Reviewed By
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Embryology of the Female Genital Organs

Objectives:

- → List the steps that determine the sexual differentiation into male or female during embryonic development.
- → Describe the embryologic development of the female genital tract (internal and external).

Congenital Malformations of the Genital Tract:

- → Identify the incidence, clinical presentation, complication and management of the various types of congenital tract malformation including:
  - → Mullerian agenesis.
  - → Disorder of lateral fusion of the mullerian ducts: uterus didelphys, septate uterus, unicornuate uterus, bicornuate uterus.
  - → Disorder of the ventricle fusion of the mullerian ducts: vaginal septum, cervical agenesis, dysgenesis.
  - → Defects of the external genitalia: imperforate hymen & ambiguous genitalia.
- → List the steps that determine the sexual differentiation into male or female during embryonic development.

Intersex (Abnormal Sexual Development):

- → List the causes of abnormal sexual development
- → List the types of intersex:
  - → Masculinized female: congenital abdominal hyperplasia or maternal exposure to androgen.
  - → Under masculinized male: anatomical or enzymatic testicular failure or endogen insensitivity.
  - → True hermaphrodites.
  - → Discuss the various types of intersex in term of clinical presentation, differential diagnosis and management.

- → Slides
- → Important
- → Golden notes
- → Extra
- → Doctor's notes
- → Previous Doctor's notes
- → Reference

Kaplan Video

Editing File

Embryology of the Female Genital Organs

Sexual Differentiation:

→ **First step in sexual differentiation:** determination of genetic/chromosomal sex (XX or XY).

1. **Genetic / Chromosomal Sex**[1]
2. **Gonadal Sex**[1]
3. **Phenotypic Sex**[1]

Males

→ **Male sexual development depends on:** presence of functioning testes secreting testosterone and responsive end organ.
→ XX exposed to androgen by external hormones or hormone secreting tumor from the mother → male external genitalia development or ambiguous genitalia (*elongated clitoris & fused labia*).
→ XY male but there is no androgen → female external genitalia.

Females

→ **Female dexual development depends on:** absence of Y chromosome, and **not**:
  → Presence of ovaries.
  → Presence of 2 X chromosomes.
→ Even embryos who have only one egg will still develop as females.
→ Exposed to androgens in-utero → musculanized.

External Genitalia:

1. ***Undifferentiated Stage at 4 - 8 weeks***

→ **Neutral genitalia, includes:**
  → Genital tubercle (phallus).
  → Labioscrotal swellings.
  → Urogenital folds.
  → Urogenital sinus.
→ At this stage, neither male or female.

2. ***Female and Male External Genital Development at 9 - 12 weeks***

→ By 12 weeks gestation male & female genitalia can be differentiated.
→ Absence of androgens → female external genitalia develop.
→ Development of male genitalia requires the action of androgens, specifically **DHT**.
→ No hormonal stimulation is needed for differentiation of the external genitalia into labia majora, labia minora, clitoris, and distal vagina.

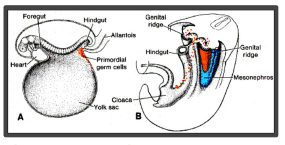
Testosterone —(**5-alpha reductase**)→ DHT

1. Are all different.

Embryology of the Female Genital Organs

Internal Genitalia:

01 Gonads (Testes & Ovaries):

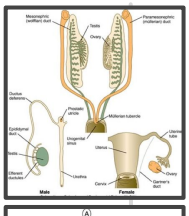


→ Undifferentiated gonads **begin** to develop on the **5th week** *memorize those numbers*.
→ Gonads develop as **primordial germ cells** originate in **yolk sac** (form in the wall of yolk sac close to allantois) → migrate along the dorsal mesentery of hindgut to the **genital ridge**.
→ Germ cells migrate to developing gonads → form ovaries in females + testes in males.
→ Gonads develop from the mesothelium on the genital ridge → primary sex cords grow into mesenchyme → outer cortex and inner medulla.
→ Absence of Y chromosome → undifferentiated gonad develops into an **ovary**.
→ 45XO embryo → ovaries develop but undergo atresia → **streak ovaries** → characteristic of Turner.
→ Incomplete ovarian development, fibrous tissue that contain no or very few follicles.

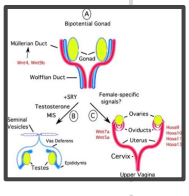
→ **Ovary** develops from **cortex** + medulla regresses.
→ The ovary contains **2 millions primary oocytes** at birth.
→ Turner syndrome → born with reduced ovarian reserve, because ovaries are replaced by fibrous tissue with few follicles → 50k, 100k, or 200k.
→ **Testes** develop from **medulla** + cortex regresses (**man** → **medulla**).
→ Development of the testes requires presence of SRY gene (Sex determining Region Y) found on Y chromosome.
→ I don't need the whole Y chromosome, I only need a whole SRY gene.

02 Uterus & Fallopian Tubes:

→ Invagination of the coelomic epithelium on the craniolateral end of the mesonephric ridge → paramesonephric ducts (mullerian ducts).



→ Mullerian duct is present in all early embryos and is the primordium of the female internal reproductive system.
→ **Females:** no hormonal stimulation is required, without MIF, development continues to form the fallopian tubes, corpus of uterus, cervix, and proximal vagina.
→ **Males:** Y chromosome induces gonadal secretion of müllerian inhibitory factor (MIF) → involuted müllerian duct + testosterone required for the development of vas deferens, seminal vesicles, epididymis, and efferent ducts.



→ **Females:** fusion of the **two PMN ducts** → fallopian tubes (sides) at 8 - 11 weeks, uterus (middle) at 12 - 16 weeks (*proliferation of mesoderm around fused lower part → muscular wall of uterus*), cervix & upper 2/3 of vagina.
→ Lower ⅓ of vagina and ovaries are not derivatives of PMN ducts.
→ **Male fetus:** testes secrete mullerian inhibiting factor (**AMH**) → **regression** of **mullerian** ducts.
→ **Beginning:** 2 systems are present side by side, **then:** either paramesonephric (female), or mesonephric (male) develops .

03 Vagina:

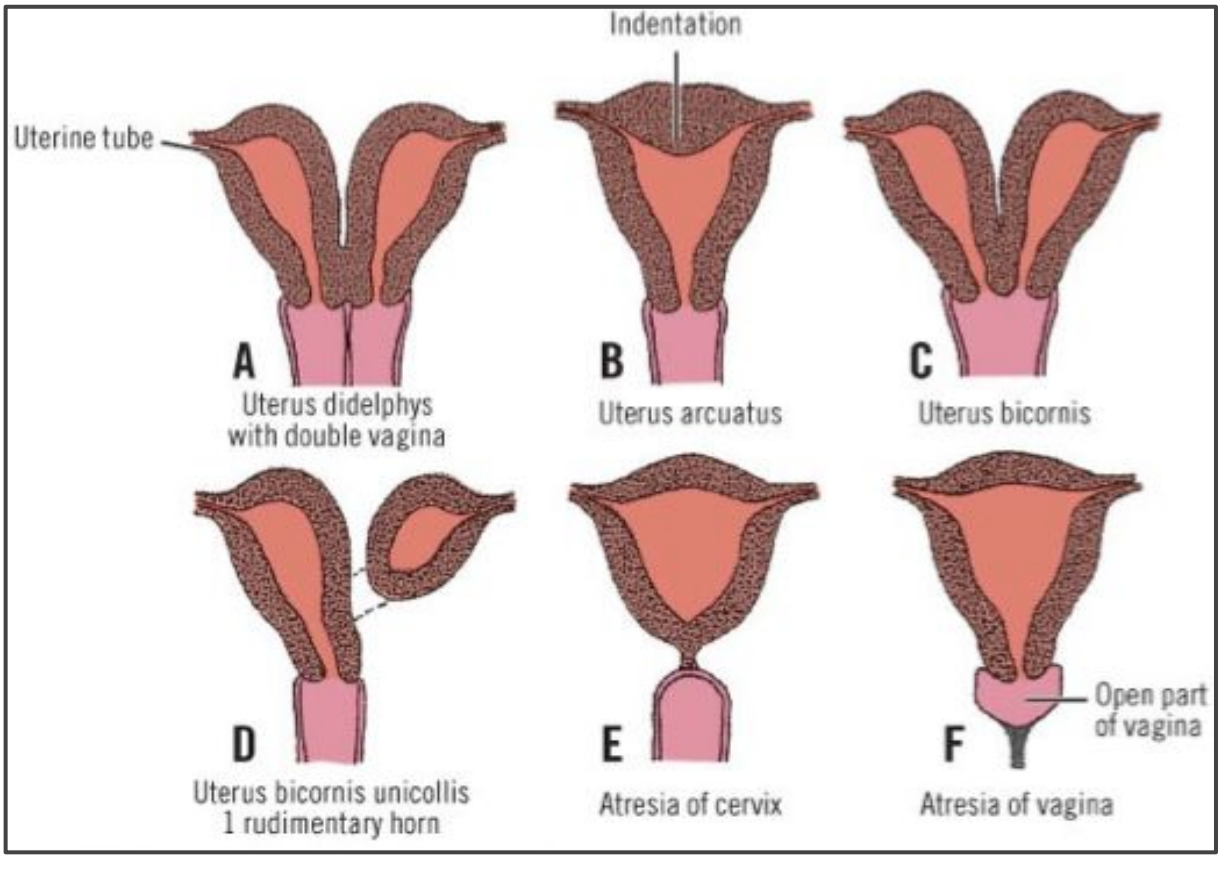
→ Caudal ends of mullerian ducts form **mullerian tubercle** at dorsal wall of urogenital sinus.
→ Mullerian tubercle is obliterated → vaginal plate → 16 - 18 week the central core breaks down → vaginal lumen.
→ Mullerian tubercle → upper ⅔ of vagina.
→ Urogenital sinus → lower ⅓ of vagina.

