microscope. These cells are found in the tissues that form the surface of the skin, the passages of the respiratory and digestive tracts, and the lining of the hollow organs of the body (such as the bladder, kidney, and uterus, including the cervix).	NCI Dictionary
Stratum basale	The deepest layer of the epidermis.	Nelson & Green, 2022
Stratum functionalis	A highly vascularized mucosal layer that undergoes monthly cyclical changes and is lost during menstruation.	
Stress incontinence	Stress urinary incontinence occurs when your bladder leaks urine during physical activity or exertion. It may happen when you cough, sneeze, lift something heavy, change positions, or exercise.	MedlinePlus
Striae	Stretch marks.	MedlinePlus
Stroma	The cells and tissues that support and give structure to organs, glands, or other tissues in the body. The stroma is mostly made up of connective tissue, blood vessels, lymphatic vessels, and nerves. It provides nutrients to the tissue or organ and removes waste and extra fluid. The stroma may also be	NCI Dictionary

Word(s)	Definition	Source
	involved in the body's immune response and in the growth and spread of cancer cells.	
Stromal cells	Connective tissue cells of an organ found in the loose connective tissue. These are most often associated with the uterine mucosa and the ovary as well as the hematopoietic system and elsewhere.	MeSH
Subcutaneous	Beneath, or under, all the layers of the skin.	Nelson & Greene, 2022
Superficial (body part)	Describes a position nearer to the surface of the body.	Nelson & Greene, 2022
Supraoptic nucleus (SO)	Hypothalamic nucleus overlying the beginning of the optic tract.	MeSH
Suspensory ligament	Bands of connective tissue that suspend the breast onto the chest wall by attachment to the overlying dermis.	Menefee et al, 2021
Symphysis pubis	see *pubic symphysis*	
Syncytiotrophoblast	Superficial cells of the trophoblast that fuse to form a multinucleated body that digests endometrial cells to firmly secure the blastocyst to the uterine wall.	Lange et al, 2023
Syphilis	A contagious venereal disease caused by the spirochete TREPONEMA PALLIDUM.	MeSH
Telomerase	An essential ribonucleoprotein reverse transcriptase that adds telomeric DNA to the ends of eukaryotic CHROMOSOMES.	MeSH
Tenaculum		
Teratogen	An agent capable of producing malformations in a developing embryo.	Menefee et al, 2024
Tertiary follicle (also antral follicles)	Ovarian follicles with a primary or secondary oocyte, multiple layers of granulosa cells, and a fully formed antrum.	Menefee et al 2021
Testes	The testes (singular = testis) are the male gonads—that is, the male reproductive organs. They produce both sperm and androgens, such as testosterone, and are active throughout the reproductive lifespan.	Lange et al, 2023

Word(s)	Definition	Source
Testosterone	A potent androgenic steroid and major product secreted by the LEYDIG CELLS of the TESTIS. Its production is stimulated by LUTEINIZING HORMONE from the PITUITARY GLAND. In turn, testosterone exerts feedback control of the pituitary LH and FSH secretion. Depending on the tissues, testosterone can be further converted to DIHYDROTESTOSTERONE or ESTRADIOL.	MeSH
Theca cells	Estrogen-producing cells in a maturing ovarian follicle.	Menefee et al, 2021
Thrombophilia	A disorder of HEMOSTASIS in which there is a tendency for the occurrence of THROMBOSIS.	MeSH
Thyrotropin	A form of thyroid-stimulating hormone (TSH) that is made in the laboratory. It is used to test for remaining or recurring cancer cells in patients who have been treated for thyroid cancer. Also called Thyrogen.	NCI Dictionary
Tonic inhibition	A form of neurotransmission usually thought to reduce the excitability of all neurons.	
Transabdominal	Through the abdomen or belly.	MedlinePlus
Transvaginal	Transvaginal means across or through the vagina. The ultrasound probe will be placed inside the vagina during the test.	MedlinePlus
Trauma	Injury or damage inflicted on the body as the direct or indirect result of an external force, with or without disruption of structural continuity.	MeSH
Trichomonas	genus of parasitic flagellate EUKARYOTES distinguished by the presence of four anterior flagella, an undulating membrane, and a trailing flagellum.	MeSH
Trigon	Area at the base of the bladder marked by the two ureters in the posterior–	Menefee et al 2021

Word(s)	Definition	Source
	lateral aspect and the urethral orifice in the anterior aspect oriented like points on a triangle.	
Trisomy 21/Down Syndrome	A chromosome disorder associated either with an extra CHROMOSOME 21 or an effective TRISOMY for chromosome 21. Clinical manifestations include HYPOTONIA, short stature, BRACHYCEPHALY, upslanting palpebral fissures, epicanthus, Brushfield spots on the iris, protruding tongue, small ears, short, broad hands, fifth finger clinodactyly, single transverse palmar crease, and moderate to severe INTELLECTUAL DISABILITY.	MeSH
Trophoblast	Fluid-filled shell of squamous cells destined to become the chorionic villi, placenta, and associated fetal membranes.	Lange et al, 2023
Trophoblastic tumor	Trophoblastic growth, which may be gestational or nongestational in origin. Trophoblastic neoplasia resulting from pregnancy is often described as gestational trophoblastic disease to distinguish it from germ cell tumors which frequently show trophoblastic elements, and from the trophobla	MeSH

