

# Reproductive

*“Life is always a rich and steady time when you are waiting for something to happen or to hatch.”*

—E.B. White, *Charlotte’s Web*

*“Love is only a dirty trick played on us to achieve continuation of the species.”*

—W. Somerset Maugham

*“I liked that in obstetrics you end up with twice the number of patients you started with.”*

—Adam Kay

*“Life is a sexually transmitted disease and the mortality rate is one hundred percent.”*

—R.D. Laing

Organizing the reproductive system by key concepts such as embryology, endocrinology, pregnancy, and oncology can help with understanding this complex topic. Study the endocrine and reproductive chapters together, because mastery of the hypothalamic-pituitary-gonadal axis is key to answering questions on ovulation, menstruation, disorders of sexual development, contraception, and many pathologies.

Embryology is a nuanced subject that spans multiple organ systems. Approach it from a clinical perspective. For instance, make the connection between the presentation of DiGeorge syndrome and the 3rd/4th pharyngeal pouch, and between the Müllerian/Wolffian systems and disorders of sexual development.

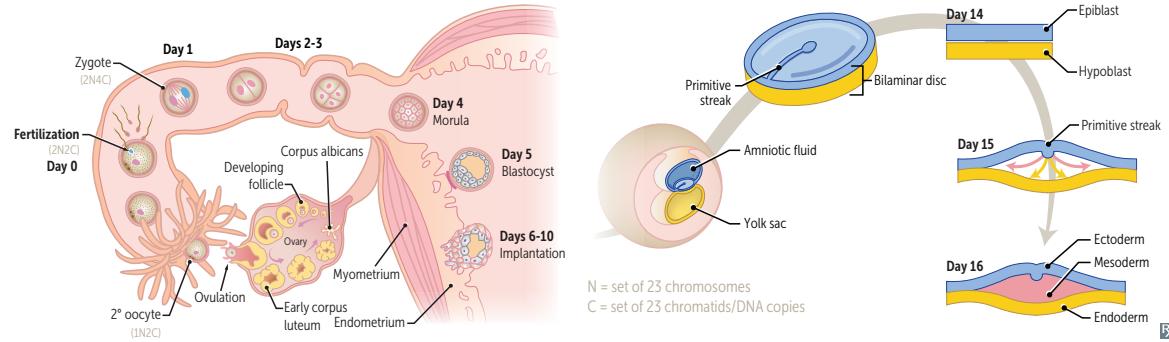
As for oncology, don’t worry about remembering screening or treatment guidelines. It is more important to recognize the clinical presentation (eg, signs and symptoms) of reproductive cancers and their associated labs, histopathology, and risk factors. In addition, some of the testicular and ovarian cancers have distinct patterns of hCG, AFP, LH, or FSH derangements that serve as helpful clues in exam questions.

► Embryology	632
► Anatomy	644
► Physiology	649
► Pathology	657
► Pharmacology	675

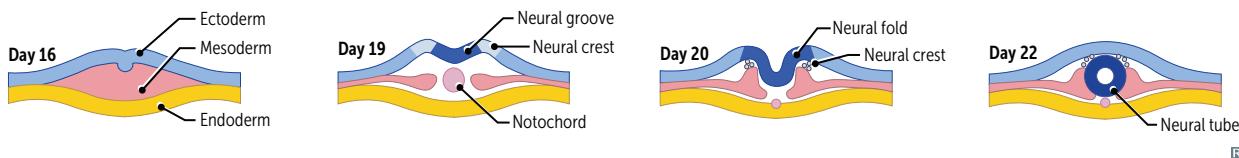
## ► REPRODUCTIVE—EMBRYOLOGY

**Important genes of embryogenesis**

GENE	CHARACTERISTICS
<b>Homeobox (<i>HOX</i>) genes</b>	Produced at multiple locations → segmental organization of embryo in cranial-caudal axis. Mutations → limb malformations. Isotretinoin → ↑ HOX gene expression.
<b>Sonic hedgehog (<i>SHH</i>)</b>	Produced at notochord, limb buds (zone of polarizing activity) → CNS development, anterior-posterior limb axis patterning. Mutations → holoprosencephaly.
<b><i>Wnt-7</i></b>	Produced at limb buds (apical ectodermal ridge) → dorsal-ventral limb axis patterning.
<b>Fibroblast growth factor (<i>FGF</i>)</b>	Produced at limb buds (apical ectodermal ridge) → proximal-distal limb outgrowth.

**Early embryonic development**

<b>Week 1</b>	hCG secretion begins around the time of blastocyst implantation. Blastocyst “sticks” on day <b>six</b> .
<b>Week 2</b>	Formation of <b>bilaminar</b> embryonic disc; <b>two</b> layers = epiblast, hypoblast.
<b>Week 3</b>	Formation of <b>trilaminar</b> embryonic disc via gastrulation (epiblast cell invagination through primitive streak); <b>three</b> layers = endoderm, mesoderm, ectoderm. Notochord arises from midline mesoderm and induces overlying ectoderm (via SHH) to become neural plate, which gives rise to neural tube via neurulation.
<b>Week 4</b>	Heart begins to beat ( <b>four</b> chambers). Cardiac activity visible by transvaginal ultrasound. Upper and lower limb buds begin to form ( <b>four</b> limbs).
<b>Week 8</b>	Genitalia have male/female characteristics (pronounce “gene <b>eight</b> alia”).

**Embryologic derivatives****Ectoderm**

<b>Surface ectoderm</b>	Epidermis; adenohypophysis (from Rathke pouch); lens of eye; epithelial linings of oral cavity, sensory organs of ear, and olfactory epithelium; anal canal below the pectinate line; parotid, sweat, mammary glands.	<b>External/outer layer</b>  <b>Craniopharyngioma</b> —benign Rathke pouch tumor with cholesterol crystals, calcifications.
<b>Neural tube</b>	Brain (neurohypophysis, CNS neurons, oligodendrocytes, astrocytes, ependymal cells, pineal gland), retina, spinal cord.	Neuroectoderm—think CNS.
<b>Neural crest</b>	Enterochromaffin cells, Melanocytes, Odontoblasts, PNS ganglia (cranial, dorsal root, autonomic), Adrenal medulla, Schwann cells, Spiral membrane (aorticopulmonary septum), Endocardial cushions (also derived partially from mesoderm), Skull bones.	<b>EMO PASSES</b> Neural crest—think PNS and non-neural structures nearby.
<b>Mesoderm</b>	Muscle, bone, connective tissue, serous linings of body cavities (eg, peritoneum, pericardium, pleura), spleen (develops within foregut mesentery), cardiovascular structures, lymphatics, blood, wall of gut tube, proximal vagina, kidneys, adrenal cortex, dermis, testes, ovaries, microglia, tracheal cartilage. Notochord induces ectoderm to form neuroectoderm (neural plate); its only postnatal derivative is the nucleus pulposus of the intervertebral disc.	Middle/“meat” layer. Mesodermal defects = <b>VACTERL</b> association: <b>V</b> ertebral defects <b>A</b> nal atresia <b>C</b> ardiac defects <b>T</b> racheo- <b>E</b> sophageal fistula <b>R</b> enal defects <b>E</b> limb defects (bone and muscle)
<b>Endoderm</b>	Gut tube epithelium (including anal canal above the pectinate line), most of urethra and distal vagina (derived from urogenital sinus), luminal epithelial derivatives (eg, lungs, liver, gallbladder, pancreas, eustachian tube, thymus, parathyroid, thyroid follicular and parafollicular [C] cells).	“ <b>E</b> nternal” layer.

**Teratogens** Most susceptible during organogenesis in embryonic period (before week 8 of development). Before implantation, “all-or-none” effect. After week 8 (fetal period), growth and function affected.

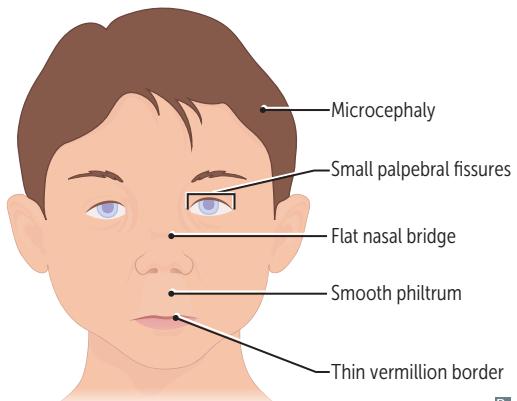
TERATOGEN	EFFECT ON FETUS
<b>Medications</b>	
ACE inhibitors	Renal failure, oligohydramnios, hypocalvaria.
Alkylating agents	Multiple anomalies (eg, ear/facial abnormalities, absence of digits).
Aminoglycosides	<b>Ototoxicity.</b> “A mean guy hit the baby in the <b>ear</b> .”
Antiepileptic drugs	Neural tube defects, cardiac defects, cleft palate, skeletal abnormalities (eg, phalanx/nail hypoplasia, facial dysmorphism). Most commonly due to valproate, carbamazepine, phenytoin, phenobarbital; high-dose folate supplementation recommended.
Diethylstilbestrol	Vaginal clear cell adenocarcinoma, congenital Müllerian anomalies.
Fluoroquinolones	Cartilage damage.
Folate antagonists	Neural tube defects. Most commonly due to trimethoprim, methotrexate.
Isotretinoin	Craniofacial (eg, microtia, dysmorphism), CNS, cardiac, and thymic defects. Contraception mandatory. Pronounce “iso <b>terat</b> inoin” for its <b>teratogenicity</b> .
Lithium	Ebstein anomaly.
Methimazole	Aplasia cutis congenita (congenital absence of skin, typically on scalp).
Tetracyclines	Discolored <b>teeth</b> , inhibited bone growth. Pronounce “teeth <b>racyclines</b> .”
Thalidomide	<b>Limb</b> defects (eg, phocomelia—flipperlike limbs). Pronounce “thal <b>limb</b> domide.”
Warfarin	Bone and cartilage deformities (stippled epiphyses, nasal and limb hypoplasia), optic nerve atrophy, cerebral hemorrhage. Use heparin during pregnancy (does not cross placenta).
<b>Substance use</b>	
Alcohol	Fetal alcohol syndrome.
Cocaine	Preterm birth, low birth weight, fetal growth restriction (FGR). Cocaine → vasoconstriction.
Tobacco smoking	Preterm birth, low birth weight (leading cause in resource-rich countries), FGR, sudden infant death syndrome (SIDS), ADHD. Nicotine → vasoconstriction, CO → impaired O <sub>2</sub> delivery.
<b>Other</b>	
Iodine lack or excess	Congenital hypothyroidism.
Maternal diabetes	Caudal regression syndrome, cardiac defects (eg, transposition of great arteries, VSD), neural tube defects, macrosomia, neonatal hypoglycemia (due to islet cell hyperplasia), polycythemia, respiratory distress syndrome.
Maternal PKU	Fetal growth restriction, microcephaly, intellectual disability, congenital heart defects.
Methylmercury	Neurotoxicity. ↑ concentration in top-predator fish (eg, shark, swordfish, king mackerel, tilefish).
X-rays	Microcephaly, intellectual disability. Effects minimized by use of lead shielding.

**Types of errors in morphogenesis**

<b>Agenesis</b>	Absent organ due to absent primordial tissue.
<b>Aplasia</b>	Absent organ despite presence of primordial tissue.
<b>Hypoplasia</b>	Incomplete organ development; primordial tissue present.
<b>Disruption</b>	2° breakdown of tissue with normal developmental potential (eg, amniotic band syndrome).
<b>Deformation</b>	Extrinsic mechanical distortion (eg, congenital torticollis); occurs during fetal period.
<b>Malformation</b>	Intrinsic developmental defect (eg, cleft lip/palate); occurs during embryonic period.
<b>Sequence</b>	Abnormalities result from a single 1° embryologic event (eg, oligohydramnios → Potter sequence).
<b>Field defect</b>	Disturbance of tissues that develop in a contiguous physical space (eg, holoprosencephaly).

**Fetal alcohol syndrome**

One of the leading preventable causes of intellectual disability in the US. 2° to maternal alcohol use during pregnancy. Newborns may present with developmental delay, microcephaly, facial abnormalities (eg, smooth philtrum, thin vermillion border, small palpebral fissures, flat nasal bridge), limb dislocation, heart defects. Holoprosencephaly may occur in more severe presentations. One mechanism is due to impaired migration of neuronal and glial cells.

**Neonatal abstinence syndrome**

Complex disorder involving CNS, ANS, and GI systems. 2° to maternal substance use (most commonly opioids) during pregnancy. Newborns may present with uncoordinated sucking reflexes, irritability, high-pitched crying, tremors, tachypnea, sneezing, diarrhea, and possibly seizures. Treatment (for opioid use): methadone, morphine, buprenorphine. Universal screening for substance use is recommended in all pregnant patients.

**Placenta**

1<sup>o</sup> site of nutrient and gas exchange between mother and fetus.

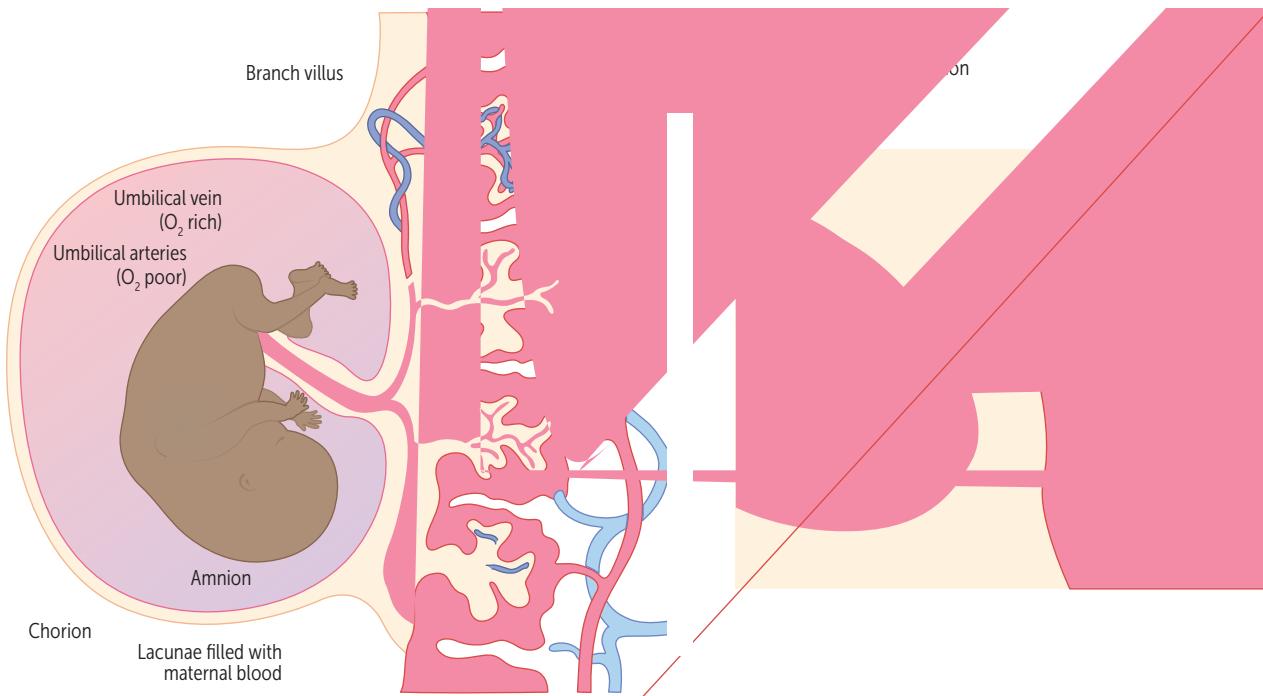
**Fetal component**

**Cytotrophoblast** Inner layer of chorionic villi; creates cells.

**Syncytiotrophoblast** Outer layer of chorionic villi; synthesizes and secretes hormones, eg, hCG (structurally similar to LH; stimulates corpus luteum to secrete progesterone during first trimester). Lacks MHC I expression → ↓ chance of attack by maternal immune system.