Embryology of the Female Genital Organs

Internal Genitalia:

TABLE 1-2
Male and Female Derivatives of Embryonic Urogenital Structures

Embryonic Structure	Derivatives	
	Male	Female
Labioscrotal swellings	Scrotum	Labia majora
Urogenital folds	Ventral portion of penis	Labia minora
Phallus	Penis	Clitoris
	Glans, corpora cavernosa penis, and corpus spongiosum	Glans, corpora cavernosa, bulb of the vestibule
Urogenital sinus	Urinary bladder Prostate gland Prostatic utricle Bulbourethral glands Seminal colliculus	Urinary bladder Urethral and paraurethral glands Vagina Greater vestibular glands Hymen
Paramesonephric duct	Appendix of testes	Hydatid of Morgagni Uterus and cervix Fallopian tubes
Mesonephric duct	Appendix of epididymis Ductus of epididymis Ductus deferens Ejaculatory duct and seminal vesicle	Appendix vesiculosis Duct of epoophoron Gartner's duct
Metanephric duct	Ureter, renal pelvis, calyces, and collecting system	—
Mesonephric tubules	Ductuli efferentes Paradidymis	Ureter, renal pelvis, calyces, and collecting system Epoophoron Paroophoron
Undifferentiated gonad	Testis	Ovary
Cortex	Seminiferous tubules	Ovarian follicles
Medulla	—	Medulla
	Rete testis	Rete ovarii
Gubernaculum	Gubernaculum testis	Round ligament of uterus



Congenital Malformations of the Female Genital Tract

Mullerian Agenesis:

- → **Mayer- Rokitansky-Kuster-Hauser Syndrome.**
- → **Etiology:** failure of mullerian duct development → **absence** of upper vagina, cervix & uterus (*uterine remnants -fundus- may be found*).
  - → Ovaries & fallopian tubes are **present**, they have ovaries because ovaries don't develop from Mullerian ducts.
- → Normal 46XX female with normal external genitalia.

Features:

- → Patients presents with primary amenorrhea, completely normal female but no menses + no uterus on US.
- → 47% have associated urinary tract anomalies → do intravenous pyelogram (IVP).
- → 12% skeletal anomalies.
  - → Structures that give rise to urinary tract lie close to Müllerian ducts & are affected by the same injurious insult → anomalies of female genital tract are commonly associated with urinary tract anomalies.

Management:

- → **Psychological counseling:** can have normal sexual life but can't have children.
  - → Now we have uterine transplantation → option to have children.
- → **Surgical:**
  - → **Vaginoplasty:** create a space between urethra & rectum at the site of the vagina + dissect this space → take a skin graft from the thigh and place it inside (*because if you make an opening and leave it, it will close again*) → the graft will implant there + will form a functioning vagina for the patient.
  - → **Vaginal dilators:** because they have short vagnia.
  - → **Excision of uterine remnant:** if it has functioning endometrium.

Disorders of Lateral Fusion of the Mullerian Duct:

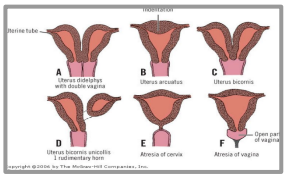
- → Most patients can conceive without difficulty.
- → ↑ **incidence of:**
  - → Recurrent abortions.
  - → Premature birth.
  - → Fetal loss.
  - → C-section.
  - → Fetal malpresentation.
  - → **Cervix incompetence:** managed by cervical cerclage during pregnancy → 🚫 abortions.

Features:

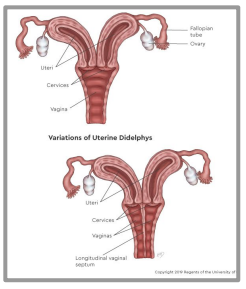
- → Shortly after menarche → if obstruction to uterine blood flow.
- → Difficulty in intercourse → longitudinal vaginal septum.
- → Dysmenorrhea or menorrhagia.
- → Abnormality detected on D&C.
- → **U/S, laparoscopy or laparotomy:** asymptomatic, as incidental finding.
- → Blockage of the menstrual blood → palpable mass.
- → **Complications of pregnancy:** recurrent abortion - preterm delivery.
- → HSG → during infertility or RFL investigations.
- → **Presentation depends on:**
  - → One patent part + other obstructed part → blood collection in one side + pain + mass.
  - → Both parts are patent → menorrhagia.

Non Obstructive Malformations of Mullerian Ducts

Non Obstructive Malformations of Mullerian Ducts:

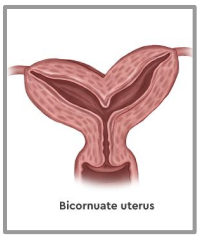


Uterus Didelphys



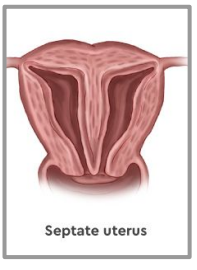
- → Complete duplication of the uterus, cervix & vagina.
- → **Cause:** failure of fusion of the two mullerian ducts.
- → ↑ **pregnancy wastage:** late preterm delivery.
- → **Diagnosis:** HSG or laparoscopy / laparotomy.
- → **Treatment:** if affecting pregnancy outcome → surgical correction (metroplasty).
  - → Join the two cavities together (*only in severe forms*).

Bicornuate Uterus



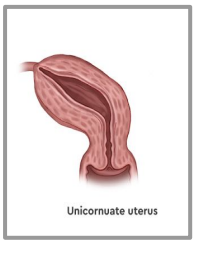
- → Incomplete fusion of the two mullerian ducts.
- → ↑ **pregnancy wastage:** outside dimple → preterm labor.
- → **Diagnosis:** HSG or laparoscopy / laparotomy.
- → **Treatment:** if affecting pregnancy outcome → surgical correction (metroplasty).
  - → Not always requiring surgery, most patients with mild bicornuate don't need treatment (*can carry pregnancy near term*).
  - → Repeated 2nd trimester abortions → think about surgery.

Septate Uterus



- → External contour of the uterus is normal but there is intrauterine septum of varying length & thickness.
- → **Cause:** two Müllerian ducts fuse normally, but there is a failure in degeneration of the median septum.
- → Worst pregnancy outcome → recurrent abortions + implantation.
- → **Diagnosis:** HSG + laparoscopy.
- → **Treatment:** hysteroscopic excision of septum.
  - → You have to treat it.
  - → Remove septum through vagina with hysteroscope.

Unicornuate Uterus



- → Banana-shaped.
- → **Cause:** development of only one mullerian duct, the other one regresses.
- → Almost all patients have associated single kidney.
- → **Pregnancy outcome:** similar to patients with didelphic uterus.
- → **Diagnosis:** HSG or surgery.
- → **Treatment:**
  - → No corrective surgery.
  - → Associated cervix incompetence → cervix cerclage.

- → In 65% of women with a unicornuate uterus, the remaining Müllerian duct may form an incomplete (rudimentary) horn.
- → There may be no cavity in this rudimentary horn or it may have a small space within it, but there is no opening that communicates with unicornuate uterus & vagina.
  - → **Non-Communicating (Blocked) Horn:**
    - → Present with cyclic pelvic pain, mass, ectopic pregnancy in the rudimentary horn or endometriosis & blood collection.
    - → **Treatment:** surgical excision horn.
  - → **Communicating Horn:**
    - → Present with ectopic pregnancy in rudimentary horn.
    - → ↑ pregnancy wastage.

Disorder of Vertical Fusion of the Mullerian Ducts

Vaginal Septum:

→ Faults in junction between mullerian tubercle & urogenital sinus → could be very thick or thin.
→ 85% in upper two thirds the vagina which is more difficult to excise.
→ ↑ incidence of endometriosis.

Features:
→ Primary amenorrhea.
→ Hematocolpos.
→ Mass.
→ Cyclic abdominal pain.

Management:
→ Surgical excision.

Cervix Agenesis / Dysgenesis:

→ Very rare.

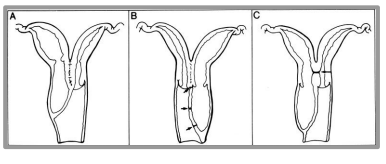
Management:
→ Hysterectomy.
  → Difficult, unsuccessful surgical correction.
  → Surgical correction is difficult, we can't create a cervix.
    → Create a hole for the menaustral flow, and when she gets pregnant she delivers by c-section.
  → Difficulty in creating a hole for menstruation → suppress menstruation + complete her family by IVF → hysterectomy.

Part of the Objectives

Unusual Configuration of Vertical / Lateral Fusion Defects

Unusual Configuration of Vertical / Lateral Fusion Defects:

→ Combined lateral & vertical defects.
→ Do not fit in other categories.
→ **Example:** double uterus with obstructed hemivagina.



01

Complete Vaginal Obstruction
→ Uterus didelphys with one blocked side → remove blockage.

02

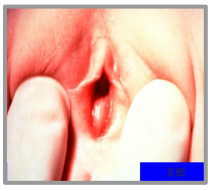
Incomplete Vaginal Obstruction
→ There are fenestrations, might get infected.