Word(s)	Definition	Source
	stic differentiation which sometimes occurs in a wide variety of epithelial cancers. Gestational trophoblastic growth has several forms, including HYDATIDIFORM MOLE and CHORIOCARCINOMA.	
True labor	regular contractions that immediately precede childbirth; they do not abate with hydration or rest, and they become more frequent and powerful with time.	Lange et al, 2023
Tuberculous salpingitis	Inflammation of the uterine salpinx, the	MeSH
	trumpet-shaped FALLOPIAN TUBES, usually caused by ascending infections of organisms from the lower reproductive tract. Salpingitis can lead to tubal scarring, hydrosalpinx, tubal occlusion, INFERTILITY, and ectopic pregnancy (PREGNANCY, ECTOPIC).	
Tunica albuginea	Membrane (tunica albuginea) surrounding the erectile tissue.	MeSH
Tunica vaginalis	Membrane (tunica vaginalis) covering the TESTIS in the SCROTUM.	MeSH
Umbilicale	Pit in the center of the ABDOMINAL WALL marking the point where the UMBILICAL CORD entered in the FETUS.	MeSH
Unicornuate	One-sided	MedlinePlus
uterus	uterus.	
Unification defect		
Upregulation	In biology, the process by which a cell increases its response to a substance or signal from outside the cell to carry out a specific function. For example, a cell may increase the number or activity of protein receptors or other molecules on its surface to make it more sensitive to a hormone or drug	NCI Dictionary
Ureters	A pair of thick-walled tubes that transports urine from the KIDNEY PELVIS to the URINARY BLADDER.	MeSH
Urethra	Transports urine from the bladder to the outside environment.	Menefee et al 2021
Urinary bladder	A musculomembranous sac along the URINARY TRACT. URINE flows	MeSH

Word(s)	Definition	Source
	from the KIDNEYS into the bladder via the ureters (URETER), and is held there until URINATION.	
Urinary tract	Bundle of axons in the central nervous system having the same function and point of origin.	Menefee et al, 2021
Uterine fibroids	Most common noncancerous (benign) tumors in women of childbearing age.	MedlinePlus
Uterine prolapse	Uterine prolapse occurs when the womb (uterus) drops down and presses into the vaginal area.	MedlinePlus
Uterine tubes (also fallopian tubes of oviducts)	Ducts that facilitate transport of an ovulated oocyte to the uterus.	Menefee et al, 2021
Uterosacral ligament	The uterosacral ligaments provide, along with the cardinal ligaments, the key support for the uterus within the pelvis and attach from the cervix below the peritoneum backward to the anterior aspect of the sacrum.	Chaudhry et al, 2023
Uterotonics		
Uterus	Muscular organ that nourishes and supports the growing embryo. Its average size is approximately 5 cm wide by 7 cm long, and it has three sections.	Nelson & Greene, 2022
Vacuolated	Containing one or more vacuoles (small cavity or space in the tissues of an organism containing air or fluid).	Encyclopedia Brtiannica. *Merriam Webster Dictionary.*
Vagina	Muscular canal (approximately 10 cm long) that is the entrance to the reproductive tract. It also serves as the exit from the uterus during menses and childbirth.	Nelson & Greene, 2022
	The outer walls of the anterior and posterior vagina are columns with ridges. The superior fornix meets the uterine cervix. The cervix is the opening to the uterus.	
Vaginosis	Abnormal condition of the vagina.	Nelson & Greene, 2022
Vas deferen	The duct that transports sperm from the epididymis through the spermatic cord and into the ejaculatory duct; also referred as the vas deferens.	Nelson & Greene, 2022
Vascularization	Process of becoming vascular (channel for the conveyance of a body fluid (such as blood).	Encyclopedia Brtiannica. *Merriam Webster Dictionary.*
Vascularized	Tissue that has numerous blood vessels.	Menefee et al 2024
Vascularization	Process of becoming vascular (channel for the conveyance of a body fluid (such as blood).	Encyclopedia Brtiannica. *Merriam Webster Dictionary.*
Vasovagal syncope	Loss of consciousnes	MeSH

Word(s)	Definition	Source
	s due to a reduction in blood pressure that is associated with an increase in vagal tone and peripheral vasodilation.	
Vena Cavae	The inferior (venous trunk which receives blood from the lower extremities and from the pelvic and abdominal organs) and superior (venous trunk which returns blood from the head, neck, upper extremities and chest) venae cavae.	MeSH
Vernix caseosa	Waxy, cheese-like substance that protects the delicate fetal skin until birth.	Lange et al, 2023
Vertebral column	The spine.	Menefee et al, 2024
Visceral	Pertaining to internal organs.	Nelson & Greene, 2022
Visceral branches	Branches of the descending aorta that supply blood to the viscera.	Menefee et al, 2021
Wharton Jelly	Jelly-like connective tissue of the UMBILICAL CORD that contains MESENCHYMAL STEM CELLS.	
Whorled	Linear or spiral pattern.	MedlinePlus
Xenoestrogens	Foreign synthetic chemicals that mimic natural estrogens and can bind to estrogen receptors in the body.	
Yeast infection Vulvovaginal candidiasis.	Infection of the VULVA and VAGINA with a fungus of the genus CANDIDA.	MeSH.
Yolk sac	membrane associated with primitive circulation to the developing embryo; source of the first blood cells and germ cells and contributes to the umbilical cord structure.	Lange et al, 2023
Zona pellucida	A tough transparent membrane surrounding the OVUM. It is penetrated by the sperm during FERTILIZATION.	MeSH
Zygote	The fertilized ovum resulting from the fusion of a male and a female gamete.	MeSH

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Overview

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