**Maternal component**

**Decidua basalis** Derived from endometrium. Maternal blood in lacunae.

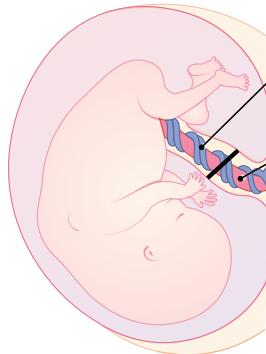




**Umbilical cord**

Two umbilical arteries return deoxygenated blood from fetal internal iliac arteries to placenta.

One umbilical vein supplies oxygenated blood from placenta to fetus; drains into IVC or via ductus venosus.

**Urachus**

Allantois forms from yolk sac and extends to median plate called the urachus, a duct between bladder and foregut. Failure to involute may lead to anomalies that may increase risk of cancer if not treated. Obliterated urachus is a median umbilical ligament which is covered by median umbilical fold.

**Patent urachus**

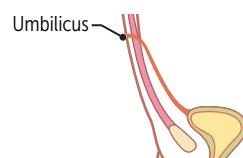
Total failure of urachus to obliterate → patent urachus.

**Urachal cyst**

Partial failure of urachus to obliterate → urachal diverticulum or urachal cyst at umbilicus and bladder. Cyst can become infected.

**Vesicourachal diverticulum**

Slight failure of urachus to obliterate → vesicourachal diverticulum.



Normal

**Vitelline duct**

Also called omphalomesenteric duct. Remnant of development.

**Patent vitelline duct**

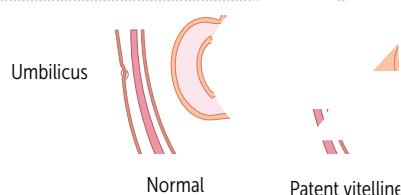
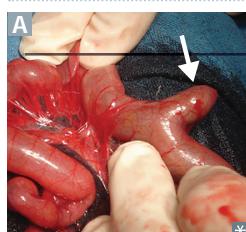
Total failure of vitelline duct to obliterate → patent vitelline duct.

**Vitelline duct cyst**

Partial failure of vitelline duct to obliterate → vitelline diverticulum.

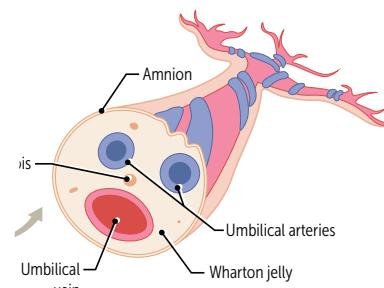
**Meckel diverticulum**

Slight failure of vitelline duct to obliterate → Meckel diverticulum (A). Usually asymptomatic. May contain heterotopic tissue (eg, intestinal mucosa, pancreatic tissue).



Single umbilical artery (2-vessel cord) is associated with congenital and chromosomal anomalies.

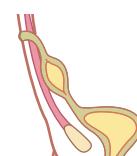
Umbilical arteries and vein are derived from allantois.



Intra-abdominal remnant of allantois is called urachal diverticulum or urachal cyst. Failure of urachus to involute can lead to infection and/or malignancy (eg, adenocarcinoma) of urachus. It is located in median umbilical ligament after birth, within peritoneum.

Urachal diverticulum originates from umbilicus.

Urachal diverticulum is lined with uroepithelium, between rectal folds. It may be present as painful mass below umbilicus or as diverticulum of bladder.



Urachal diverticulum



Urachal cyst

Urachal diverticulum → obliterates during week 12 of midgestation.

Urachal diverticulum → may become infected from umbilicus.

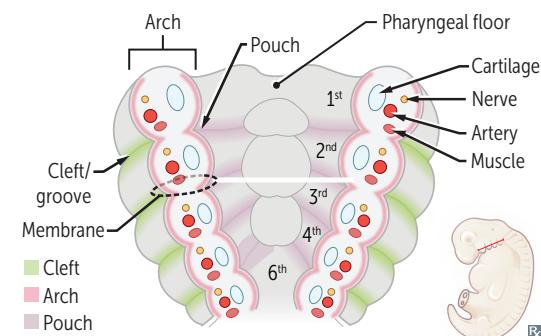
Meckel diverticulum → originates from ileum (true diverticulum, arrow) and/or contains heterotopic tissue (eg, pancreatic tissue → melena, hematochezia).

**Pharyngeal apparatus**

Composed of pharyngeal (branchial) clefts, arches, pouches.  
 Pharyngeal clefts—derived from ectoderm. Also called pharyngeal grooves.  
 Pharyngeal arches—derived from mesoderm (muscles, arteries) and neural crest (bones, cartilage).  
 Pharyngeal pouches—derived from endoderm.

CAP covers outside to inside:

Clefts = ectoderm  
 Arches = mesoderm + neural crest  
 Pouches = endoderm

**Pharyngeal cleft derivatives**

1st cleft develops into external auditory meatus.  
 2nd through 4th clefts form temporary cervical sinuses, which are obliterated by proliferation of 2nd arch mesenchyme.

**Pharyngeal cleft cyst**—persistent cervical sinus; presents as lateral neck mass anterior to sternocleidomastoid muscle that does not move with swallowing (vs thyroglossal duct cyst).

**Pharyngeal pouch derivatives**

**Ear, tonsils, bottom-to-top:** 1 (ear), 2 (tonsils), 3 dorsal (bottom = **inferior** parathyroids), 3 ventral (to = thymus), 4 (top = **superior** parathyroids).

POUCH	DERIVATIVES	NOTES
<b>1st pharyngeal pouch</b>	Middle ear cavity, eustachian tube, mastoid air cells	1st pouch contributes to endoderm-lined structures of ear
<b>2nd pharyngeal pouch</b>	Epithelial lining of palatine tonsil	
<b>3rd pharyngeal pouch</b>	Dorsal wings → <b>inferior</b> parathyroids Ventral wings → thymus	Third pouch contributes to thymus and both inferior parathyroids Structures from 3rd pouch end up <b>below</b> those from 4th pouch
<b>4th pharyngeal pouch</b>	Dorsal wings → <b>superior</b> parathyroids Ventral wings → ultimopharyngeal body → parafollicular (C) cells of thyroid	4th pharyngeal pouch forms para“4”llicular cells

**Pharyngeal arch derivatives** When at the restaurant of the golden **arches**, children tend to first **chew** (1), then **smile** (2), then **swallow stylishly** (3) or **simply swallow** (4), and then **speak** (6).

ARCH	NERVES <sup>a</sup>	MUSCLES	CARTILAGE	NOTES
1st pharyngeal arch	CN V <sub>3</sub> <b>chew</b>	Muscles of mastication (temporalis, masseter, lateral and <b>medial pterygoids</b> ), <b>mylohyoid</b> , anterior belly of digastric, tensor tympani, anterior 2/3 of tongue, tensor veli palatini	<b>Maxillary process</b> → <b>maxilla</b> , <b>zygomatic bone</b> <b>Mandibular process</b> → <b>meckel cartilage</b> → <b>mandible</b> , <b>malleus</b> and <b>incus</b> , <b>sphenomandibular ligament</b>	<b>Pierre Robin sequence</b> —micrognathia, glossptosis, cleft palate, airway obstruction <b>Treacher Collins syndrome</b> —autosomal dominant neural crest dysfunction → craniofacial abnormalities (eg, zygomatic bone and mandibular hypoplasia), hearing loss, airway compromise
2nd pharyngeal arch	CN VII ( <b>seven smile</b> ) (facial expression)	Muscles of facial expression, <b>stapedius</b> , <b>stylohyoid</b> , <b>platysma</b> , posterior belly of digastric	Reichert cartilage: <b>stapes</b> , <b>styloid process</b> , <b>lesser horn of hyoid</b> , <b>stylohyoid ligament</b>	
3rd pharyngeal arch	CN IX <b>swallow stylishly</b>	<b>Stylopharyngeus</b>	Greater horn of hyoid	
4th and 6th pharyngeal arches	4th arch: CN X (superior laryngeal branch) <b>simply swallow</b> 6th arch: CN X (recurrent/inferior laryngeal branch) <b>speak</b>	4th arch: most pharyngeal constrictors; cricothyroid, levator veli palatini 6th arch: all intrinsic muscles of larynx except cricothyroid	<b>Arytenoids</b> , <b>Cricoid</b> , <b>Corniculate</b> , <b>Cuneiform</b> , <b>Thyroid</b> (used to sing and <b>ACCCT</b> )	Arches 3 and 4 form posterior 1/3 of tongue Arch 5 makes no major developmental contributions

<sup>a</sup>Sensory and motor nerves are not pharyngeal arch derivatives. They grow into the arches and are derived from neural crest (sensory) and neuroectoderm (motor).

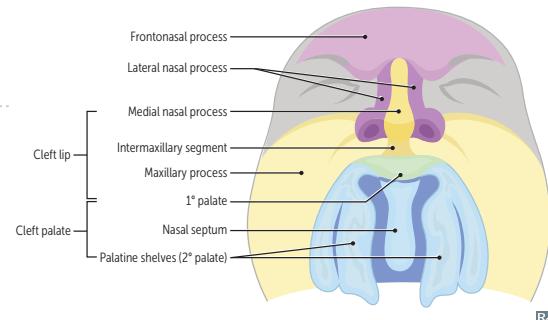
**Orofacial clefts****Cleft lip**

Cleft lip and cleft palate have distinct, multifactorial etiologies, but often occur together.

**Cleft lip** Due to failure of fusion of the intermaxillary segment (merged medial nasal processes) with the maxillary process (formation of 1° palate).

**Cleft palate**

**Cleft palate** Due to failure of fusion of the two lateral palatine shelves or failure of fusion of lateral palatine shelf with the nasal septum and/or 1° palate (formation of 2° palate).



Rx

**Genital embryology****Female**

Default development. Mesonephric duct degenerates and paramesonephric duct develops.

**Male**

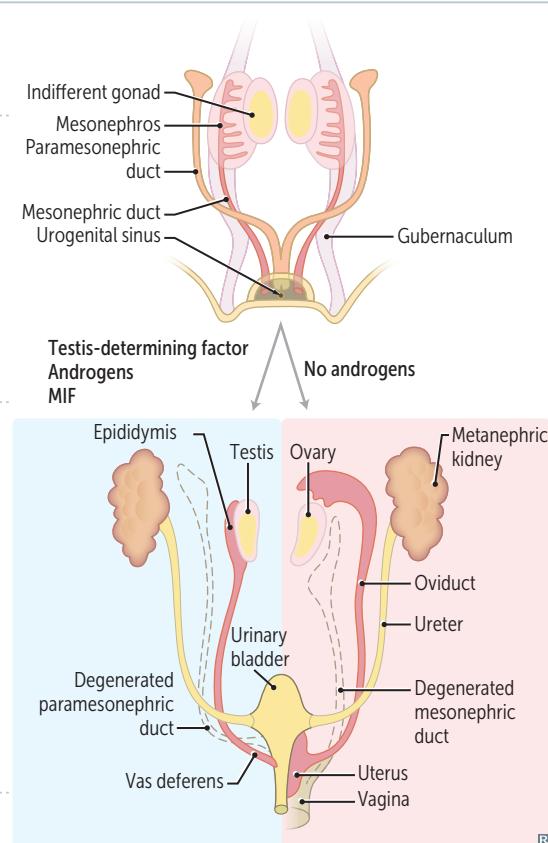
SRY gene on Y chromosome—produces testis-determining factor → testes development. Sertoli cells secrete Müllerian inhibitory factor (MIF, also called antimüllerian hormone) that suppresses development of paramesonephric ducts. Leydig cells secrete androgens that stimulate development of mesonephric ducts.

**Paramesonephric (Müllerian) duct**

Develops into female internal structures—fallopian tubes, uterus, proximal vagina (distal vagina from urogenital sinus). Male remnant is appendix testis. **Müllerian agenesis (Mayer-Rokitansky-Küster-Hauser syndrome)**—1° amenorrhea with absent uterus, blind vaginal pouch, normal female external genitalia and 2° sexual characteristics (functional ovaries). Associated with urinary tract anomalies (eg, renal agenesis).

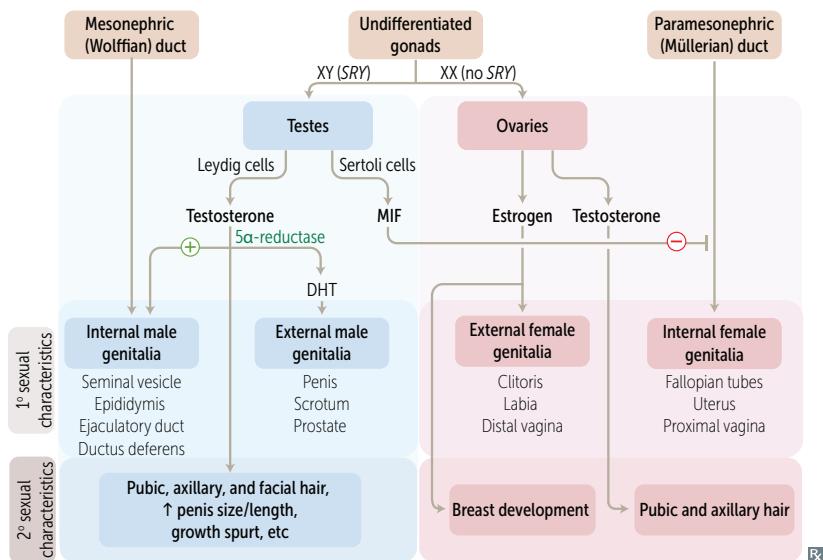
**Mesonephric (Wolffian) duct**

Develops into male internal structures (except prostate)—Seminal vesicles, Epididymis, Ejaculatory duct, Ductus deferens (**SEED**). Female remnant is Gartner duct.