03

Complete Obstruction with Common Double Uterus

Defects of the External Genitalia

Defects of the External Genitalia:



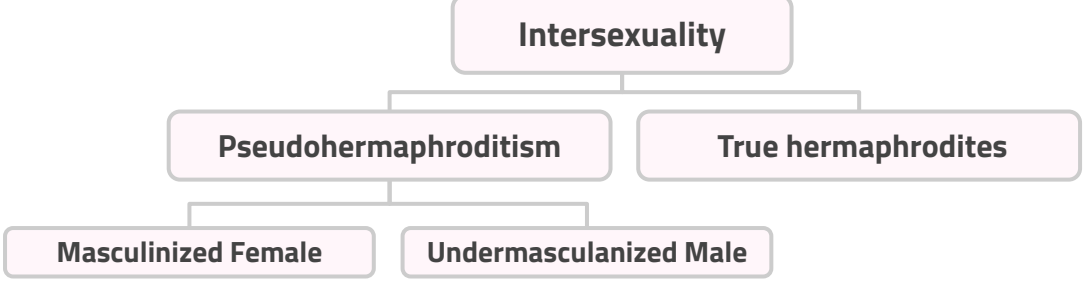
- → Ambiguous genitalia → congenital adrenal hyperplasia hermaphrodites
- → Defects of the clitoris → Uncommon → bifid clitoris
- → Hypertrophied→ androgen effect
- → Imperforate Hymen
  - → Hymen is formed at the junction of the urogenital sinus & sinovaginal bulbs
  - → Pt presents with 1ry amenorrhea with cyclic abdominal pain or hematocolpos / hematometra.
  - → When examining the patient, you find a bulging bluish membrane that has blood behind it, you can feel a uterine mass if they present late
  - → Rx → Cruciate incision.
    - → We excise part of it, because if you just incise it and leave it open it'll close again.

Part of the Objectives

Intersexuality

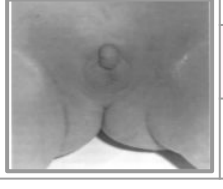
General Causes of Abnormal Sexual Development:

- → Sex chromosome abnormality mosaicism associated with gonadal dysgenesis → 45X/46XY have turner syndrome (45X).
- → Testis incapable of producing testosterone → female external genitalia, but no internal organs.
  - → Testis can produce MIF, but if the testes are destroyed very early during embryonic development, then he will have female internal organs.
- → **End organs incapable of utilizing testosterone:** 5α reductase deficiency - failure of testosterone binding to receptors (androgen insensitivity) → develop as a female.
- → Testis regression → deficient MIF production (important in 🚫 female mullerian duct development) → female internal genital organs in otherwise normal males.
- → ↑ androgen (**Example:** congenital adrenal hyperplasia) → masculinization of female external genitalia → genitalia will have different degrees of virilization depending on case severity.
- → Rarely 46XX male due to the presence of a gene the SRY gene (Sex Determining Region Y).
  - → Responsible for testis development.
- → True hermaphroditism → presence of testicular & gonadal tissue in the same individual (*testis & ovaries in the same person*).



Intersexuality

Pseudohermaphroditism:

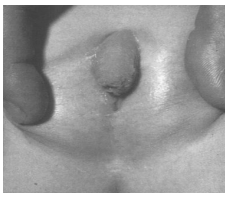
<table>
<tr><th colspan="2">Pseudohermaphroditism</th></tr>
<tr><th>Masculinized Female</th><th>Undermasculanized Male</th></tr>
<tr><td>→ 46XX
→ Family history may be positive.
→ Exposed to androgens in utero → varying degrees of masculinization of external genitalia.</td><td></td></tr>
<tr><td>1. Congenital adrenal hyperplasia (CAH)</td><td>1. Anatomical testicular failure</td></tr>
<tr><td>See next slide.</td><td>Pure gonadal dysgenesis
→ Testes did not develop probably despite XY.
→ Normal chromosomes 46XY.
→ Uterus present.
→ Variable features of ambiguous genitalia (mild to severe) normal female, with mild musculanization.
→ Mild: start secreting MIF so internal organs will not develop → MIF stop functioning → ambiguous external genitalia (not like male and not like female).
→ Sever: looks completely like a female, internal organs (uterus - upper vagina - fallopian tubes) are present because testes did not secrete MIF, but no ovaries (complete normal female but no ovaries & XY).
Mosaicism 45X/46XY
→ Variable features (normal female, ambiguous genitalia, nearly normal male).</td></tr>
<tr><td>2. Exposure of the mother to androgens</td><td>2. Enzymatic testicular failure</td></tr>
<tr><td>→ Rare
→ Androgen secreting tumors e.g. luteoma, arrhenoblastoma
→ Drugs
→ Picture showing Masculinization of female child → mother exposed to methyl testosterone.
  </td><td>→ Enzymatic defects in testosterone biosynthesis.
→ Defects are usually incomplete → varying degrees of masculinization of external genitalia.
→ Uterus & tubes: absent (MIF produced by testes.
→ Testosterone is not secreted → external genitalia will be like a female if complete block or ambiguous if incomplete.</td></tr>
<tr><td></td><td>3. Androgen insensitivity</td></tr>
<tr><td></td><td>See next slide.</td></tr>
</table>

Intersexuality

Pseudohermaphroditism: *Congenital Adrenal Hyperplasia (CAH)*

→ Late-onset CAH is one of the most common autosomal recessive genetic disorders.
→ Most common cause of female intersex.
→ **Etiology:** deficiencies of various enzymes required for cortisol & aldosterone biosynthesis.
  → 21-hydroxylase.
  → 11β-hydroxylase (*commonest defect 90%*).
  → 3β hydroxysteroid dehydrogenase.

Features:
→ **Female may present at birth with ambiguous genitalia:**
  → Enlargement of the clitoris.
  → Excessive fusion of genital folds (closed → looks more like a scrotum + darker in color) obscuring the vagina & urethra.
  → Thickening & rugosity of the labia majora resembling the scrotum.
→ A dangerous salt losing syndrome due to deficiency of aldosterone (in some patients).
  → They will have electrolyte imbalance (a baby with ambiguous genitalia → emergency condition → check for electrolyte imbalance which could be fatal).
→ Delayed menarche & menstrual irregularities



Investigation:
→ Karyotyping to make sure that it is a normal XX.
→ ↑ 17-α-hydroxyprogesterone.
→ 17-ketosteroids (androgens) in urine.
→ Electrolytes & U/S.

Management:
→ Cortisol or its synthetic derivatives → suppress the adrenals → ↓ androgen production.
→ **Corrective surgery:**
  → Neonatal period → clitroplasty.
  → Delayed till puberty → division of the fused labial.
  → Vaginoplasty, better delayed till puberty, because if done in childhood it become stenotic.

Pseudohermaphroditism: *Androgen Insensitivity*

1. 5α Reductase Deficiency:
→ Most common.
→ Autosomal recessive.
→ Formation of the male external genitalia requires 5α reductase.
→ Testosterone → dihydrotestosterone we need it for formation of external genitalia → if not present, external genitalia will develop as female.
→ Formation of the internal wolffian structures respond directly to testosterone.
→ External genitalia female with mild masculinization.
→ Absent uterus because the testes secrete MIF.
→ **At puberty:** ↑ testosterone secretion → virilization.

Intersexuality

Pseudohermaphroditism: *Androgen Insensitivity*

1. Androgen Insensitivity (Testicular Feminization):

A. Complete (Classical TF):

→ **Etiology:** lack of androgen receptors and high levels of androgens present.

Features:

→ Normal female external genitalia with blind vagina.
→ Absent uterus.
→ Primary amenorrhea.
→ **Breast development:** breast is present because the testosterone in converted to estrogen in the periphery.
→ **Attractive female:** tall & no hair in the body because they don't respond to testosterone.
→ Testes found in abdomen or inguinal canal.
→ Normal male testosterone level.

Management:

→ ↑ incidence of malignant change (5%) → **gonadectomy** after puberty.
→ ↑ temperatures associated with intra-abdominal position of testes → testicular cancer → testis removal at age 20 + estrogen replacement is then needed.
→ Estrogen replacement → normal sexual life, but can't have children.

B. Incomplete

→ **Etiology:** lack of androgen receptors and high levels of androgens present.

Features:

→ Ambiguous genitalia with varying degrees.
→ Breast development.
→ Musculanization at puberty.

Management:

→ Partial androgen insensitivity.
→ Genitalia is not completely normal (ambiguous).

True hermaphrodites:

True Hermaphrodites

→ **Have both ovarian & testicular tissue:**
  → Ovotestes on one side & ovary or testes on the other.
  → Ovary on one side & testes on the other.
  → Bilateral ovotestes.
→ Varying degrees of sexual ambiguity.
→ **Karyotyping:**
  → **46XX:** most common.
  → 46XX/XY
  → 46XY
  → 46XY/47XXY

Klinefelter Syndrome

→ 47XXY.
→ Testicular atrophy.
→ Normal male external genitalia.
→ Tall stature.
→ Gynecomastia.
→ Azoospermia (infertility).
→ Truncal obesity.
→ **Common Problems:**
  → Learning disorders.
  → Autoimmune diseases.
  → Low IQ.

439 Summary

Embryology Overview

- Chromosomal sex: determined by chromosome count
  - Genetically female individuals have XX
  - Genetically male individuals have XY
- Gonadal sex: development of the undifferentiated gonads into testes or ovaries
  - Determined primarily by the presence or absence of the **SRY gene** on the Y chromosome
    - Y chromosome with SRY gene → development of testes
    - Absence of Y chromosome → ovarian development (default)
- Phenotypic sex:
  - Ductal differentiation: development of embryonic ducts into internal sex organs
  - External genitalia differentiation: relies on estradiol & dihydrotestosterone (DHT)

Internal genitalia:

Gonads: ovaries and testes	• Begins in the 5th week. Germ cells originate in the yolk sac and migrate to the genital ridge → development of **undifferentiated** gonads
	• **Differentiation** is determined primarily by the presence or absence of the **SRY gene** on the Y chromosome
	  ○ Y chromosome with SRY gene → development of testes
	  ○ Absence of Y chromosome → ovarian development (default)

Uterus, fallopian tubes & proximal vagina	• Both male and female embryos have mesonephric/wolffian ducts and **mullerian/paramesonephric ducts**
	• Males:
	  ○ Sertoli cells → secrete **Mullerian inhibitory factor (MIF)** from testes→ causes degeneration of paramesonephric ducts
	  ○ Leydig cells → secrete Testosterone → stimulate differentiation of mesonephric duct into male internal genitalia
	  ▪ Mesonephric/wolffian duct develops into male internal structures (except prostate):
	  • Seminal vesicles, Epididymis, Ejaculatory duct, Ductus deferens (SEED)
	  ▪ In the testes:
	  • Leydig leads to male (internal and external) sexual differentiation
	  • Sertoli shuts down female (internal) sexual differentiation
	• Females:
	  ○ Default phenotype: no hormonal stimulation is required
	  ○ Absence of MIF → differentiation/fusion of mullerian (paramesonephric) ducts into female internal genitalia
	  ▪ Mullerian (paramesonephric) duct develops into:
	  • Cervix, uterus, fallopian tubes, proximal vagina
	  ○ Absence of testosterone → degeneration of mesonephric ducts

External genitalia:

- By 9-12 weeks, external genitalia can be differentiated in both males and females.
- Primarily driven by the presence or absence of estradiol and dihydrotestosterone
  - Male: testosterone → dihydrotestosterone; DHT (via 5α-reductase) → differentiation of embryonic structures into male external genitalia, bulbourethral glands, and prostate gland
  - Female: estradiol and absence of DHT → differentiation of embryonic structures into female external genitalia
    - Urogenital sinus → distal vagina, hymen, greater vestibular glands (Bartholin), urethral and paraurethral glands, vestibule, bladder, urethra
    - Genital tubercle → glans clitoris
    - Labioscrotal swellings → labia majora
    - Urogenital folds → labia minora

Anomalies of female genital tract

Includes topics from embryology & amenorrhea lectures

Definition:

- Structural anomalies of the female genital tract may be present at birth or may be acquired later in life

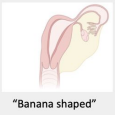
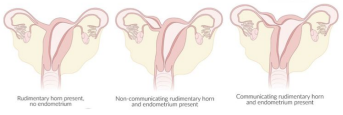
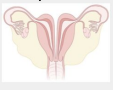
Overview: Mullerian duct anomalies:

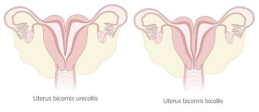
- Failure in formation/development:
  - Mullerian agenesis (MRKH Syndrome)
  - Unicornuate uterus
- Failure in fusion:
  - Horizontal fusion defect - bicornuate uterus, uterus didelphys
  - Vertical fusion defect - imperforate hymen, transverse vaginal septum
- Failure in resorption:
  - Septate uterus

Uterus anomalies:

Anomalies of mullerian duct fusion		
Definition	• Defective fusion of the Müllerian (also known as paramesonephric) ducts during embryonic development • Normally functioning gonads (ovaries) and female karyotype (XX) → normal development of **secondary sexual characteristics (e.g., breast, pubic hair)**	

Types	**Müllerian agenesis** (Mayer-Rokitansky-Kuster-Hauser Syndrome, MRKH Syndrome)	• Failure of both mullerian ducts development→ absence of uterus, cervix, upper vagina
		• Ovaries & **tubes** are present
		• Features:
		  ○ **Karyotype: 46,XX**
		  ○ Primary amenorrhea
		  ○ Fully-developed secondary sexual characteristics

	Unicornuate uterus  "Banana shaped"	• One of the mullerian ducts fails to develop (other one regressed) • Almost all pts have associated single kidney • **Not corrected by surgery**  Rudimentary horn present, no endometrium · Non-communicating rudimentary horn and endometrium present · Communicating rudimentary horn and endometrium present
	Didelphic uterus 	• **Complete** lack of mullerian duct fusion → double uterus, double cervix, double vagina

	Bicornuate uterus	• **Incomplete** fusion of the mullerian ducts to various degrees
		  ○ Uterus bicornis unicollis: double uterus, single cervix, and single vagina
		  ○ Uterus bicornis bicollis: double uterus and double cervix with/without a vaginal septum
		 
		Uterus bicornis unicollis · Uterus bicornis bicollis

	Septate uterus 	The mullerian ducts fuse, but the septa between the two ducts fails to degeneration either partially (subseptate uterus) or completely (septate uterus)

Clinical features	• Asymptomatic before puberty
	• **Infertility and dyspareunia**
	• In some cases, periodic lower abdominal pain
	• Increased risk of the following obstetric complications:
	  ○ Cervical incompetence
	  ○ Ectopic pregnancy
	  ○ Preterm labor
	  ○ Recurrent midtrimester **abortions**
	  ○ Fetal malpresentation
	  ○ Fetal loss
	  ○ Cesarean delivery
	• Associated with urological complications (e.g., renal agenesis, pelvic kidney, horseshoe kidney) and skeletal malformations

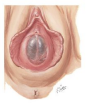
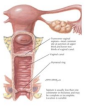
Diagnosis	• Screening tests
	  ○ **Hysterosalpingography**
	  ○ Laparoscopy
	  ○ Transvaginal or abdominal ultrasound
	• Confirmatory test: MRI
	• Renal ultrasound should be performed in all patients to screen for renal abnormalities

Treatment	• Surgical treatment is usually not recommended in the following situations:
	  ○ Another treatable cause of infertility co-exists
	  ○ The woman is asymptomatic
	• Metroplasty: reconstruction of the uterus
	• Septoplasty: a type of metroplasty that only involves resection of the septum in a separate uterus

Intrauterine adhesions (asherman's syndrome)	
Etiology	• **Following uterine dilation or curettage (D&C):** most common cause • Postinflammatory (e.g., chlamydia)
Clinical features	• Usually asymptomatic • **Abnormal uterine bleeding** • **Secondary amenorrhea** • Infertility • Recurrent pregnancy loss • Periodic abdominal pain
Diagnosis	• **Progesterone withdrawal test:** bleeding does not occur following progestin withdrawal given block of the outflow tract • Hysterosalpingography: ~~honeycomb appearance of the uterus~~ • **Confirmatory test: hysteroscopy** to directly visualize adhesions
Treatment	• Only indicated if patients are symptomatic. • Hysteroscopic resection of the adhesions→ insert IUD to deter reformation→ HRT

439 Summary

Vaginal anomalies:

	Agenesis of upper vagina	Imperforate hymen	Transverse vaginal septum
Overview	• Mullerian agenesis • Associated with absent or malformed uterus and cervix (in almost all cases) & skeletal anomalies	• Congenital defect • Hymen without an opening • Cryptomenorrhea at puberty→ hematocolpos (accumulation of blood in the vagina) and/or hematometra (accumulation of blood in the uterus)	• Failure of recanalization of the mullerian duct → transverse septum • Cryptomenorrhea → hematocolpos
Illustration			
Clinical Features	• **Asymptomatic before puberty** • **Primary amenorrhea** • **Normal development of secondary sexual characteristics**		
	• Infertility, dyspareunia • Perineal examination: vaginal dimple and a hymenal fringe	• Possible palpable lower abdominal mass • Cyclic abdominal pain • Perineal examination: bulging/bluish membrane in the vulva	• Infertility, possible palpable lower abdominal mass • Cyclic abdominal pain • Perineal examination: normal vulva and external genitalia
Diagnosis	Normal levels of LH, FSH, prolactin, estradiol, and testosterone	Clinical diagnosis	Transvaginal ultrasonography or MRI
Treatment	Vaginoplasty	Incise membrane (hymenectomy)	• Vaginal dilators • Vaginoplasty

Disorders of Sexual Development (DSD)

Includes topics from embryology & amenorrhea lectures

Definition:

- Group of congenital conditions characterized by the atypical development of chromosomal, gonadal, and/or phenotypic sex.