Rx

### Sexual differentiation



Absence of Sertoli cells or lack of Müllerian inhibitory factor → develop both male and female internal genitalia and male external genitalia (streak gonads)

5α-reductase deficiency—ability to convert testosterone into DHT → male internal genitalia, atypical external genitalia until puberty (when ↑ testosterone levels cause masculinization)

In the testes:

Leydig leads to male (internal and external) sexual differentiation.

Sertoli shuts down female (internal) sexual differentiation.

### Uterine (Müllerian duct) anomalies

↓ fertility and ↑ risk of complicated pregnancy (eg, spontaneous abortion, prematurity, FGR, malpresentation). Hysterosalpingogram of normal uterus demonstrates normal uterine cavity and intraperitoneal spill of contrast (indicative of patent fallopian tubes).

#### Septate uterus

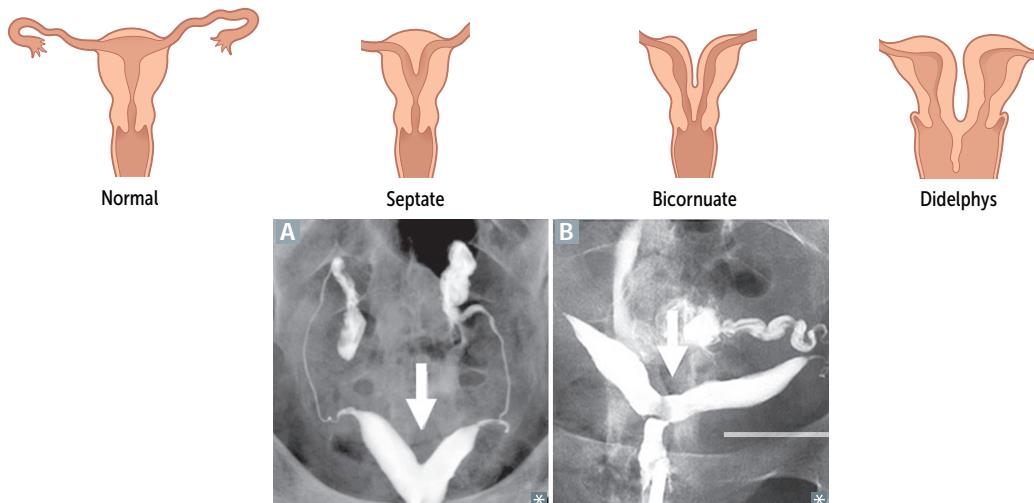
Incomplete resorption of septum **A**. Common anomaly. Treat with septoplasty.

#### Bicornuate uterus

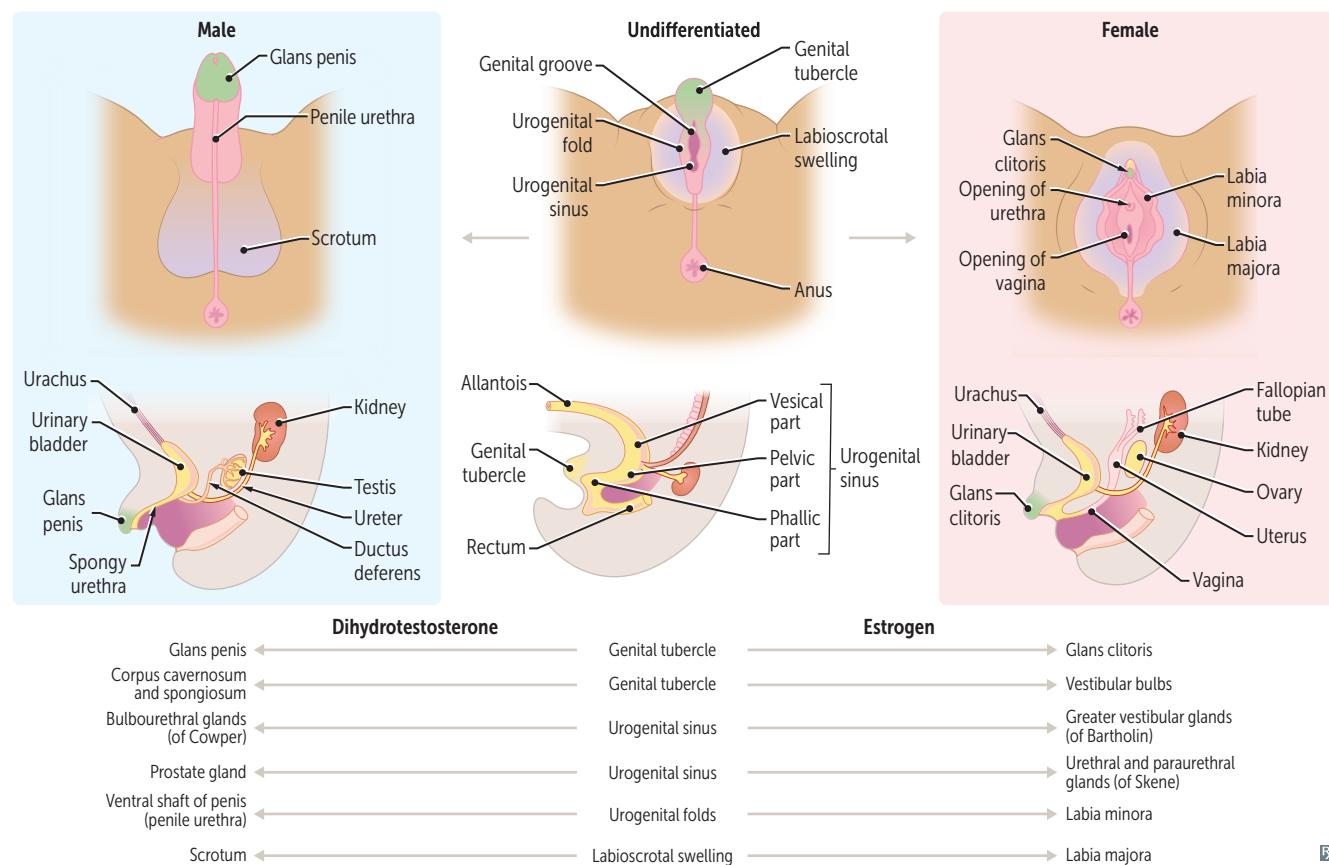
Incomplete fusion of Müllerian ducts **B**.

#### Uterus didelphys

Complete failure of fusion → double uterus, cervix, vagina.

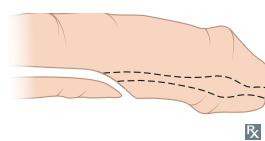


### Male/female genital homologs



### Congenital penile abnormalities

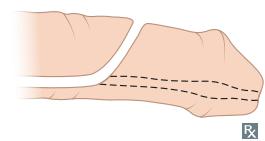
#### Hypospadias



Abnormal opening of penile urethra on ventral (under) surface due to failure of urethral folds to fuse.

Hypospadias is more common than epispadias. Associated with inguinal hernia, cryptorchidism, chordee (downward or upward bending of penis). Can be seen in  $5\alpha$ -reductase deficiency.

#### Epispadias



Abnormal opening of penile urethra on dorsal (top) surface due to faulty positioning of genital tubercle.

Exstrophy of the bladder is associated with epispadias.

**Descent of testes and ovaries**

	DESCRIPTION	MALE REMNANT	FEMALE REMNANT
Gubernaculum	Band of fibrous tissue	Anchors testes within scrotum	Ovarian ligament + round ligament of uterus
Processus vaginalis	Evagination of peritoneum	Forms tunica vaginalis Persistent patent processus vaginalis → hydrocele	Obliterated

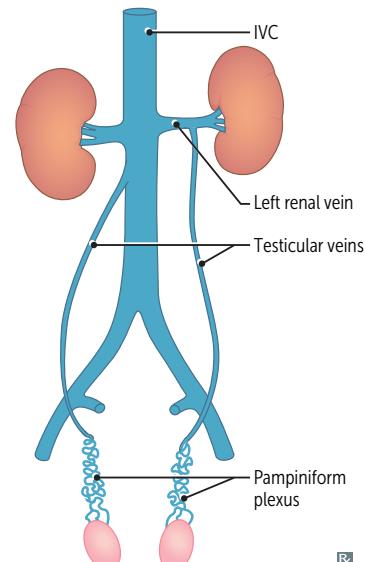
## ► REPRODUCTIVE—ANATOMY

**Gonadal drainage****Venous drainage**

Left ovary/testis → left gonadal vein → left renal vein → IVC.  
Right ovary/testis → right gonadal vein → IVC.

Because the left testicular vein enters the left renal vein at a 90° angle, flow is less laminar on left than on right → left venous pressure > right venous pressure → varicocele more common on the left.

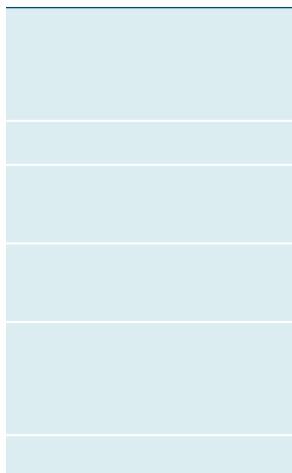
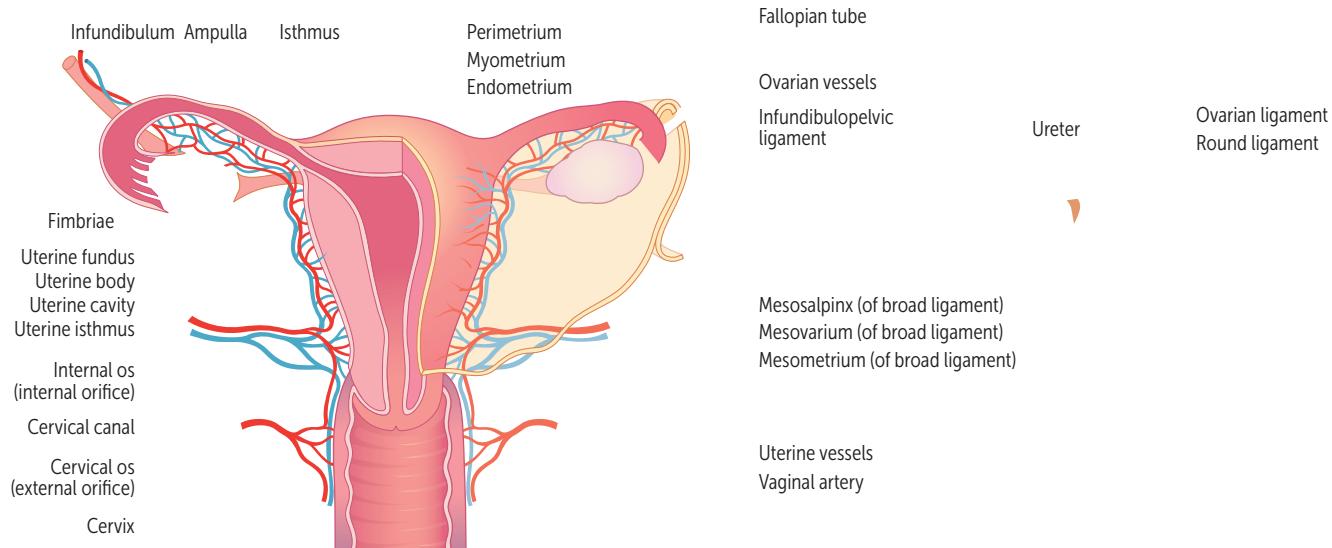
“Left gonadal vein takes the longer way.”



Rx

**Lymphatic drainage**

Ovaries/testes/fundus of uterus → para-aortic lymph nodes.  
Body of uterus/cervix/superior part of bladder → external iliac nodes.  
Prostate/cervix/corpus cavernosum/proximal vagina/inferior part of bladder → internal iliac nodes.  
Distal vagina/vulva/scrotum/distal anus → superficial inguinal nodes.  
Clitoris/glans penis → deep inguinal nodes.

**Female reproductive anatomy**

**Female reproductive epithelial histology**

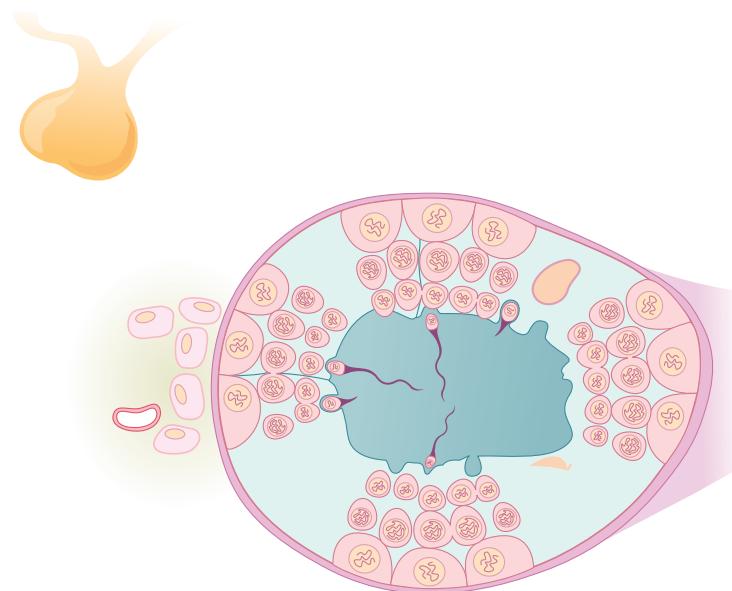
TISSUE	HISTOLOGY/NOTES
Vulva	Stratified squamous epithelium
Vagina	Stratified squamous epithelium, nonkeratinized
Ectocervix	Stratified squamous epithelium, nonkeratinized
Transformation zone	Squamocolumnar junction (most common area for cervical cancer; sampled in Pap test)
Endocervix	Simple columnar epithelium
Uterus	Simple columnar epithelium with long tubular glands in proliferative phase; coiled glands in secretory phase
Fallopian tube	Simple columnar epithelium, ciliated
Ovary, outer surface	Simple cuboidal epithelium (germinal epithelium covering surface of ovary)

**Male reproductive anatomy**



**Seminiferous tubules**

CELL	FUNCTION	LOCATION/NOTES
<b>Spermatogonia</b>	Maintain germ cell pool and produce 1° spermatocytes	Line seminiferous tubules <b>A</b> Germ cells
<b>Sertoli cells</b>	Secret inhibin B → inhibit FSH Secret androgen-binding protein → maintain local levels of testosterone Produce MIF Tight junctions between adjacent Sertoli cells form blood-testis barrier → isolate gametes from autoimmune attack Support and nourish developing spermatozoa Regulate spermatogenesis Temperature sensitive; ↓ sperm production and ↓ inhibin B with ↑ temperature	Line seminiferous tubules Non-germ cells Convert testosterone and androstenedione to estrogens via aromatase <b>S</b> ertoli cells are temperature <b>s</b> ensitive, line <b>s</b> eminiferous tubules, <b>s</b> upport <b>s</b> pERM <b>s</b> ynthesis, and inhibit <b>F</b> SH Homolog of female granulosa cells
<b>Leydig cells</b>	Secret testosterone in the presence of <b>LH</b> ; testosterone production unaffected by temperature	↑ temperature seen in varicocele, cryptorchidism Interstitial Endocrine cells Homolog of female theca interna cells Inhibin BGnRH