Disorders:

	Pathophysiology	Features	Diagnosis	Management
Complete androgen insensitivity syndrome **(Testicular feminization syndrome)**	• **Karyotype: 46,XY** • **X-linked recessive** • **Defective androgen receptors→** varying degrees of end organ insensitivity to androgens	• Female external genitalia & breast development • Blind-ended vaginal pouch • Fallopian tube, uterine & vaginal agenesis • **Primary amenorrhea, sparse/**scant or no pubic hair • Absent male internal genitalia: except for **undescended** testes (may be interlabial, **inguinal**, or abdominal)	• Clinical presentation & genetic testing • Before puberty: ↑ testosterone • After puberty: ↑ LH, ↑ estrogen, ↑ testosterone levels	• Estrogen replacement • Gonadectomy of undescended testes: prevents malignant transformation
5-alpha-reductase deficiency	• **Karyotype: 46,XY** • Autosomal recessive • Defective 5-α-reductase → ↓ dihydrotestosterone (DHT) → ↓ DHT-dependent masculinization of external genitalia	• Female external genitalia • Male internal genitalia • Puberty→ ↑ testosterone secretion→ development of the secondary sexual male characteristics	• Clinical presentation & genetic testing • Normal/↑ testosterone, ↓ DHT	• Female gender identity: gonadectomy and estrogen therapy • Male gender identity: testosterone substitution
Klinefelter syndrome	• **Karyotype: 47,XXY** • Chromosomal nondisjunction during meiosis, associated with advanced maternal age • **Testicular dysgenesis and subsequent testosterone deficiency**	• **Symptoms manifests at puberty** • Tall, slim stature with long extremities • **Normal male external genitalia** but malfunctioning **streak gonads** • Testicular atrophy, gynecomastia, micropenis, infertility • Neurocognitive dysfunction	• ↑ **FSH and LH, ↓ Testosterone** • Karyotyping: confirmatory test	• Life-long testosterone substitution

Disorders:

	Pathophysiology	Features	Diagnosis	Management
Turner syndrome **(Gonadal dysgenesis)** Most common cause of ovarian dysgenesis and primary ovarian insufficiency	• **Karyotype: 45,XO** or (45,XO/46,XX): sex chromosomal mosaicism • Chromosomal nondisjunction during meiosis or mitosis	• Normal female internal & external genitalia except for ovaries • Ovaries: Malfunctioning **streak gonads** with connective tissue instead of normal germ cells • Primary ovarian insufficiency with: delayed puberty, primary amenorrhea, infertility • Short stature, shield chest, webbed neck, cubitus valgus • Aortic dissection, coarctation of aorta • Malformations of the kidney and ureters	• Hypergonadotropic hypogonadism: ↓ estrogen, ↓ androgens, ↑ FSH, ↑ LH	• HRT • Growth hormone (GH) therapy • Surgical removal of streak gonads
46,XY gonadal dysgenesis **(Swyer syndrome)**	• Karyotype: 46,XY • **Mutation in SRY gene** results in impairment of testicular development • Underproduction of testosterone and anti-Mullerian hormone	• Genetically male with female internal and external genitalia • Testes: **Malfunctioning streak gonads** with connective tissue instead of normal germ cells • Puberty: Primary amenorrhea, Infertility, **Small uterus**, Enlarged clitoris, **Absence of breast enlargement**		

Disorders:

	Pathophysiology	Features	Diagnosis	Management
Congenital adrenal hyperplasia (Masculinized female pseudohermaphroditism)	• Can affect both male and female; presentation is clearer in females • Autosomal recessive • Due to defects in adrenal enzymes (most commonly **21β-**hydroxylase) that are responsible for the production of cortisol • ↓Cortisol → lack of negative feedback to the pituitary → ↑ ACTH → adrenal hyperplasia and ↑adrenal precursor steroids	In Females: • Masculinized/virilized female pseudohermaphroditism (ambiguous genitalia → clitoromegaly) along with a uterus and ovaries • **Precocious puberty** • Virilization, irregular menstrual cycles, infertility • Salt losing syndrome may occur due to aldosterone deficiency In males: • Normal male external genitalia at birth • Precocious puberty = early virilization	•↑17-hydroxyprogesterone • Hypocortisolism (Masculinized female pseudohermaphroditism can also be caused by exposure of mother to androgens. E.g., drugs such as danazole)	• Glucocorticoid replacement therapy Corrective surgeries: • Neonate→ clitroplasty • Puberty→ vaginoplasty
Ovotesticular disorder **(previously known as true hermaphroditism)**	• Karyotype: varies but typically normal (46,XX is more common than 46,XY)	• Ambiguous genitalia (ovotestis) • Infertility	• Clinical presentation & genetic testing	
Kallmann's syndrome	Defective migration of GnRH-releasing neurons from the olfactory bulbs to the hypothalamic nuclei → ↓ GnRH secretion and underdevelopment of the olfactory bulbs	• Hypogonadotropic hypogonadism **with hyposmia/anosmia** • Females: **primary amenorrhea** • Males: cryptorchidism, testicular atrophy, and low sperm count	↓ GnRH, FSH, LH, estrogen/testosterone	• HRT • Gonadotropins to increase fertility

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Mullerian agenesis VS. Androgen insensitivity syndrome

Mullerian agenesis	Androgen insensitivity syndrome Also known as **testicular feminization syndrome**
Genetically female Karyotype: 46, XX	Genetically male Karyotype: 46, XY
Gonad: Functional ovaries	Gonad: testes; undescended (bilateral mass palpated in groin)
Absent uterus, cervix, vagina	Absent uterus, cervix, vagina
Primary amenorrhea	Primary amenorrhea
Female external genitalia	Female external genitalia
Female secondary sexual characteristics: **fully-developed** breast and pubic hair present	Female secondary sexual characteristics: developed breast, but sparse/scant or absent pubic hair

Quiz

Question 1:

→ **Female Sexual development depend on:**

A. Presence of ovaries
B. Absence of Y chromosome

Question 2:

→ **During the development of the female genital organs. Which one of the following forms the uterus and cervix?**

A. Mesonephric duct
B. Mullerian duct
C. Wolffian duct
D. Genital ridge

Question 3:

→ **In Mullerian Agenesis the ovaries are present.**

A. True
B. False

Question 4:

→ **The ovary contains 2 millions primary oocytes at birth.**

A. True
B. False

1	2	3	4
B	B	A	A

Quiz

Question 1:

→ **Fusion of the PMN happens at?**

A. 12 - 16 weeks
B. 16 - 18 weeks
C. 5th week
D. 8 - 11 weeks

Question 2:

→ **Which of the following structures are not formed by the PMN "Mullerian" Ducts?**

A. Upper ⅔ of vagina and Ovaries
B. Lower ⅓ of vagina and Ovaries
C. Lower ⅓ of vagina and Uterus
D. Upper ⅔ of vagina and Uterus

Question 3:

→ **The Female sexual development depends on the presence of ovaries?**

A. True
B. False

Question 4:

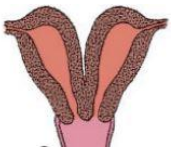
→ **Germ cells originate in _ and migrate to the _.**

A. Yolk sac, genital ridge
B. Yolk sac, neural tube
C. Genital ridge, yolk sac
D. Neural tube, yolk sac

Question 5:

→ **Which of the following Uterus anomalies is shown in the picture:**

A. Arcuate Uterus
B. Uterus didelphys
C. Bicornuate Uterus
D. Septate Uterus



1	2	3	4	5
D	B	C	A	C

Reference

CHAPTER 3

Female Reproductive Anatomy and Embryology

JOSEPH C. GAMBONE

CLINICAL KEYS FOR THIS CHAPTER

- The upper vagina, cervix, uterus, and fallopian tubes are formed from the paramesonephric (müllerian) ducts. The absence of the Y chromosome leads to the development of the müllerian (female) system with virtual total regression of the mesonephric (wolffian) or male system. With the Y chromosome present, a testis is formed and müllerian-inhibiting substance is produced, creating the reverse situation.
- The vagina is a flattened tube extending from the hymenal ring at the vaginal introitus up to the fornices that surround the uterine cervix. The vaginal epithelium, which is stratified squamous in type, and not mucosal, is nonkeratinized and devoid of mucous glands and hair follicles.
- The blood supply to the ovaries is provided by the ovarian arteries, which arise from the abdominal aorta immediately below the renal arteries. The venous drainage of each ovary differs in that the right ovary drains directly into the inferior vena cava whereas the left ovary drains into the left renal vein.
- At the time of pelvic examination when a woman is in the dorsal-lithotomy position, the uterus may be palpated to be tilted forward in an anterior or anteverted position, in a midline position, or tilted backward in a posterior or retroverted position. The top or corpus of the uterus may also be folded forward (anteflexed) or backward (retroflexed). Most of the time this represents normal anatomic variation.
- Gynecologic surgeons use several types of skin incisions for the performance of "open" surgical procedures. The most common is the low transverse or Pfannenstiel incision. When more exposure is needed than anticipated, the skin incision can be extended and the rectus abdominis muscles divided with diathermy. This is called a Maylard incision. For most open operations for cancer, vertical incisions are desirable, because they can be readily extended to allow access to the upper abdomen.

Other chapters in this book deal with the disruptive deviations from normal female anatomy and physiology, whether they be congenital, functional, traumatic, inflammatory, neoplastic, or even iatrogenic. As the etiology and pathogenesis of clinical problems are considered in these other chapters, each should be studied in the context of normal anatomy, development, and physiology. A physician cannot practice obstetrics and gynecology effectively without understanding the physiologic processes that transpire in a woman's life as she passes through infancy, adolescence, reproductive maturity, and the climacteric. As the various clinical problems are addressed, it is important to consider those anatomic, developmental, and physiologic changes that normally take place at key points in a woman's life cycle.

This chapter presents the normal anatomy of the female reproductive tract along with its embryologic development and the anatomy of some important surrounding structures. Applied anatomic issues, such as the normal variation in uterine position and the types of surgical incisions used by gynecologic surgeons, are also covered.