## ► REPRODUCTIVE—PHYSIOLOGY

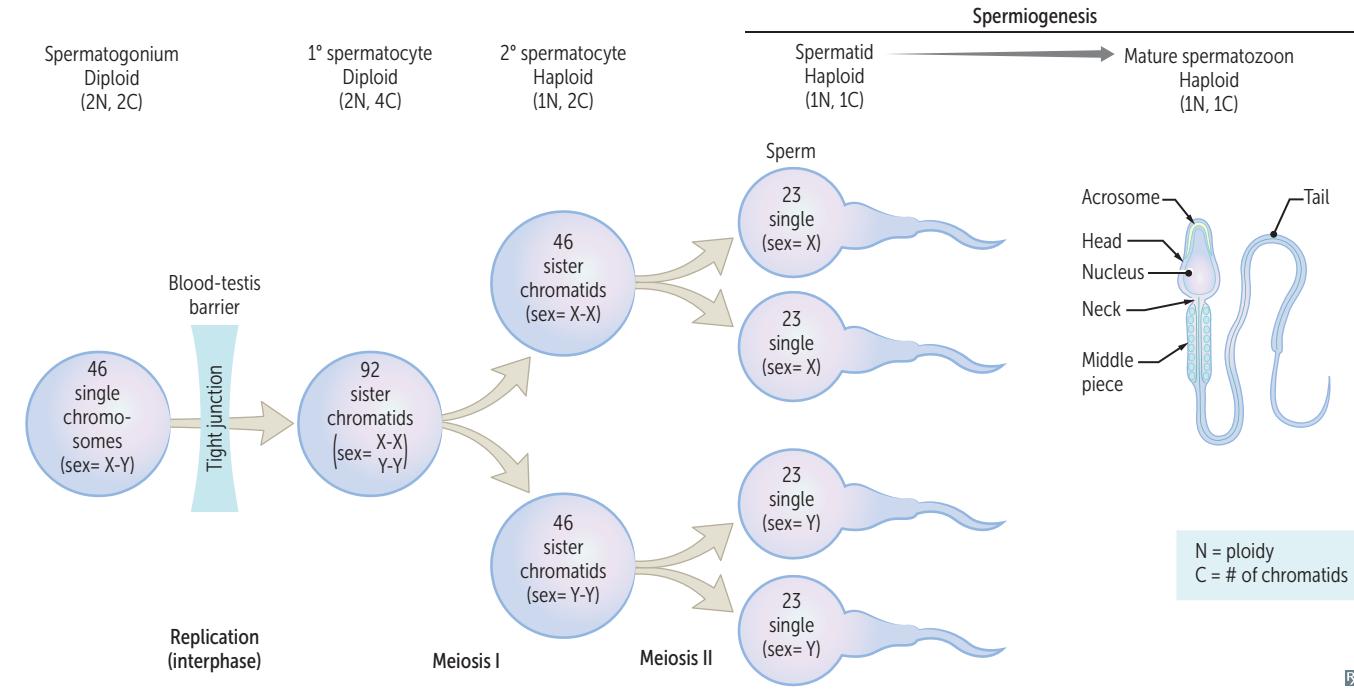
**Spermatogenesis**

Begins at puberty with spermatogonia. Full development takes 2 months. Occurs in seminiferous tubules. Produces spermatids that undergo spermiogenesis (loss of cytoplasmic contents, gain of acrosomal cap) to form mature spermatozoa.

“Gonium” is going to be a sperm; “zoon” is “zooming” to egg.

Tail mobility impaired in ciliary dyskinesia/ Kartagener syndrome → infertility.

Tail mobility normal in cystic fibrosis (in CF, absent vas deferens → infertility).

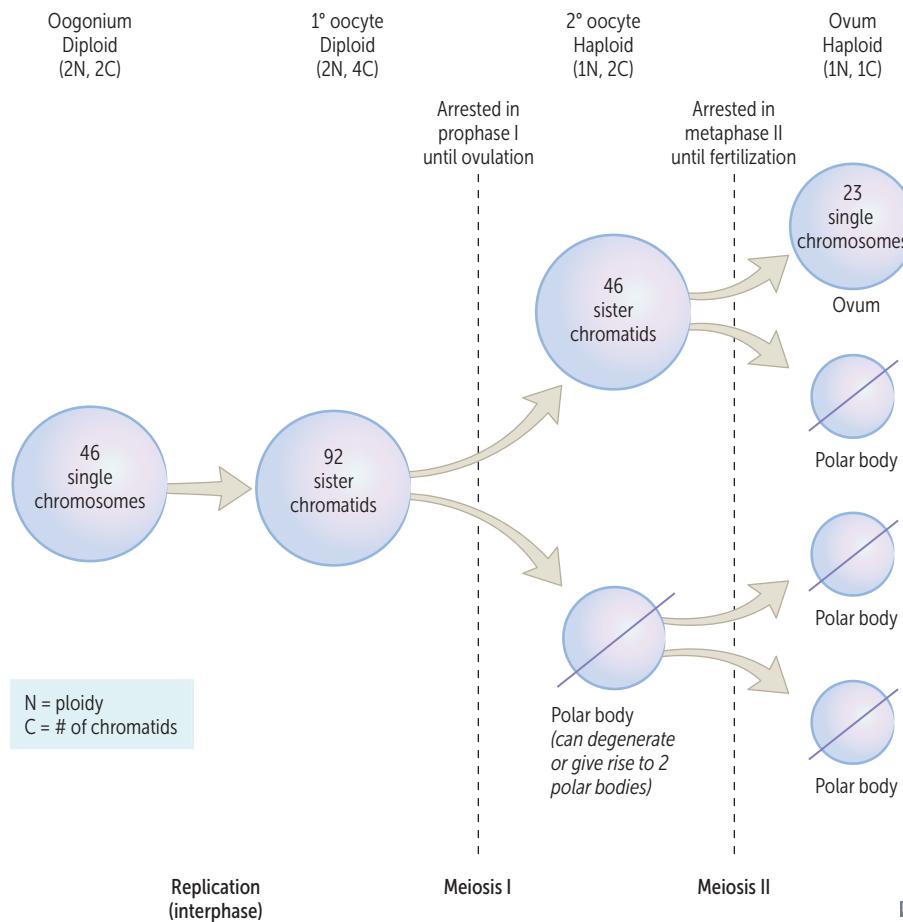


**Estrogen**

SOURCE	Ovary (17 $\beta$ -estradiol), placenta (estriol), adipose tissue (estrone via aromatization).	Potency: estradiol > estrone > estriol. Estradiol is produced from <b>2</b> ovaries.
FUNCTION	Development of internal/external genitalia, breasts, female fat distribution. Growth of follicle, endometrial proliferation, ↑ myometrial excitability. Upregulation of estrogen, LH, and progesterone receptors; feedback inhibition of FSH and LH, then LH surge; stimulation of prolactin secretion, ↓ prolactin action on breasts. ↑ transport proteins, SHBG; ↑ HDL; ↓ LDL.	Pregnancy: <ul style="list-style-type: none"><li>■ 50-fold ↑ in estradiol and estrone</li><li>■ 1000-fold ↑ in estriol (indicator of fetal well-being)</li></ul> Estrogen receptors expressed in cytoplasm; translocate to nucleus when bound by estrogen.

**Oogenesis**

1° oocytes begin meiosis I during fetal life and complete meiosis I just prior to ovulation.  
 Meiosis I is arrested in prophase I (**one**) for years until ovulation (1° oocytes).  
 Meiosis II is arrested in metaphase II (**two**) until fertilization (2° oocytes).  
 If fertilization does not occur within 1 day, the 2° oocyte degenerates.

**Ovulation**

Follicular rupture and 2° oocyte release.  
 Caused by sudden LH release (LH surge) at **midcycle**. Estrogen normally inhibits LH release, but high estrogen at midcycle transiently stimulates LH release → LH surge → ovulation.

**Mittelschmerz** (“middle hurts”)—pain with ovulation. Associated with peritoneal irritation from normal bleeding upon follicular rupture. Typically unilateral and mild, but can mimic acute appendicitis.



**Abnormal uterine bleeding**

Deviation from normal menstruation volume, duration, frequency, regularity, or intermenstrual bleeding.

Causes (**PALM-COEIN**):

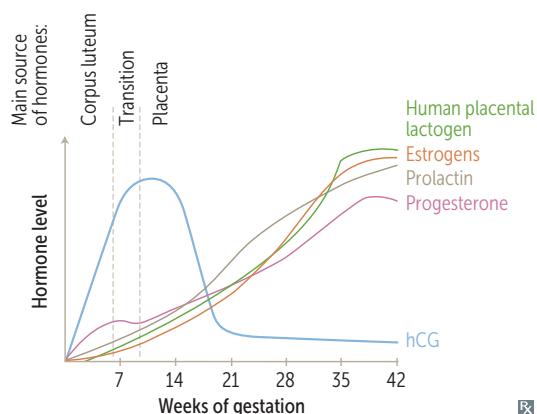
- Structural: **Polyp**, **Adenomyosis**, **Leiomyoma**, **Malignancy/hyperplasia**
- Nonstructural: **Coagulopathy**, **Ovulatory**, **Endometrial**, **Iatrogenic**, **Not yet classified**

Terms such as dysfunctional uterine bleeding, menorrhagia, metrorrhagia, polymenorrhea, and oligomenorrhea are no longer recommended.

**Pregnancy**

Fertilization (conception) most commonly occurs in upper end of fallopian tube (the ampulla). Occurs within 1 day of ovulation. Implantation in the uterine wall occurs 6 days after fertilization. Syncytiotrophoblasts secrete hCG, which is detectable in blood 1 week after fertilization and on home urine tests 2 weeks after fertilization. Embryonic/developmental age—time since fertilization. Used in embryology. Gestational age—time since first day of last menstrual period. Used clinically. Gravidity (“gravida”)—number of pregnancies. Parity (“para”)—number of pregnancies that resulted in live births.

Placental hormone secretion generally increases over the course of pregnancy, but hCG peaks at 8–10 weeks of gestation.

**Physiologic changes in pregnancy**

Maternal changes that nurture the developing fetus and prepare the mother for labor and delivery. Mediated by ↑ hormones (eg, estrogen, progesterone) and mechanical effects of gravid uterus.

**CARDIOVASCULAR**

↓ SVR (↓ afterload) and ↑ blood volume (↑ preload) → ↑ SV → ↑ CO → ↑ placental perfusion. ↑ HR is the major contributor to ↑ CO in late pregnancy. Hemodilution → ↓ oncotic pressure → peripheral edema.

**ENDOCRINE**

↑ insulin resistance and secretion → ↑ lipolysis and fat utilization (to preserve glucose and amino acids for fetus). Pituitary enlargement (lactotroph hyperplasia). ↑ TBG, ↑ CBG, ↑ SHBG.

**GASTROINTESTINAL**

↓ GI motility, ↓ LES tone, gallbladder stasis; predispose to constipation, GERD, gallstones.

**HEMATOLOGIC**

Dilutional anemia (↑↑ plasma volume, ↑ RBC mass), hypercoagulable state (to ↓ blood loss at delivery). ↑ micronutrient requirements predispose to deficiency (eg, iron, folate).

**MUSCULOSKELETAL**

Lordosis (to realign gravity center), joint laxity (to facilitate fetal descent).

**SKIN**

Hyperpigmentation (eg, melasma, linea nigra, areola darkening), striae gravidarum (stretch marks), vascular changes (eg, spider angiomas, palmar erythema, varicosities).

**RENAL**

Vasodilation → ↑ renal plasma flow → ↑ GFR → ↓ BUN and ↓ creatinine. Mild glucosuria, proteinuria. Hydronephrosis and hydroureter (more prominent on the right) predispose to pyelonephritis.

**RESPIRATORY**

Respiratory center stimulation → chronic hyperventilation (↑  $V_T$ , unchanged RR) → mild respiratory alkalosis (to ↑ fetal  $\text{CO}_2$  elimination).

## Human chorionic gonadotropin

SOURCE	Syncytiotrophoblast of placenta.
FUNCTION	Maintains corpus luteum (and thus progesterone) for first 8–10 weeks of gestation by acting like LH (otherwise no luteal cell stimulation → abortion). Luteal-placental shift is complete after 8–10 weeks; placenta synthesizes its own estriol and progesterone and corpus luteum degenerates. Used to detect pregnancy because it appears early in urine (see above). Has identical $\alpha$ subunit as LH, FSH, TSH (states of ↑ hCG can cause hyperthyroidism). $\beta$ subunit is unique (pregnancy tests detect $\beta$ subunit). hCG is ↑ in multifetal gestation, hydatidiform mole, choriocarcinoma, and some cancers.

**Lactation**

After parturition and delivery of placenta, rapid ↓ in estrogen and progesterone disinhibits prolactin → initiation of lactation. Suckling is required to maintain milk production and ejection, since ↑ nerve stimulation → ↑ oxytocin and prolactin.

Prolactin—induces and maintains lactation and ↓ reproductive function.

Oxytocin—assists in milk letdown; also promotes uterine contractions.

Breast milk is the ideal nutrition for infants < 6 months old. Contains immunoglobulins (conferring passive immunity; mostly IgA), macrophages, lymphocytes. Breast milk reduces infant infections and is associated with ↓ risk for child to develop asthma, allergies, diabetes mellitus, and obesity. Guidelines recommend exclusively breastfed infants get vitamin D and possibly iron supplementation.

Breastfeeding facilitates bonding with the child. Breastfeeding or donating milk ↓ risk of breast and ovarian cancers.

**Menopause**

Diagnosed by amenorrhea for 12 months. ↓ estrogen production due to age-linked decline in number of ovarian follicles. Average age at onset is 51 years (earlier in people who smoke tobacco).

Usually preceded by 4–5 years of abnormal menstrual cycles. Source of estrogen (estrone) after menopause becomes peripheral conversion of androgens, ↑ androgens → hirsutism.

↑↑ FSH is specific for menopause (loss of negative feedback on FSH due to ↓ estrogen).

Hormonal changes: ↓ estrogen, ↑↑ FSH, ↑ LH (no surge), ↑ GnRH.

Causes **HAVOCS**: Hot flashes (most common), Atrophy of the Vagina, Osteoporosis, Coronary artery disease, Sleep disturbances.

Menopause before age 40 suggests 1° ovarian insufficiency (premature ovarian failure); may occur in females who have received chemotherapy and/or radiation therapy.