Development of the External Genitalia

Before the seventh week of development, the appearance of the external genital area is the same in males and females. Elongation of the genital tubercle into a phallus with a clearly defined terminal glans portion is noted in the 7th week, and gross inspection at this time may lead to faulty sexual identification. Ventrally and caudally, the urogenital membrane, made up of both endodermal and ectodermal cells, further differentiates into the genital folds laterally and the urogenital folds medially. **The lateral genital folds develop into the labia majora, whereas the urogenital folds develop subsequently into the labia minora and prepuce of the clitoris.**

The external genitalia of the fetus are readily distinguishable as female at approximately 12 weeks (Figure 3-1). In the male, the urethral ostium is located conspicuously on the elongated phallus by this time and is smaller, because of urogenital fold fusion dorsally, which produces a prominent raphe from the anus to the urethral ostium. In the female, the hymen is usually perforated by the time delivery occurs.

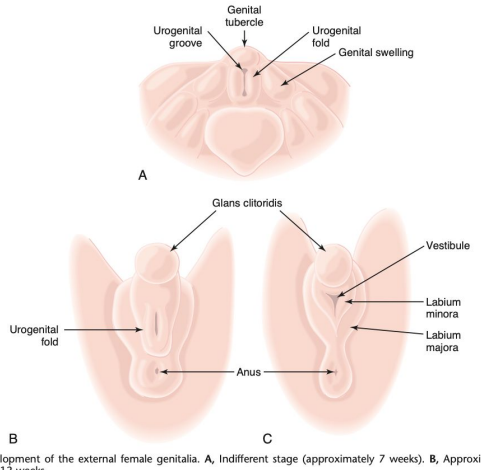


FIGURE 3-1 Development of the external female genitalia. **A**, Indifferent stage (approximately 7 weeks). **B**, Approximately 10 weeks. **C**, Approximately 12 weeks.

Internal Genital Development

The upper vagina, cervix, uterus, and fallopian tubes are formed from the paramesonephric (müllerian) ducts. Although human embryos, whether male or female, possess both paired paramesonephric and mesonephric (wolffian) ducts, **the absence of Y chromosomal influence leads to the development of the paramesonephric system** with virtual total regression of the mesonephric system. With a Y chromosome present, a testis is formed and müllerian-inhibiting substance is produced, creating the reverse situation.

Mesonephric duct development occurs in each urogenital ridge between weeks 2 and 4 and is thought to influence the growth and development of the paramesonephric ducts. **The mesonephric ducts terminate caudally by opening into the urogenital sinus.** First evidence of each paramesonephric duct is seen at 6 weeks' gestation as a groove in the coelomic epithelium of the paired urogenital ridges, lateral to the cranial pole of the mesonephric duct. **Each paramesonephric duct opens into the coelomic cavity cranially** at a point destined to become a tubal ostium. Coursing caudally at first, parallel to the developing mesonephric duct, the blind distal end of each paramesonephric duct eventually crosses dorsal to the mesonephric duct, and the two ducts approximate in the midline. **The two paramesonephric ducts fuse terminally at the urogenital septum, forming the uterovaginal primordium.** The distal point of fusion is known as the **müllerian tubercle (Müller tubercle)** and can be seen protruding into the urogenital sinus dorsally in embryos at 9 to 10 weeks' gestation (Figure 3-4). **Later dissolution of the septum between the fused paramesonephric ducts leads to the development of a single uterine fundus, cervix, and, according to some investigators, the upper vagina.**

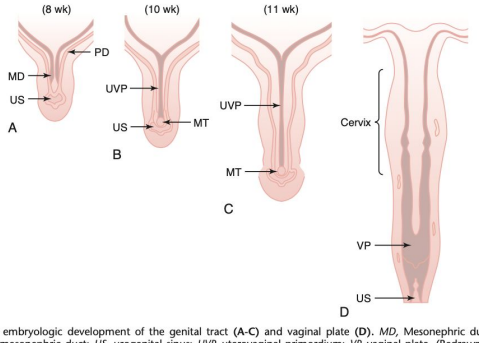


FIGURE 3-4 Early embryologic development of the genital tract (**A-C**) and vaginal plate (**D**). *MD*, Mesonephric duct; *MT*, müllerian tubercle; *PD*, paramesonephric duct; *US*, urogenital sinus; *UVP*, uterovaginal primordium; *VP*, vaginal plate. (Redrawn from Didusch JF, Koff AK: Development of the vagina in the human fetus. *Contrib Embryol Carnegie Inst* 24:61, 1933.)

Degeneration of the mesonephric ducts is progressive from 10 to 16 weeks in the female fetus, although vestigial remnants of the latter may be noted in the adult (Gartner duct cyst, paroöphoron, epoöphoron) (Figure 3-5). The myometrium and endometrial stroma are derived from adjacent mesenchyme; the glandular epithelium of the fallopian tubes, uterus, and cervix is derived from the paramesonephric duct.

Solid vaginal plate formation and lengthening occur from the 12th through the 20th weeks, followed by caudad to cephalad canalization, which is usually completed in utero. Controversy surrounds the relative contribution of the urogenital sinus and paramesonephric ducts to the development of the vagina, and it is uncertain whether the whole of the vaginal plate is formed secondary to growth of the endoderm of the urogenital sinus or whether the upper vagina is formed from the paramesonephric ducts.

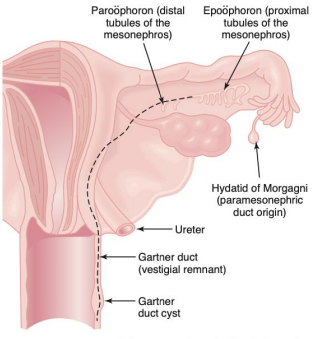


FIGURE 3-5 Remnants of the mesonephric (wolffian) ducts that may persist in the anterolateral vagina or adjacent to the uterus within the broad ligament or mesosalpinx.

VAGINA

The vagina is a flattened tube extending posterosuperiorly from the hymenal ring at the introitus up to the fornices that surround the cervix (Figure 3-6). **Its epithelium, which is stratified squamous in type, is normally devoid of mucous glands and hair follicles and is nonkeratinized.** Gestational exposure to diethylstilbestrol (taken by the mother) may result

Reference

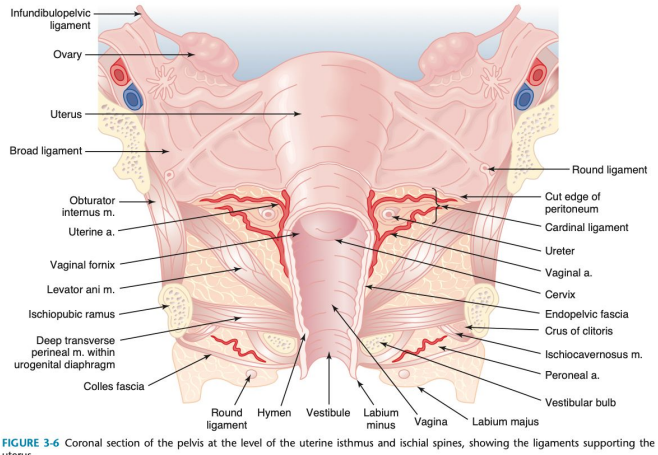


FIGURE 3-6 Coronal section of the pelvis at the level of the uterine isthmus and ischial spines, showing the ligaments supporting the uterus.

in columnar glands interspersed with the squamous epithelium of the upper two-thirds of the vagina (vaginal adenosis). Deep to the vaginal epithelium are the muscular coats of the vagina, which consist of an inner circular and an outer longitudinal smooth muscle layer. Remnants of the mesonephric ducts may sometimes be demonstrated along the vaginal wall in the subepithelial layers and may give rise to **Gartner duct cysts.** The adult vagina averages about 8 cm in length, although its size varies considerably with age, parity, and the status of ovarian function. An important anatomic feature is the immediate proximity of the posterior fornix of the vagina to the pouch of Douglas, which allows easy access to the peritoneal cavity from the vagina, by either culdocentesis or colpotomy.

UTERUS

The uterus consists of the cervix and the uterine corpus, which are joined by the isthmus. The uterine isthmus represents a transitional area wherein the endocervical epithelium gradually changes into the endometrial lining. In late pregnancy, this area elongates and is referred to as the lower uterine segment.

The cervix is generally 2 to 3 cm in length. In infants and children, the cervix is proportionately longer than the uterine corpus (Figure 3-7). The portion that protrudes into the vagina and is surrounded by the fornices is covered with a nonkeratinizing squamous epithelium. **At about the external cervical os, the squamous epithelium covering the exocervix (or ectocervix) changes to simple columnar epithelium, the site of transition being referred to as the squamocolumnar junction.** The cervical canal is lined by irregular, arborized, simple columnar epithelium, which extends into the stroma as cervical "glands" or crypts.

The uterine corpus is a thick, pear-shaped organ, somewhat flattened anteroposteriorly, that consists of largely interlacing smooth muscle fibers. The endometrial lining of the uterine corpus may vary from 2 to 10 mm in thickness (which may be measured by ultrasonic imaging), depending on the stage of the menstrual cycle. Most of the surface of the uterus is covered by the peritoneal mesothelium.

Four paired sets of ligaments are attached to the uterus (Figure 3-8). Each round ligament inserts on the anterior surface of the uterus just in front of the fallopian tube, passes to the pelvic side wall in a fold of the broad ligament, traverses the inguinal canal, and ends in the labium majus. **The round ligaments are of little supportive value in preventing uterine prolapse** but help to keep the uterus anteverted. **The uterosacral ligaments** are condensations of the endopelvic fascia that arise from the sacral fascia and insert into the posteroinferior portion of the uterus at about the level of the isthmus. These ligaments contain sympathetic and parasympathetic nerve fibers that supply the uterus. They provide important support for the uterus and are also significant in precluding the development of an enterocele. **The cardinal ligaments (Mackenrodt)** are the other important supporting structures of the uterus that prevent prolapse. They extend from the pelvic fascia on the lateral pelvic walls and insert into the lateral portion of the cervix and vagina, reaching superiorly to the level of the isthmus. **The pubocervical ligaments** pass anteriorly around the bladder to the posterior surface of the pubic symphysis.

In addition, there are four peritoneal folds. Anteriorly, **the vesicouterine fold** is reflected from the level of the uterine isthmus onto the bladder. Posteriorly, **the rectouterine fold** passes from the posterior wall of the uterus, to the upper fourth of the vagina, and thence onto the rectum. The pouch between the cervix and vagina anteriorly and rectum posteriorly forms a cul-de-sac, called the pouch of Douglas. Laterally, the **two broad ligaments** each pass from the side of the uterus to the lateral wall of the pelvis. Between the two leaves of each broad ligament are contained the fallopian tube, the round ligament, and the ovarian ligament, in addition to nerves, blood vessels, and lymphatics. **The fold of broad ligament containing the fallopian tube is called the mesosalpinx.** Between the end of the tube and ovary and the pelvic side wall, where the ureter passes over the common iliac vessels, is the infundibulopelvic ligament, which contains the vessels and nerves for the ovary. The ureter may be injured when this ligament is ligated during a salpingo-oophorectomy procedure if it is not clearly identified first.

The anatomic position of the uterus may vary within the pelvic cavity as palpated during a pelvic examination. With respect to the horizontal plane on the surface of the examination table, the straight line axis extending from the cervix to the fundal end of the uterine corpus may be in one of three positions. The uterus may tilt in a forward position (anteverted), it may be only slightly forward and in mid-position, or it may tilt in a backward direction (retroverted). Additionally, the fundal portion of the uterus may fold forward (anteflexed) or backward (retroflexed). Most of the time this variation in position is normal and without clinical significance. On occasion the identification of this anatomic variation is important. For example, extreme flexion (ante or retro) may make insertion of an instrument or of an intrauterine device (IUD) higher risk. A retroverted and retroflexed uterus may also be a finding in a woman with pelvic adhesions due to endometriosis or pelvic inflammation due to infection. Figure 3-9 illustrates the potential positions of the uterus within the pelvis.

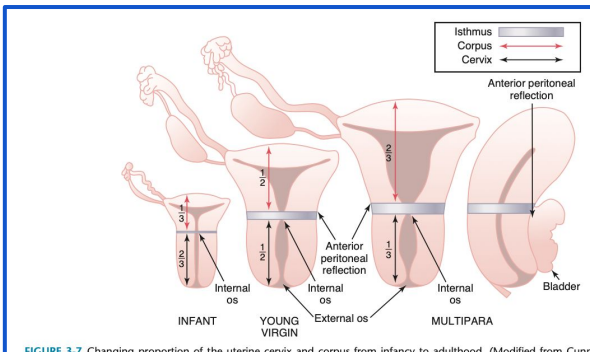


FIGURE 3-7 Changing proportion of the uterine cervix and corpus from infancy to adulthood. (Modified from Cunningham FG, MacDonald PC, Gant NF, et al, editors: *Williams obstetrics,* ed 20, East Norwalk, Conn, 1997, Appleton & Lange.)

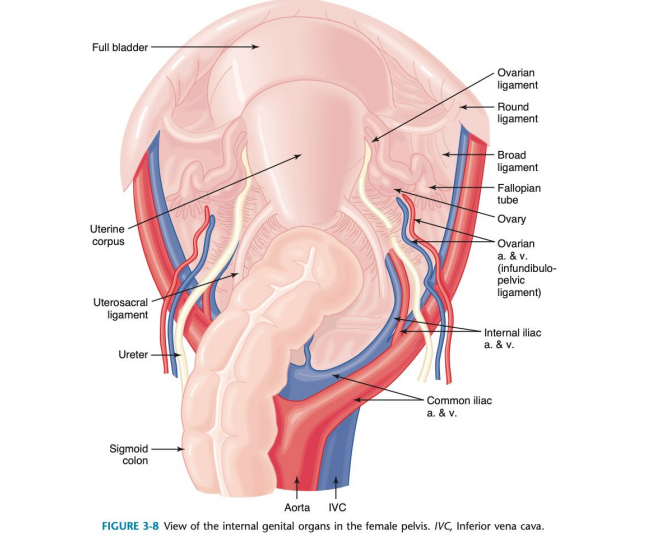


FIGURE 3-8 View of the internal genital organs in the female pelvis. *IVC,* Inferior vena cava.

FALLOPIAN TUBES

The oviducts are bilateral muscular tubes (about 10 cm in length) with lumina that connect the uterine cavity with the peritoneal cavity. They are enclosed in the medial four-fifths of the superior aspect of the broad ligament. The tubes are lined by a ciliated, columnar epithelium that is thrown into branching folds. That segment of the tube within the wall of the uterus is referred to as the **interstitial portion.** The medial portion of each tube is superior to the round ligament, anterior to the ovarian ligament, and relatively fixed in position. This nonmobile portion of the tube has a fairly narrow lumen and is referred to as the **isthmus.** As the tube proceeds laterally, it is located anterior to the ovary; it then passes around the lateral portion of the ovary and down toward the cul-de-sac. The **ampullary and fimbriated portions** of the tube are suspended from the broad ligament by the mesosalpinx and are quite mobile. The mobility of the fimbriated end of the tube plays an important role in fertility. The ampullary portion of the tube is the most common site of ectopic pregnancies.

Normal Embryologic Development of the Ovary

The earliest anatomic event in gonadogenesis is noted at approximately 4 weeks' gestational age (i.e., 4 weeks from conception), when a thickening of the peritoneal, or coelomic, epithelium on the ventromedial surface of the urogenital ridge occurs. A bulging **genital ridge** is subsequently produced by rapid proliferation of the coelomic epithelium in an area that is medial, but parallel, to the mesonephric ridge. Prior to the 5th week, this indifferent gonad consists of germinal epithelium

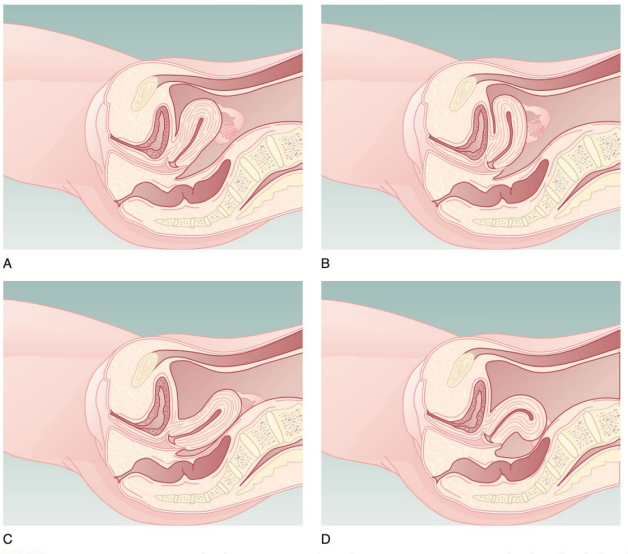


FIGURE 3-9 Uterine positions: **A,** Anteverted is the most common (normal) uterine position; **B,** anteverted and anteflexed when the uterine fundus is further forward toward the bladder; **C,** retroverted when the uterus is tilted backward toward the rectum. This position is not always abnormal but could indicate endometriosis affecting the uterosacral ligaments; and **D,** retroverted and retroflexed when there is an additional backward angle of the uterine fundus. A retroverted and retroflexed uterine position is more likely to be associated with endometriosis (see Chapter 25).

surrounding the internal blastema, a primordial mesenchymal cellular mass designated to become the ovarian medulla. After 5 weeks, projections from the germinal epithelium extend like spokes into the mesenchymal blastema to form **primary sex cords.** Soon thereafter in the 7th week, a testis can be identified histologically if the embryo has a Y chromosome. In the absence of a Y chromosome, definitive ovarian characteristics do not appear until somewhere between the 12th and 16th weeks.

As early as 3 weeks' gestation, relatively large primordial germ cells appear intermixed with other cells in the endoderm of the yolk sac wall of the primitive hindgut. These germ cell precursors migrate along the hindgut dorsal mesentery (Figure 3-10) and are all contained in the mesenchyme of the undifferentiated urogenital ridge by 8 weeks' gestation. Subsequent replication of these cells by mitotic division occurs, with maximal mitotic activity noted up to 20 weeks' gestation and cessation noted by term. These oogonia, the end result of this germ cell proliferation, are incorporated into the cortical sex cords of the genital ridge.

Histologically, the first evidence of follicles is seen at about 20 weeks, with germ cells surrounded by flattened cells derived from the cortical sex cords. These flattened cells are recognizable as granulosa

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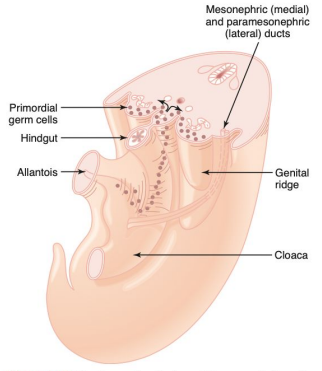

FIGURE 3-10 Migratory path of primordial germ cells from the yolk sac, along the hindgut mesentery, to the urogenital ridge at approximately 5 weeks.

cells of coelomic epithelial origin and theca cells of mesenchymal origin. The oogonia enter the prophase of the first meiotic division and are then called **primary oocytes** (see Chapter 4). It has been estimated that more than 2 million primary oocytes, or their precursors, are present at 20 weeks' gestation, but only about 300,000 primordial follicles are present by 7 years of age.