**Androgens**

Testosterone, dihydrotestosterone (DHT), androstenedione.

**SOURCE**

DHT and testosterone (testis), **androstenedione (adrenal)**

Potency: DHT > testosterone > androstenedione.

**FUNCTION**

Testosterone:

- Differentiation of epididymis, vas deferens, seminal vesicles (internal genitalia, except prostate)
- Growth spurt: penis, seminal vesicles, sperm, muscle, RBCs
- Deepening of voice
- Closing of epiphyseal plates (via estrogen converted from testosterone)
- Libido

Testosterone is converted to DHT by

$5\alpha$ -reductase, which is inhibited by finasteride. In the male, **androgens** are converted to **estrogens** by **aromatase** (primarily in adipose tissue and testes).

DHT:

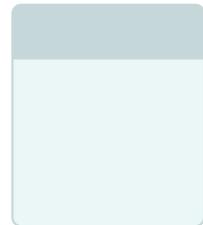
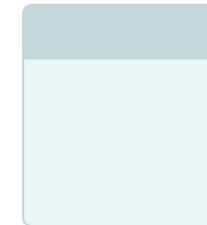
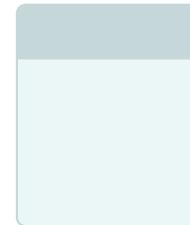
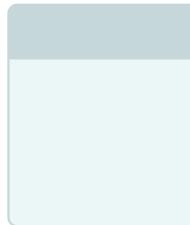
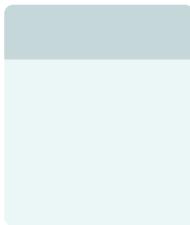
- Early—differentiation of penis, scrotum, prostate
- Late—prostate growth, balding, sebaceous gland activity

**Anabolic-androgenic steroid use**—↑ fat-free mass, muscle strength, performance. Suspect in males who present with changes in behavior (eg, aggression), acne, gynecomastia, erythrocytosis (↑ risk of thromboembolism), small testes (exogenous testosterone → hypothalamic-pituitary-gonadal axis inhibition → ↓ intratesticular testosterone → ↓ testicular size, ↓ sperm count, azoospermia). Females may present with virilization (eg, hirsutism, acne, breast atrophy, male pattern baldness).

**Tanner stages of sexual development**

Tanner stage is assigned independently to genitalia, pubic hair, and breast (eg, a person can have Tanner stage 2 genitalia, Tanner stage 3 pubic hair). Earliest detectable secondary sexual characteristic is breast bud development in females, testicular enlargement in males.

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## ► REPRODUCTIVE—PATHOLOGY

<b>Sex chromosome disorders</b>	Aneuploidy most commonly due to meiotic nondisjunction.	
<b>Klinefelter syndrome</b>	Male, 47,XXY. Small, firm testes; infertility (azoospermia); tall stature with eunuchoid proportions (delayed epiphyseal closure → ↑ long bone length); gynecomastia; female hair distribution. May present with developmental delay. Presence of inactivated X chromosome (Barr body). Common cause of hypogonadism seen in infertility workup. ↑ risk of breast cancer.	Dysgenesis of seminiferous tubules → ↓ inhibin B → ↑ FSH. Abnormal Leydig cell function → ↓ testosterone → ↑ LH.
<b>Turner syndrome</b>	Female, 45,XO. <b>Short</b> stature (associated with <b>SHOX</b> gene, preventable with growth hormone therapy), ovarian dysgenesis (streak ovary), broad chest with widely spaced nipples, bicuspid aortic valve, coarctation of the aorta (femoral < brachial pulse), lymphatic defects (result in webbed neck or cystic hygroma; lymphedema in feet, hands), horseshoe kidney, high-arched palate, shortened 4th metacarpals. Most common cause of 1° amenorrhea. No Barr body.	Menopause before menarche. ↓ estrogen leads to ↑ LH, FSH. Sex chromosome (X, or rarely Y) loss often due to nondisjunction during meiosis or mitosis. Meiosis errors usually occur in paternal gametes → sperm missing the sex chromosome. Mitosis errors occur after zygote formation → loss of sex chromosome in some but not all cells → mosaic karyotype (eg. 45,X/46XX). (45,X/46,XY) mosaicism associated with increased risk for gonadoblastoma. Pregnancy is possible in some cases (IVF, exogenous estradiol-17 $\beta$ and progesterone).
<b>Double Y males</b>	47, XYY. Phenotypically normal (usually undiagnosed), very tall. Normal fertility. May be associated with severe acne, learning disability, autism spectrum disorders.	
<b>Other disorders of sex development</b>	Formerly called intersex states. Discrepancy between phenotypic sex (external genitalia, influenced by hormonal levels) and gonadal sex (testes vs ovaries, corresponds with Y chromosome).	
<b>46,XX DSD</b>	Ovaries present, but external genitalia are virilized or atypical. Most commonly due to congenital adrenal hyperplasia (excessive exposure to androgens early in development).	
<b>46,XY DSD</b>	Testes present, but external genitalia are feminized or atypical. Most commonly due to androgen insensitivity syndrome (defect in androgen receptor).	
<b>Ovotesticular DSD</b>	46,XX > 46,XY. Both ovarian and testicular tissue present (ovotestis); atypical genitalia.	

Diagnosing disorders by sex hormones	Testosterone	LH	Diagnosis
	↑	↑	Androgen insensitivity syndrome
	↑	↓	Testosterone-secreting tumor, exogenous androgenic steroids
	↓	↑	Hypergonadotropic (1°) hypogonadism
	↓	↓	Hypogonadotropic (2°) hypogonadism

Diagnosing disorders by physical characteristics	Uterus	Breasts	Diagnosis
	⊕	⊖	Hypergonadotropic (1°) hypogonadism in genotypic female Hypogonadotropic (2°) hypogonadism in genotypic female
	⊖	⊕	Müllerian agenesis in genotypic female Androgen insensitivity syndrome in genotypic male

Aromatase deficiency	Inability to synthesize endogenous estrogens. Autosomal recessive. During fetal life, DHEA produced by fetal adrenal glands cannot be converted to estrogen by the placenta and is converted to testosterone peripherally → virilization of both female infant (atypical genitalia) and mother (acne, hirsutism; fetal androgens can cross placenta).
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Androgen insensitivity syndrome	Defect in androgen receptor resulting in female-appearing genetic male (46,XY DSD); female external genitalia with scant axillary and pubic hair, rudimentary vagina; uterus and fallopian tubes absent due to persistence of anti-Müllerian hormone from testes. Patients develop normal functioning testes (often found in labia majora; surgically removed to prevent malignancy). ↑ testosterone, estrogen, LH (vs sex chromosome disorders).
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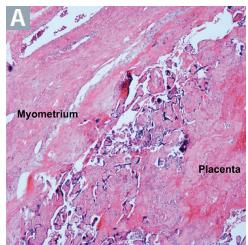
5α-reductase deficiency	Autosomal recessive; sex limited to genetic males (46,XY DSD). Inability to convert testosterone to DHT. Atypical genitalia until puberty, when ↑ testosterone causes masculinization/↑ growth of external genitalia. Testosterone/estrogen levels are normal; LH is normal or ↑. Internal genitalia are normal.
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Kallmann syndrome	Failure to complete puberty; a form of hypogonadotropic hypogonadism. Defective migration of neurons and subsequent failure of olfactory bulbs to develop → ↓ synthesis of GnRH in the hypothalamus; hyposmia/anosmia; ↓ GnRH, FSH, LH, testosterone. Infertility (low sperm count in males; amenorrhea in females).
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## Placental disorders

### Placenta accreta spectrum



Formerly called morbidly adherent placenta. Abnormal invasion of trophoblastic tissue into uterine wall **A**. Risk factors: prior C-section or other uterine surgery (areas of uterine scarring impair normal decidualization), placenta previa, ↑ maternal age, multiparity. Three types depending on depth of trophoblast invasion:

- **Placenta accreta**—attaches to myometrium (instead of overlying decidua basalis) without invading it. Most common type.
- **Placenta increta**—partially invades **into** myometrium.
- **Placenta percreta**—completely invades (“**perforates**”) through myometrium and serosa, sometimes extending into adjacent organs (eg, bladder → hematuria).

Presents with difficulty separating placenta from uterus after fetal delivery and severe postpartum hemorrhage upon attempted manual removal of placenta (often extracted in pieces).

**Uterine rupture**

Full-thickness disruption of uterine wall. Risk factors: prior C-section (usually occurs during labor in a subsequent pregnancy), abdominal trauma. Presents with painful vaginal bleeding, fetal heart rate abnormalities (eg, bradycardia), easily palpable fetal parts, loss of fetal station. May be life threatening for both mother and fetus.

**Postpartum hemorrhage**

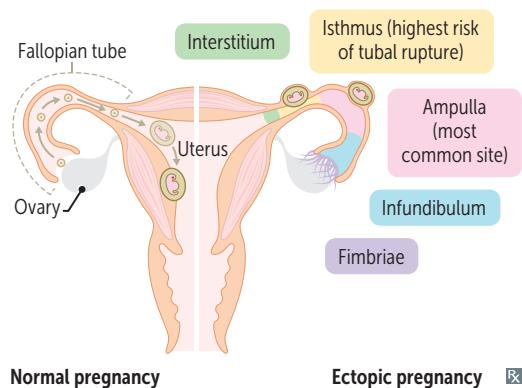
Greater-than-expected blood loss after delivery. Leading cause of maternal mortality worldwide. Etiology (4 T's): **T**one (uterine atony → soft, boggy uterus; most common), **T**rauma (eg, lacerations, incisions, uterine rupture), **T**issue (retained products of conception), **T**hrombin (coagulopathy). Treatment: uterine massage, oxytocin. If refractory, surgical ligation of uterine or internal iliac arteries (fertility is preserved since ovarian arteries provide collateral circulation).

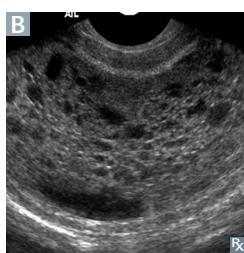
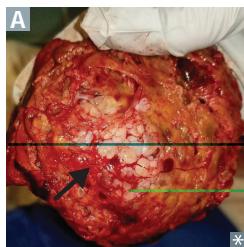
**Ectopic pregnancy**

Implantation of fertilized ovum in a site other than the uterus, most often in ampulla of fallopian tube **A**. Risk factors: tubal pathologies (eg, scarring from salpingitis [PID] or surgery), previous ectopic pregnancy, IUD, IVF.

Presents with first-trimester bleeding and/or lower abdominal pain. Often clinically mistaken for appendicitis. Suspect in patients with history of amenorrhea, lower-than-expected rise in hCG based on dates. Confirm with ultrasound, which may show extraovarian adnexal mass.

Treatment: methotrexate, surgery.



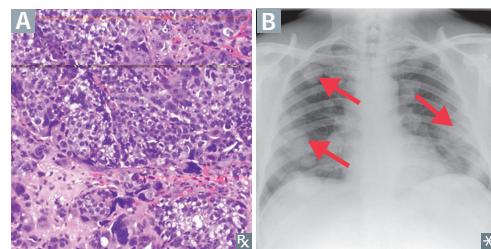
**Hydatidiform mole**

Cystic swelling of chorionic villi and proliferation of chorionic epithelium (only trophoblast).  
Presents with vaginal bleeding, emesis, uterine enlargement more than expected, pelvic pressure/pain. Associated with hCG-mediated sequelae: hyperthyroidism, theca lutein cysts, hyperemesis gravidarum, early preeclampsia (before 20 weeks of gestation).  
Treatment: dilation and curettage +/- methotrexate. Monitor hCG.

	<b>Complete mole</b>	<b>Partial mole</b>
KARYOTYPE	46,XX (most common); 46,XY	69,XXX; 69,XXY; 69,XYY
COMPONENTS	Most commonly enucleated egg + single sperm (subsequently duplicates paternal DNA)	2 sperm + 1 egg
HISTOLOGY	Hydropic villi, circumferential and diffuse trophoblastic proliferation	Only some villi are hydropic, focal/minimal trophoblastic proliferation
FETAL PARTS	No	Yes ( <b>partial</b> = fetal <b>parts</b> ) ⊕ (maternally expressed) <b>Partial mole is P57 positive</b>
STAINING FOR P57 PROTEIN	⊖ (paternally imprinted)	
UTERINE SIZE	↑	—
hCG	↑↑↑↑	↑
IMAGING	“Honeycombed” uterus or “clusters of grapes” <b>A</b> , “snowstorm” <b>B</b> on ultrasound	Fetal parts
RISK OF INVASIVE MOLE	15–20%	< 5%
RISK OF CHORIOCARCINOMA	2%	Rare

**Choriocarcinoma**

Rare malignancy of trophoblastic tissue **A** (cytotrophoblasts, syncytiotrophoblasts), without chorionic villi present. Most commonly occurs after an abnormal pregnancy (eg, hydatidiform mole, abortion); can occur nongestationally in gonads. Presents with abnormal uterine bleeding, hCG-mediated sequelae, dyspnea, hemoptysis. Hematogenous spread to lungs → “cannonball” metastases **B**. Treatment: methotrexate.

**Hypertension in pregnancy****Gestational hypertension**

BP > 140/90 mm Hg after 20 weeks of gestation. No preexisting hypertension. No proteinuria or end-organ damage. Hypertension prior to 20 weeks of gestation suggests chronic hypertension. Treatment: antihypertensives (**Hydralazine**,  **$\alpha$ -methyldopa**, **labetalol**, **nifedipine**), deliver at 37–39 weeks. **Hypertensive moms love nifedipine**.

**Preeclampsia**

New-onset hypertension with either proteinuria or end-organ dysfunction after 20 weeks of gestation (onset of preeclampsia < 20 weeks of gestation may suggest molar pregnancy). Caused by abnormal placental spiral arteries → endothelial dysfunction, vasoconstriction, ischemia. Risk factors: history of preeclampsia, multifetal gestation, chronic hypertension, diabetes, chronic kidney disease, autoimmune disorders (eg, antiphospholipid syndrome), obesity, age > 35 years. Complications: placental abruption, coagulopathy, renal failure, pulmonary edema, uteroplacental insufficiency; may lead to eclampsia and/or HELLP syndrome. Treatment: antihypertensives, IV magnesium sulfate (to prevent seizure); definitive is delivery. Prophylaxis: aspirin.

**Eclampsia**

Preeclampsia with seizures. Death due to stroke, intracranial hemorrhage, ARDS. Treatment: IV magnesium sulfate, antihypertensives, immediate delivery.

**HELLP syndrome**

Preeclampsia with thrombotic microangiopathy of the liver. **Hemolysis**, **Elevated Liver enzymes**, **Low Platelets**. May occur in the absence of hypertension and proteinuria. Blood smear shows schistocytes. Can lead to hepatic subcapsular hematomas (rupture → severe hypotension) and DIC (due to release of tissue factor from injured placenta). Treatment: immediate delivery.

**Supine hypotensive syndrome**

Also called aortocaval compression syndrome. Seen at > 20 weeks of gestation. Supine position → compression of abdominal aorta and IVC by gravid uterus → ↓ placental perfusion (can lead to pregnancy loss) and ↓ venous return (hypotension). Relieved by left lateral decubitus position.

**Gynecologic tumor epidemiology**

Incidence (US)—endometrial > ovarian > cervical; cervical cancer is more common worldwide due to lack of screening or HPV vaccination.

Prognosis: Cervical (**best** prognosis, diagnosed < 45 years old) > Endometrial (middle-aged, about 55 years old) > Ovarian (**worst** prognosis, > 65 years).

CEOs often go from **best** to **worst** as they get older.

**Vulvar pathology****Non-neoplastic****Bartholin cyst and abscess**

Due to blockage of Bartholin gland duct causing accumulation of gland fluid. May lead to abscess 2° to obstruction and inflammation **A**. Usually in reproductive-age females.

**Lichen sclerosus**

Chronic, progressive inflammatory disease characterized by porcelain-white plaques **B** that can be hemorrhagic, eroded, or ulcerated. May extend to anus producing figure-eight appearance. ↑ incidence in prepubertal and peri-/postmenopausal females. Presents with intense pruritus, dyspareunia, dysuria, dyschezia. Benign, but slightly ↑ risk for SCC.

**Lichen simplex chronicus**

Hyperplasia of vulvar squamous epithelium. Presents with leathery, thick vulvar skin with enhanced skin markings due to chronic rubbing or scratching. Benign, no risk of SCC.

**Neoplastic****Vulvar carcinoma**

Carcinoma from squamous epithelial lining of vulva **C**. Rare. Presents with leukoplakia, biopsy often required to distinguish carcinoma from other causes.

HPV-related vulvar carcinoma—associated with high-risk HPV types 16, 18. Risk factors: multiple partners, early coitarche. Usually in reproductive-age females.

Non-HPV vulvar carcinoma—usually from long-standing lichen sclerosus. Females > 70 years old.

**Extramammary Paget disease**

Intraepithelial adenocarcinoma. Carcinoma in situ, low risk of underlying carcinoma (vs Paget disease of the breast, which is always associated with underlying carcinoma). Presents with pruritus, erythema, crusting, ulcers **D**.



**Imperforate hymen**

Incomplete degeneration of the central portion of the hymen. Accumulation of vaginal mucus at birth → self-resolving bulge in introitus. If untreated, leads to 1° amenorrhea, cyclic abdominal pain, hematocolpos (accumulation of menstrual blood in vagina → bulging and bluish hymenal membrane).

**Vaginal tumors****Squamous cell carcinoma**

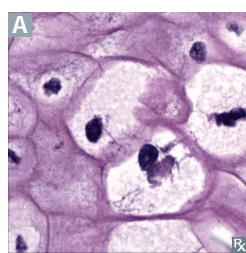
Usually 2° to cervical SCC; 1° vaginal carcinoma rare.

**Clear cell adenocarcinoma**

Arises from vaginal adenosis (persistence of glandular columnar epithelium in proximal vagina), found in females who had exposure to diethylstilbestrol in utero.

**Sarcoma botryoides**

Embryonal rhabdomyosarcoma variant. Affects females < 4 years old; spindle-shaped cells; desmin +. Presents with clear, grapelike, polypoid mass emerging from vagina.

**Cervical pathology****Dysplasia and carcinoma in situ**

Disordered epithelial growth; begins at basal layer of squamocolumnar junction (transformation zone) and extends outward. Classified as CIN 1, CIN 2, or CIN 3 (severe, irreversible dysplasia or carcinoma in situ), depending on extent of dysplasia. Associated with HPV-16 and HPV-18, which produce both the E6 gene product (inhibits TP53) and E7 gene product (inhibits pRb) (6 before 7; P before R). Koilocytes (cells with wrinkled "raisinoid" nucleus and perinuclear halo A) are pathognomonic of HPV infection. May progress slowly to invasive carcinoma if left untreated. Typically asymptomatic (detected with Pap smear) or presents as abnormal vaginal bleeding (often postcoital).

Risk factors: multiple sexual partners, HPV, smoking, early coitarche, DES exposure, immunocompromise (eg, HIV, transplant).

**Invasive carcinoma**

Often squamous cell carcinoma. Pap smear can detect cervical dysplasia before it progresses to invasive carcinoma. Diagnose via colposcopy and biopsy. Lateral invasion can block ureters → hydronephrosis → renal failure.

**Primary ovarian insufficiency**

Also called premature ovarian failure.

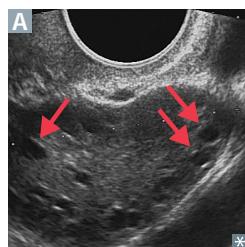
Premature atresia of ovarian follicles in females of reproductive age. Most often idiopathic; associated with chromosomal abnormalities (eg, Turner syndrome, fragile X syndrome premutation), autoimmunity. Need karyotype screening. Patients present with signs of menopause after puberty but before age 40. ↓ estrogen, ↑ LH, ↑ FSH.

**Most common causes of anovulation**

Pregnancy, polycystic ovarian syndrome, obesity, HPO axis abnormalities/immaturity, premature ovarian failure, hyperprolactinemia, thyroid disorders, eating disorders, competitive athletics, Cushing syndrome, adrenal insufficiency, chromosomal abnormalities (eg, Turner syndrome).

**Functional hypothalamic amenorrhea**

Also called exercise-induced amenorrhea. Severe caloric restriction, ↑ energy expenditure, and/or stress → functional disruption of pulsatile GnRH secretion → ↓ LH, FSH, estrogen. Pathogenesis includes ↓ leptin (due to ↓ fat) and ↑ cortisol (stress, excessive exercise). Associated with eating disorders and “female athlete triad” (↓ calorie availability/excessive exercise, ↓ bone mineral density, menstrual dysfunction).

**Polycystic ovarian syndrome**

Hyperinsulinemia and/or insulin resistance hypothesized to alter hypothalamic hormonal feedback response → ↑ LH:FSH, ↑ androgens (eg, testosterone) from theca interna cells, ↓ rate of follicular maturation → unruptured follicles (cysts) + anovulation. Common cause of ↓ fertility in females.

Diagnosed based on ≥ 2 of the following: cystic/enlarged ovaries on ultrasound (arrows in A), oligo-/anovulation, hyperandrogenism (eg, hirsutism, acne). Associated with obesity, acanthosis nigricans. ↑ risk of endometrial cancer 2° to unopposed estrogen from repeated anovulatory cycles.

Treatment: cycle regulation via weight reduction (↓ peripheral estrone formation), OCPs (prevent endometrial hyperplasia due to unopposed estrogen); clomiphene (ovulation induction); spironolactone, finasteride, flutamide to treat hirsutism.

**Primary dysmenorrhea**

Painful menses, caused by uterine contractions to ↓ blood loss → ischemic pain. Mediated by prostaglandins. Treatment: NSAIDs, acetaminophen, hormonal contraceptives.

**Ovarian cysts**

Usually asymptomatic, but may rupture, become hemorrhagic, or lead to adnexal torsion.

**Follicular cyst**

Functional (physiologic) cyst. Most common ovarian mass in young females. Caused by failure of mature follicle to rupture and ovulate. May produce excess estrogen. Usually resolves spontaneously.

**Corpus luteal cyst**

Functional cyst. Caused by failure of corpus luteum to involute after ovulation. May produce excess progesterone. Usually resolves spontaneously.

**Theca lutein cyst**

Also called hyperreactio luteinalis. Caused by hCG overstimulation. Often bilateral/multiple. Associated with gestational trophoblastic disease (eg, hydatidiform mole, choriocarcinoma).

**Ovarian tumors**

Most common adnexal mass in females > 55 years old. Present with abdominal distention, bowel obstruction, pleural effusion.

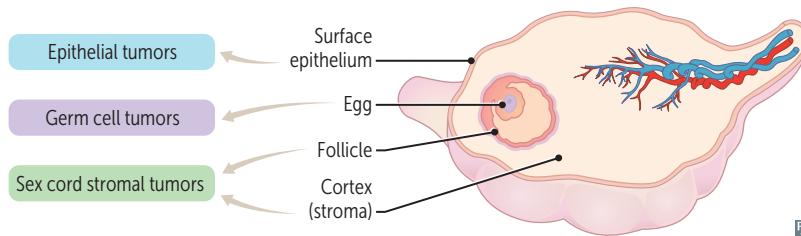
Risk ↑ with advanced age, ↑ number of lifetime ovulations (early menarche, late menopause, nulliparity), endometriosis, genetic predisposition (eg, *BRCA1/BRCA2* mutations, Lynch syndrome).

Risk ↓ with previous pregnancy, history of breastfeeding, OCPs, tubal ligation.

Epithelial tumors are typically serous (lined by serous epithelium natively found in fallopian tubes, and often bilateral) or mucinous (lined by mucinous epithelium natively found in cervix). Monitor response to therapy/relapse by measuring CA 125 levels (not good for screening).

Germ cell tumors can differentiate into somatic structures (eg, teratomas), or extra-embryonic structures (eg, yolk sac tumors), or can remain undifferentiated (eg, dysgerminoma).

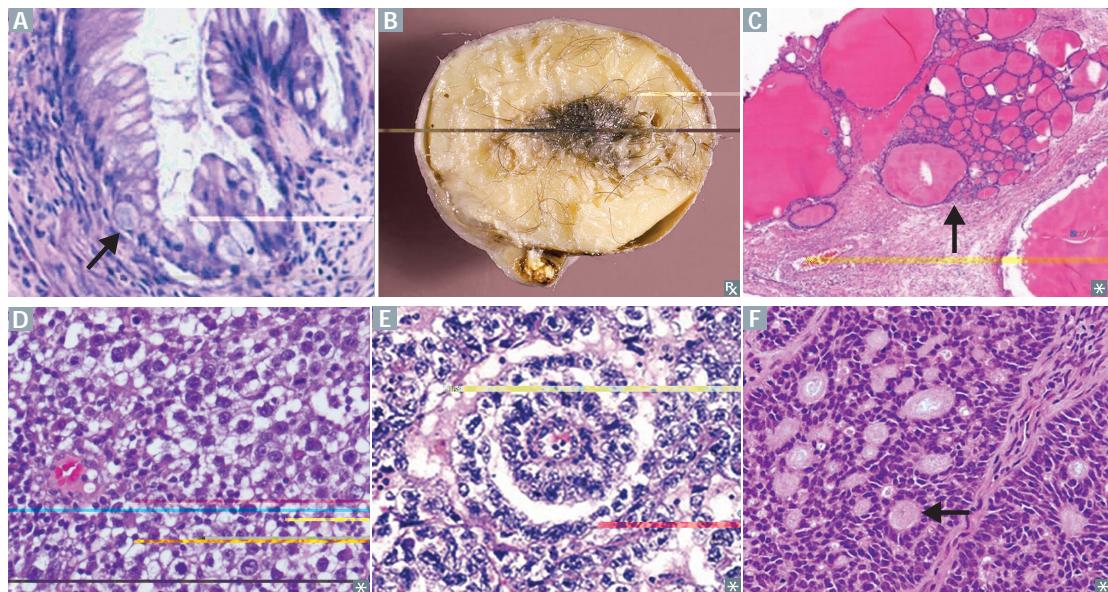
Sex cord stromal tumors develop from embryonic sex cord (develops into theca and granulosa cells of follicle, Sertoli and Leydig cells of seminiferous tubules) and stromal (ovarian cortex) derivatives.



TYPE	CHARACTERISTICS
<b>Epithelial tumors</b>	
<b>Serous cystadenoma</b>	Benign. Most common ovarian neoplasm. Lined by fallopian tube-like epithelium.
<b>Mucinous cystadenoma</b>	Benign. Multiloculated, large. Lined by mucus-secreting epithelium <b>A</b> .
<b>Brenner tumor</b>	Usually benign. Nests of urothelial-like (bladderlike) epithelium with “coffee bean” nuclei.
<b>Serous carcinoma</b>	Most common malignant ovarian neoplasm. Psammoma bodies.
<b>Mucinous carcinoma</b>	Malignant. Rare. May be metastatic from appendiceal or other GI tumors. Can result in pseudomyxoma peritonei (intraperitoneal accumulation of mucinous material).

**Ovarian tumors (continued)**

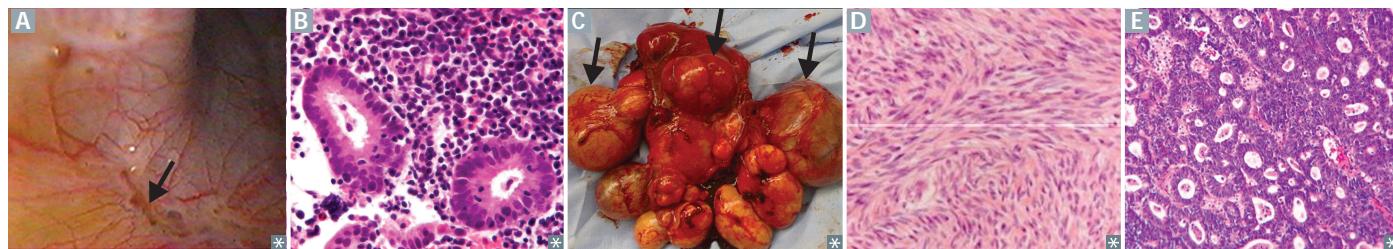
TYPE	CHARACTERISTICS
<b>Germ cell tumors</b>	
Mature cystic teratoma	Also called dermoid cyst. Benign. Most common ovarian tumor in young females. Cystic mass with elements from all 3 germ layers (eg, teeth, hair, sebum) <b>B</b> . May be painful 2° to ovarian enlargement or torsion. Monodermal form with thyroid tissue (struma ovarii <b>C</b> ) may present with hyperthyroidism. Malignant transformation rare (usually to squamous cell carcinoma).
Immature teratoma	Malignant, aggressive. Contains fetal tissue, neuroectoderm. Commonly diagnosed before age 20. Typically represented by immature/embryoniclike neural tissue.
Dysgerminoma	Malignant. Most common in adolescents. Equivalent to male seminoma but rarer. Sheets of uniform “fried egg” cells <b>D</b> . Tumor markers: ↑ hCG, ↑ LDH.
Yolk sac tumor	Also called endodermal sinus tumor. Malignant, aggressive. Yellow, friable (hemorrhagic) mass. 50% have Schiller-Duval bodies (resemble glomeruli, arrow in <b>E</b> ). Tumor marker: ↑ AFP. Occurs in children and young adult females.
<b>Sex cord stromal tumors</b>	
Fibroma	Benign. Bundle of spindle-shaped fibroblasts.
	<b>Meigs syndrome</b> —triad of ovarian fibroma, ascites, pleural effusion. “Pulling” sensation in groin.
Thecoma	Benign. May produce estrogen. Usually presents as abnormal uterine bleeding in a postmenopausal female.
Sertoli-Leydig cell tumor	Benign. Gray to yellow-brown mass. Resembles testicular histology with tubules/cords lined by pink Sertoli cells. May produce androgens → virilization (eg, hirsutism, male pattern baldness, clitoral enlargement).
Granulosa cell tumor	Most common malignant sex cord stromal tumor. Predominantly occurs in females in their 50s. Often produces estrogen and/or progesterone. Presents with postmenopausal bleeding, endometrial hyperplasia, sexual precocity (in preadolescents), breast tenderness. Histology shows <b>Call-Exner bodies</b> (granulosa cells arranged haphazardly around collections of eosinophilic fluid, resembling primordial follicles; arrow in <b>F</b> ). Tumor marker: ↑ inhibin. “Give <b>Gran</b> ny a <b>Call</b> .”

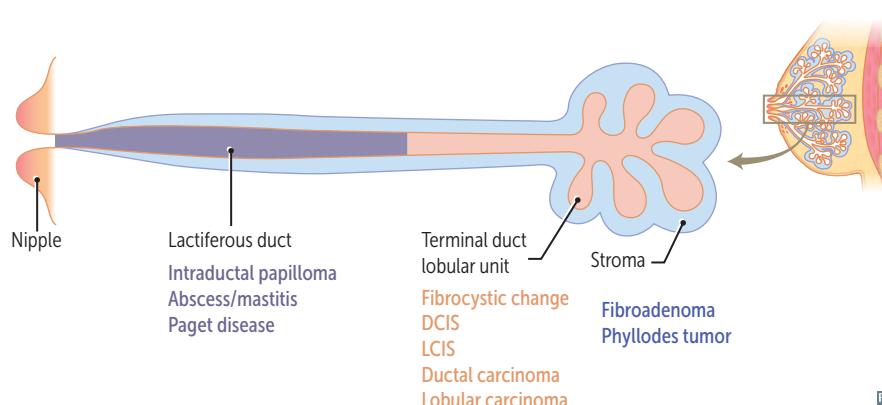


**Uterine conditions**

TYPE	CHARACTERISTICS
<b>Non-neoplastic</b>	
<b>Adenomyosis</b>	Presence of endometrial tissue (glands and stroma) in myometrium. May be due to invagination of basal layer of endometrium or metaplasia of remnant progenitor cells. Presents with abnormal uterine bleeding, dysmenorrhea. Diffusely enlarged (“globular”), soft (“boggy”) uterus on exam.
<b>Endometriosis</b>	Presence of endometrial tissue (glands and stroma) outside uterus. May be due to ectopic implantation of endometrial tissue (via retrograde menses, blood vessels, lymphatics) or metaplasia of remnant progenitor cells. Typically involves pelvic sites, such as superficial peritoneum (yellow-brown “powder burn” lesions <b>A</b> ) and ovaries (forms blood-filled “chocolate” cyst called endometrioma). Presents with chronic pelvic pain (eg, dysmenorrhea, dyspareunia), abnormal uterine bleeding, infertility. Normal-sized uterus on exam.
<b>Endometrial hyperplasia</b>	Abnormal endometrial gland proliferation. Usually caused by excess estrogen unopposed by progesterone. Associated with obesity, anovulation (eg, PCOS), hormone replacement therapy. Presents with abnormal uterine bleeding. ↑ risk for endometrial carcinoma (especially with nuclear atypia).
<b>Endometritis</b>	Inflammation of endometrium <b>B</b> . Usually occurs after delivery due to inoculation of uterine cavity by vaginal microbiota. C-section is the most important risk factor (sutures and necrotic tissue act as nidus for polymicrobial infection). Presents with fever, uterine tenderness, purulent lochia.
<b>Intrauterine adhesions</b>	Fibrous bands/tissue within endometrial cavity. Caused by damage to basal layer of endometrium, usually after dilation and curettage. Presents with abnormal uterine bleeding (↓ menses), infertility, recurrent pregnancy loss, dysmenorrhea. Also called Asherman syndrome when symptomatic.

Neoplastic	
<b>Leiomyoma</b>	Benign tumor of myometrium (also called fibroid). Most common gynecological tumor. Arises in reproductive-age females. ↑ incidence in Black population. Typically multiple; subtypes based on location: submucosal, intramural, or subserosal. Usually asymptomatic, but may present with abnormal uterine bleeding, pelvic pressure/pain, reproductive dysfunction. Estrogen sensitive; tumor size ↑ with pregnancy and ↓ with menopause. Enlarged uterus with nodular contour on exam <b>C</b> . Histology: whorled pattern of smooth muscle bundles <b>D</b> and well-demarcated borders.
<b>Endometrial carcinoma</b>	Malignant tumor of endometrium. Most common gynecological cancer in resource-rich countries. Usually arises in postmenopausal females. Presents with abnormal uterine bleeding. <b>Endometrioid carcinoma</b> —most common subtype of endometrial carcinoma. Associated with long-term exposure to unopposed estrogen. Histology: confluent endometrial glands without intervening stroma <b>E</b> .



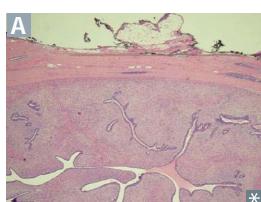
**Breast pathology****Benign breast diseases****Fibrocystic changes**

Most common in premenopausal females 20–50 years old. Present with premenstrual breast pain or lumps; often bilateral and multifocal. Nonproliferative lesions include simple cysts (fluid-filled duct dilation, blue dome), papillary apocrine change/metaplasia, stromal fibrosis. Risk of cancer is usually not increased. Proliferative lesions include

- **Sclerosing adenosis**—acini and stromal fibrosis, associated with calcifications. Slight ↑ risk for cancer.
- **Epithelial hyperplasia**—cells in terminal ductal or lobular epithelium. ↑ risk of carcinoma with atypical cells.

**Inflammatory processes**

**Fat necrosis**—benign, usually painless, lump due to injury to breast tissue. Calcified oil cyst on mammography; necrotic fat and giant cells on biopsy. Up to 50% of patients may not report trauma. **Lactational mastitis**—occurs during breastfeeding, ↑ risk of bacterial infection through cracks in nipple. *S aureus* is most common pathogen. Treat with antibiotics and continue breastfeeding.

**Benign tumors**

**Fibroadenoma**—most common in females < 35 years old. Small, well-defined, mobile mass. Tumor composed of fibrous tissue and glands. ↑ size and tenderness with ↑ estrogen (eg, pregnancy, prior to menstruation). Risk of cancer is usually not increased.

**Intraductal papilloma**—small fibroepithelial tumor within lactiferous ducts, typically beneath areola. Most common cause of nipple discharge (serous or bloody). Slight ↑ risk for cancer.

**Phyllodes tumor**—large mass of connective tissue and cysts with "leaflike" lobulations **A**. Most common in 5th decade. Some may become malignant.

**Gynecomastia**

Breast enlargement in males due to ↑ estrogen compared with androgen activity. Physiologic in newborn, pubertal, and older males, but may persist after puberty. Other causes include cirrhosis, hypogonadism (eg, Klinefelter syndrome), testicular tumors, drugs (eg, spironolactone).

**Breast cancer**

Commonly postmenopausal. Often presents as a palpable hard mass **A** most often in upper outer quadrant. Invasive cancer can become fixed to pectoral muscles, deep fascia, Cooper ligaments, and overlying skin → nipple retraction/skin dimpling. Usually arises from terminal duct lobular unit. Amplification/overexpression of estrogen/progesterone receptors or HER2 (an EGF receptor) is common; triple negative (ER  $\ominus$ , PR  $\ominus$ , and HER2  $\ominus$ ) form more aggressive.

Risk factors in females: ↑ age; history of atypical hyperplasia; family history of breast cancer; race (White patients at highest risk, Black patients at ↑ risk for triple  $\ominus$  breast cancer); *BRCA1/BRCA2* mutations; ↑ estrogen exposure (eg, nulliparity); postmenopausal obesity (adipose tissue converts androstenedione to estrone); ↑ total number of menstrual cycles; absence of breastfeeding; later age of first pregnancy; alcohol intake. In males: *BRCA2* mutation, Klinefelter syndrome. Axillary lymph node metastasis most important prognostic factor in early-stage disease.

TYPE	CHARACTERISTICS	NOTES
<b>Noninvasive carcinomas</b>		
<b>Ductal carcinoma in situ</b>	Fills ductal lumen (black arrow in <b>B</b> indicates neoplastic cells in duct; blue arrow shows engorged blood vessel). Arises from ductal atypia. Often seen early as microcalcifications on mammography.	Early malignancy without basement membrane penetration. Usually does not produce a mass.
<b>Paget disease</b>	Extension of underlying DCIS/invasive breast cancer up the lactiferous ducts and into the contiguous skin of nipple → eczematous patches over nipple and areolar skin <b>C</b> .	Pageat cells = intraepithelial adenocarcinoma cells.
<b>Lobular carcinoma in situ</b>	↓ E-cadherin expression. No mass or calcifications → incidental biopsy finding.	↑ risk of cancer in either breast (vs DCIS, same breast and quadrant).
<b>Invasive carcinomas</b>		
<b>Invasive ductal</b>	Firm, fibrous, “rock-hard” mass with sharp margins and small, glandular, ductlike cells in desmoplastic stroma.	Most common type of invasive breast cancer.
<b>Invasive lobular</b>	↓ E-cadherin expression → orderly row of cells (“single file” <b>D</b> ) and no duct formation. Often lacks desmoplastic response.	Often bilateral with multiple lesions in the same location. Lines of cells = Lobular.
<b>Inflammatory</b>	Dermal lymphatic space invasion → breast pain with warm, swollen, erythematous skin around exaggerated hair follicles (peau d'orange) <b>E</b> .	Poor prognosis (50% survival at 5 years). Often mistaken for mastitis or Paget disease. Usually lacks a palpable mass.



**Penile pathology****Peyronie disease**

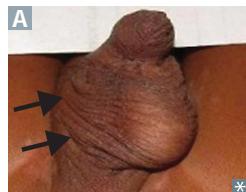
Abnormal curvature of penis **A** due to fibrous plaque within tunica albuginea. Associated with repeated minor trauma during intercourse. Can cause pain, anxiety, erectile dysfunction. Consider surgical repair or treatment with collagenase injections once curvature stabilizes. Distinct from penile fracture (rupture of tunica albuginea due to forced bending).

**Ischemic priapism**

Painful sustained erection lasting > 4 hours. Associated with sickle cell disease (sickled RBCs block venous drainage of corpus cavernosum vascular channels), medications (eg, sildenafil, trazodone). Treat immediately with corporal aspiration, intracavernosal phenylephrine, or surgical decompression to prevent ischemia.

**Squamous cell carcinoma**

Seen in the US, but more common in Asia, Africa, South America. Most common type of penile cancer **B**. Precursor in situ lesions: Bowen disease (in penile shaft, presents as leukoplakia “white plaque”), erythroplasia of Queyrat (carcinoma in situ of the glans, presents as erythroplakia “red plaque”), Bowenoid papulosis (carcinoma in situ of unclear malignant potential, presenting as reddish papules). Associated with uncircumcised males and HPV-16.

**Cryptorchidism**

Descent failure of one **A** or both testes. Impaired spermatogenesis (since sperm develop best at temperatures < 37°C) → subfertility. Can have normal testosterone levels (Leydig cells are mostly unaffected by temperature). Associated with ↑ risk of germ cell tumors. Prematurity ↑ risk of cryptorchidism. ↓ inhibin B, ↑ FSH, ↑ LH; testosterone ↓ in bilateral cryptorchidism, normal in unilateral. Most cases resolve spontaneously; otherwise, orchiopexy performed before 2 years of age.

**Testicular torsion**

Rotation of testicle around spermatic cord and vascular pedicle. Commonly presents in males 12–18 years old. Associated with congenital inadequate fixation of testis to tunica vaginalis → horizontal positioning of testes (“bell clapper” deformity). May occur after an inciting event (eg, trauma) or spontaneously. Characterized by acute, severe pain, high-riding testis, and absent cremasteric reflex. ⊖ Prehn sign.

Treatment: surgical correction (orchiopexy) within 6 hours, manual detorsion if surgical option unavailable in timeframe. If testis is not viable, orchectomy. Orchiopexy, when performed, should be bilateral because the contralateral testis is at risk for subsequent torsion.

**Varicocele**

Dilated veins in pampiniform plexus due to ↑ venous pressure; most common cause of scrotal enlargement in adult males. Most often on left side because of ↑ resistance to flow from left gonadal vein drainage into left renal vein. Right-sided varicocele may indicate IVC obstruction (eg, from RCC invading right renal vein). Can cause infertility because of ↑ temperature. Diagnosed by standing clinical exam/Valsalva maneuver (distension on inspection and “bag of worms” on palpation; augmented by Valsalva) or ultrasound **A**. Does not transilluminate. Treatment: consider surgical ligation or embolization if associated with pain or infertility.

**Extragonadal germ cell tumors** Arise in midline locations. In adults, most commonly in retroperitoneum, mediastinum, pineal, and suprasellar regions. In infants and young children, sacrococcygeal teratomas are most common.

**Benign scrotal lesions** Testicular masses that can be transilluminated (vs solid testicular tumors).

**Hydrocele**



Accumulation of serous fluid within tunica vaginalis. Types:

- **Congenital** (communicating)—due to incomplete obliteration of processus vaginalis. Common cause of scrotal swelling **A** in infants. Most resolve spontaneously within 1 year.
- **Acquired** (noncommunicating)—due to infection, trauma, tumor. Termued hematocele if bloody.

**Spermatocele**

Cyst due to dilated epididymal duct or rete testis.

Paratesticular fluctuant nodule.

**Germ cell tumors****Seminoma**

Malignant. Painless, homogenous testicular enlargement. Most common testicular tumor. Analogous to ovarian dysgerminoma. Does not occur in infancy. Large cells in lobules with watery cytoplasm and “fried egg” appearance on histology, ↑ placental alkaline phosphatase (PLAP). Highly radiosensitive. Late metastasis, excellent prognosis.

**Embryonal carcinoma**

Malignant. Painful, hemorrhagic mass with necrosis. Often glandular/papillary morphology. “Pure” embryonal carcinoma is rare; most commonly mixed with other tumor types. May present with metastases. May be associated with ↑ hCG and normal AFP levels when pure (↑ AFP when mixed). Worse prognosis than seminoma.

**Teratoma**

Mature teratoma may be malignant in adult males. Benign in children and females.

**Yolk sac tumor**

Also called endodermal sinus tumor. Malignant, aggressive. Yellow, mucinous. Analogous to ovarian yolk sac tumor. Schiller-Duval bodies resemble primitive glomeruli. ↑ AFP is highly characteristic. Most common testicular tumor in children < 3 years old.

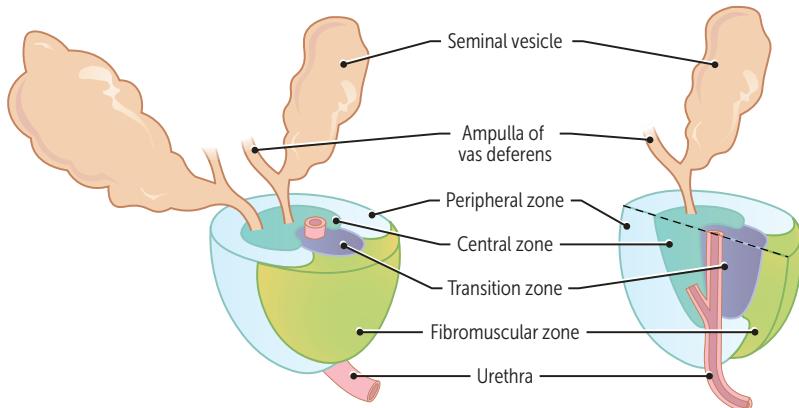
**Choriocarcinoma**

Malignant. Disordered syncytiotrophoblastic and cytotrophoblastic elements. Hematogenous metastases to lungs and brain. ↑ hCG. May produce gynecomastia, symptoms of hyperthyroidism ( $\beta$  subunit of hCG is similar to  $\beta$  subunit of TSH).

**Non–germ cell tumors**

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### Benign prostatic hyperplasia



Common in males > 50 years old. Characterized by smooth, elastic, firm nodular enlargement (hyperplasia not hypertrophy) of transition zone, which compress the urethra into a vertical slit. Not premalignant.

Often presents with ↑ frequency of urination, nocturia, difficulty starting and stopping urine stream, dysuria. May lead to distention and hypertrophy of bladder, hydronephrosis, UTIs. ↑ total PSA, with ↑ fraction of free PSA. PSA is made by prostatic epithelium stimulated by androgens.

Treatment:  $\alpha_1$ -antagonists (terazosin, tamsulosin), which cause relaxation of smooth muscle; 5 $\alpha$ -reductase inhibitors (eg, finasteride); PDE-5 inhibitors (eg, tadalafil); surgical resection (eg, TURP, ablation).

### Prostatitis

Characterized by dysuria, frequency, urgency, low back pain. Warm, tender, enlarged prostate.

Acute bacterial prostatitis—in older males most common bacterium is *E coli*; in young males consider *C trachomatis*, *N gonorrhoeae*.

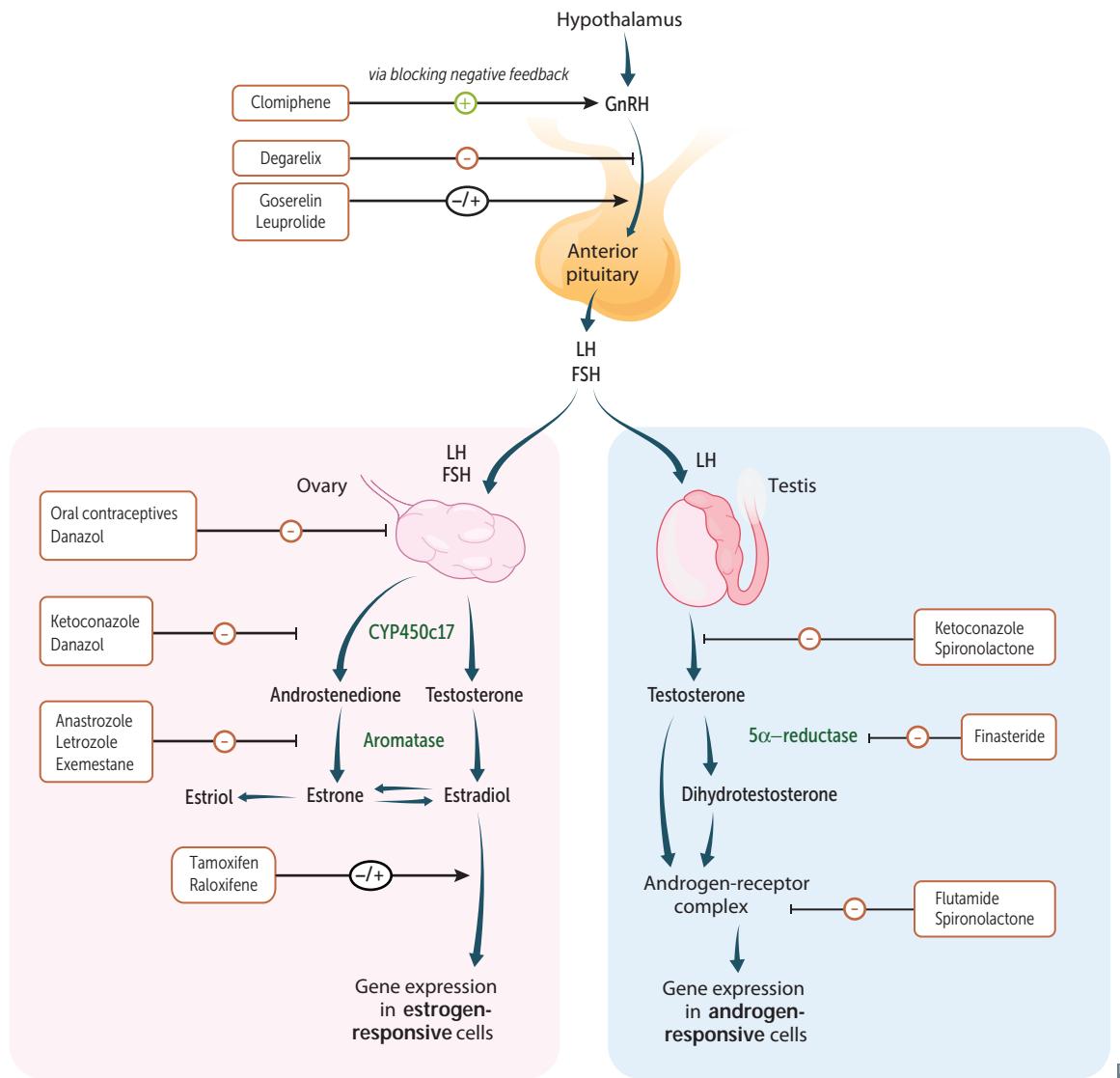
Chronic prostatitis—either bacterial or nonbacterial (eg, 2° to previous infection, nerve problems, chemical irritation).

### Prostatic adenocarcinoma

Common in males > 50 years old. Arises most often from posterior lobe (peripheral zone) of prostate gland and is most frequently diagnosed by ↑ PSA and subsequent needle core biopsies (transrectal, ultrasound-guided). Histologically graded using Gleason grade, which is based on glandular architecture and correlates closely with metastatic potential. Prostatic acid phosphatase (PAP) and PSA are useful tumor markers (↑ total PSA, with ↓ fraction of free PSA). Osteoblastic metastases in bone may develop in late stages, as indicated by lower back pain and ↑ serum ALP and PSA. Metastasis to the spine often occurs via Batson (vertebral) venous plexus.

## ► REPRODUCTIVE—PHARMACOLOGY

## Control of reproductive hormones



**Gonadotropin-releasing hormone analogs**

**Leuprorelin**, goserelin, nafarelin, histrelin.

<b>MECHANISM</b>	Act as GnRH agonists when used in pulsatile fashion. When used in continuous fashion, first transiently act as GnRH agonists (tumor flare), but subsequently act as GnRH antagonists (downregulate GnRH receptor in pituitary → ↓ FSH and ↓ LH → ↓ estrogen in females and ↓ testosterone in males). Can be used in <b>lieu</b> of GnRH.
<b>CLINICAL USE</b>	Uterine fibroids, endometriosis, precocious puberty, prostate cancer, infertility. <b>Pulsatile</b> for pregnancy, <b>continuous</b> for cancer.
<b>ADVERSE EFFECTS</b>	Hypogonadism, ↓ libido, erectile dysfunction, nausea, vomiting.

**Degarelix**

<b>MECHANISM</b>	GnRH antagonist. No start-up flare.
<b>CLINICAL USE</b>	Prostate cancer.
<b>ADVERSE EFFECTS</b>	Hot flashes, liver toxicity.

**Ethinyl estradiol**

<b>MECHANISM</b>	Binds estrogen receptors.
<b>CLINICAL USE</b>	Hypogonadism or ovarian failure, menstrual abnormalities (combined OCPs), hormone replacement therapy in postmenopausal females.
<b>ADVERSE EFFECTS</b>	↑ risk of endometrial cancer (when given without progesterone), bleeding in postmenopausal patients, clear cell adenocarcinoma of vagina in females exposed to DES in utero, ↑ risk of thrombi. Contraindications—ER + breast cancer, history of DVTs, tobacco use in females > 35 years old.

**Selective estrogen receptor modulators**

<b>Clomiphene</b>	Antagonist at estrogen receptors in hypothalamus. Prevents normal feedback inhibition and ↑ release of LH and FSH from pituitary, which stimulates ovulation. Used to treat infertility due to anovulation (eg, PCOS). May cause hot flashes, ovarian enlargement, multiple simultaneous pregnancies, visual disturbances.
<b>Tamoxifen</b>	Antagonist at breast, partial agonist at uterus, bone. Hot flashes, ↑ risk of thromboembolic events (especially with tobacco smoking), and endometrial cancer. Used to treat and prevent recurrence of ER/PR + breast cancer and to prevent gynecomastia in patients undergoing prostate cancer therapy.
<b>Raloxifene</b>	Antagonist at breast, uterus; agonist at bone; hot flashes, ↑ risk of thromboembolic events (especially with tobacco smoking), but no increased risk of endometrial cancer (vs tamoxifen, so you can “relax”); used primarily to treat osteoporosis.

**Aromatase inhibitors**

<b>MECHANISM</b>	Inhibit peripheral conversion of androgens to estrogen.
<b>CLINICAL USE</b>	ER + breast cancer in postmenopausal females.

<b>Hormone replacement therapy</b>	Used for relief or prevention of menopausal symptoms (eg, hot flashes, vaginal atrophy), osteoporosis ( $\uparrow$ estrogen, $\downarrow$ osteoclast activity). Unopposed estrogen replacement therapy $\uparrow$ risk of endometrial cancer, progesterone/progestin is added. Possible increased cardiovascular risk.
<b>Progestins</b>	Levonorgestrel, medroxyprogesterone, etonogestrel, norethindrone, megestrol.
MECHANISM	Bind progesterone receptors, $\downarrow$ growth and $\uparrow$ vascularization of endometrium, thicken cervical mucus.
CLINICAL USE	Contraception (forms include pill, intrauterine device, implant, depot injection), endometrial cancer, abnormal uterine bleeding. Progestin challenge: presence of bleeding upon withdrawal of progestins excludes anatomic defects (eg, Asherman syndrome) and chronic anovulation without estrogen.
<b>Antiprogestins</b>	Mifepristone, ulipristal.
MECHANISM	Competitive inhibitors of progestins at progesterone receptors.
CLINICAL USE	Termination of pregnancy (mifepristone with misoprostol); emergency contraception (ulipristal).
<b>Combined contraception</b>	Progestins and ethinyl estradiol; forms include pill, patch, vaginal ring. Estrogen and progestins inhibit LH/FSH and thus prevent estrogen surge. No estrogen surge $\rightarrow$ no LH surge $\rightarrow$ no ovulation. Progestins cause thickening of cervical mucus, thereby limiting access of sperm to uterus. Progestins also inhibit endometrial proliferation $\rightarrow$ endometrium is less suitable to the implantation of an embryo. Adverse effects: breakthrough menstrual bleeding, breast tenderness, VTE, hepatic adenomas. Contraindications: people $>$ 35 years old who smoke tobacco ( $\uparrow$ risk of cardiovascular events), patients with $\uparrow$ risk of cardiovascular disease (including history of venous thromboembolism, coronary artery disease, stroke), migraine (especially with aura), breast cancer, liver disease.
<b>Copper intrauterine device</b>	
MECHANISM	Produces local inflammatory reaction toxic to sperm and ova, preventing fertilization and implantation; hormone free.
CLINICAL USE	Long-acting reversible contraception. Most effective emergency contraception.
ADVERSE EFFECTS	Heavier or longer menses, dysmenorrhea. Insertion contraindicated in active PID (IUD may impede PID resolution).
<b>Tocolytics</b>	Medications that relax the uterus; include terbutaline ( $\beta_2$ -agonist action), nifedipine ( $\text{Ca}^{2+}$ channel blocker), indomethacin (NSAID). Used to $\downarrow$ contraction frequency in preterm labor and allow time for administration of glucocorticoids (to promote fetal lung maturity) or transfer to appropriate medical center with obstetrical care.

**Danazol**

MECHANISM	Synthetic androgen that acts as partial agonist at androgen receptors.
CLINICAL USE	Endometriosis, hereditary angioedema.
ADVERSE EFFECTS	Weight gain, edema, acne, hirsutism, masculinization, ↓ HDL levels, hepatotoxicity, idiopathic intracranial hypertension.

**Testosterone, methyltestosterone**

MECHANISM	Agonists at androgen receptors.
CLINICAL USE	Treat hypogonadism and promote development of 2° sex characteristics.
ADVERSE EFFECTS	Virilization in females; testicular atrophy in males. Premature closure of epiphyseal plates. ↑ LDL, ↓ HDL.

**Antiandrogens**

DRUG	MECHANISM	CLINICAL USE	ADVERSE EFFECTS
<b>Abiraterone</b>	17α-hydroxylase/17,20-lyase inhibitor (↓ steroid synthesis)	Prostate cancer	Hypertension, hypokalemia (↑ mineralocorticoids)
<b>Finasteride</b>	5α-reductase inhibitor (↓ conversion of testosterone to DHT)	BPH, male-pattern baldness	Gynecomastia, sexual dysfunction
<b>Flutamide, bicalutamide</b>	Nonsteroidal competitive inhibitors at androgen receptor (↓ steroid binding)	Prostate cancer	Gynecomastia, sexual dysfunction
<b>Ketoconazole</b>	17α-hydroxylase/17,20-lyase inhibitor	Prostate cancer	Gynecomastia
<b>Spironolactone</b>	Androgen receptor and 17α-hydroxylase/17,20-lyase inhibitor	PCOS	Amenorrhea

**Tamsulosin**

MECHANISM	$\alpha_1$ -antagonist selective for $\alpha_{1A/D}$ receptors in prostate (vs vascular $\alpha_{1B}$ receptors) → ↓ smooth muscle tone → ↑ urine flow.
CLINICAL USE	BPH.

**Minoxidil**

MECHANISM	Direct arteriolar vasodilator.
CLINICAL USE	Androgenetic alopecia (pattern baldness), severe refractory hypertension.