Regression of the primary sex cords in the medulla produces the **rete ovarii,** which are found histologically in the hilus of the ovary along with another testicular analogue called **Leydig cells,** which are thought to be derived from mesenchyme. Vestiges of the rete ovarii and of the degenerating mesonephros may also be noted at times in the mesovarium or mesosalpinx. Structural homologues in males and females are shown in Table 3-1.

CONGENITAL ANOMALIES OF THE VULVA

The most significant of the vulvar anomalies are those that pose challenges to the assignment of gender at birth. Caution, sensitivity, complete evidence collection, and clear communication with often anxious family members are all required. A thorough evaluation may include careful physical examination, pelvic ultrasonography or magnetic resonance imaging (MRI), hormonal assays, karyotyping, and often consultation with specialists before a recommendation is made to the family about which gender would be better for rearing the newborn. In general, if there is suboptimal development of penile or scrotal structures, the infant should be assigned the female gender, because reconstructive surgery for females is much more likely to be successful.

Ambiguous genitalia can present with clitoromegaly, bifid clitoris, or midline fusion of the labioscrotal folds. **Clitoromegaly** in adult women is defined as being present when the product of the length of the clitoris and the width of its base exceeds 35 mm^2, or when the clitoral base exceeds 1 cm in diameter. At birth, clitoromegaly is determined by the relative size of the clitoris in relation to the other vulvar structures. **Clitoral agenesis** may result from the failure of the

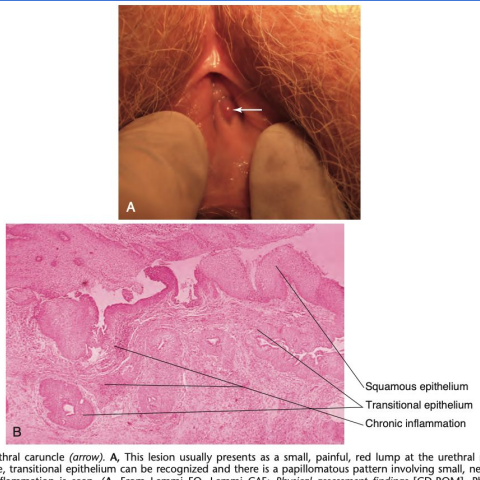

FIGURE 18-3 Urethral caruncle *(arrow).* **A,** This lesion usually presents as a small, painful, red lump at the urethral meatus. **B,** In this histologic example, transitional epithelium can be recognized and there is a papillomatous pattern involving small, neighboring glands. A little chronic inflammation is seen. (**A,** From Lemmi FO, Lemmi CAE: *Physical assessment findings* [CD-ROM], Philadelphia, 2009, Saunders.)

genital tubercle to develop. Incomplete development of the genitalia can result in a cloaca with no separation of the bladder and the vagina. Many of these defects are associated with other problems, such as bladder exstrophy.

Female pseudohermaphroditism is caused by in utero masculinization due to androgens from maternal or fetal congenital adrenal hyperplasia, androgen-producing tumors of the mother's ovary or adrenal glands, or the mother's use of exogenous androgens. Often the infant will present with ambiguous genitalia. The enlarged clitoris is the most conspicuous abnormality. Fusion of the labioscrotal folds can produce a hypospadiac urethral meatus and a malpositioned introitus, but the internal genital organs will be normal. **Male pseudohermaphroditism,** which most commonly results from mosaicism, may occur with varying degrees of virilization and müllerian development.

Androgen insensitivity syndrome (a form of male pseudohermaphroditism and formerly called testicular feminization) is a genetic deficiency of androgen receptors that results in a 46,XY infant developing female external genitalia and, later in life, secondary sexual characteristics. The syndrome may be complete or partial (Figure 18-4). In utero, müllerian-inhibiting hormone (MIH) is produced, which results in absence of the uterus and fallopian tubes. The vaginal depth is variable but seldom normal. The testes are usually located in the inguinal canals, labia, or abdomen (usually along the pelvic sidewalls) and should be removed after the young woman has experienced breast development, but before any malignant transformation of her gonads takes place. The higher body temperature in the areas where the male gonads are located is thought to play a role in this transformation. Surgical removal of gonadal tissue is recommended just after puberty in these women.

True hermaphroditism is rare. The affected child has some degree of both female and male development externally and internally; dual gonadal development occurs with either a combined ovotestes or separate gonads. The extent of masculinization depends on the relative amount of functioning testicular tissue and testosterone levels.

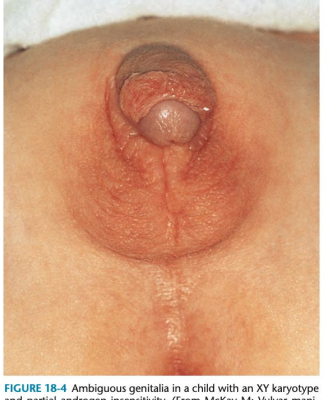

FIGURE 18-4 Ambiguous genitalia in a child with an XY karyotype and partial androgen insensitivity. (From McKay M: Vulvar manifestations of skin disorders. In Black M, McKay M, Braude P, et al, editors: *Obstetric and gynecologic dermatology,* ed 2, Edinburgh, 2003, Mosby, p 121.)

Reference

CONGENITAL ABNORMALITIES OF THE VAGINA

Vaginal agenesis represents the most extreme instance of a vaginal anomaly, with total absence of the vagina except for the most distal portion that is derived from the urogenital sinus, which may appear as a dimple on the vulva. If the uterus is absent but the fallopian tubes are spared, the defect is **müllerian agenesis** or **Rokitansky-Küster-Hauser syndrome.** Isolated vaginal agenesis with normal uterine and fallopian tube development is rare, and is thought to be the end result of isolated vaginal plate malformation. The more common structural anomalies of the vagina include canalization defects such as **imperforate hymen, transverse and longitudinal vaginal septa, partial vaginal development, and double vagina.**

Imperforate hymen represents the mildest form of these canalization abnormalities. It occurs at the site where the vaginal plate contacts the urogenital sinus. After birth, a bulging, membrane-like structure may be noticed in the vestibule, usually blocking egress of mucus. If not detected until after menarche, an imperforate hymen may be seen as a thin, dark bluish or thicker, clear membrane blocking menstrual flow at the introitus (Figure 18-6, *A* and *B*). A similar anomaly, the **transverse vaginal septum,** is most commonly found at the junction of the upper and middle thirds of the vagina (Figure 18-7). Patients with an imperforate hymen or transverse vaginal septum usually have normal development of the upper reproductive tract.

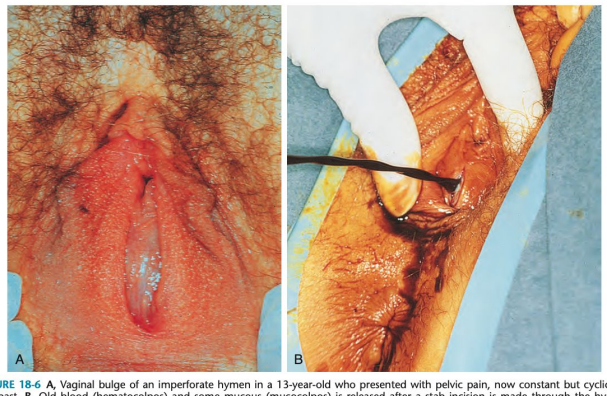

FIGURE 18-6 **A**, Vaginal bulge of an imperforate hymen in a 13-year-old who presented with pelvic pain, now constant but cyclical in the past. **B**, Old blood (hematocolpos) and some mucous (mucocolpos) is released after a stab incision is made through the hymen. (From McKay M: Vulvar manifestations of skin disorders. In Black M, McKay M, Braude P, et al, editors: *Obstetric and gynecologic dermatology,* ed 2, Edinburgh, 2003, Mosby, p 122.)

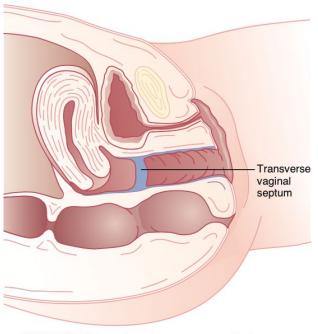

FIGURE 18-7 Illustration of a transverse vaginal septum.

A **midline longitudinal septum** may be present, creating a double vagina. The longitudinal septum may be only partially present at various levels in the upper and middle vagina, either in the midline or deviated to one side. In addition, a longitudinal septum may attach to the lateral vaginal wall, creating a blind vaginal pouch, with or without a communicating sinus tract. These septa are usually associated with a **double cervix** and one of the various duplication anomalies of the uterine fundus, although the upper tract is often entirely normal.

Adenosis of the vaginal wall consists of islands of columnar epithelium in the normal squamous epithelium. It is often located in the upper third of the vagina. The incidence of this finding is much higher in women exposed to diethylstilbestrol in utero.

Urethral diverticula are small (0.3 to 3 cm), sac-like projections that can be found along the posterior urethra in the midline of the anterior vaginal wall. They may or may not communicate with the urethra, and they may cause dyspareunia. Urethral diverticula can cause recurrent urinary tract infections (see Chapter 22).

Congenital Anomalies of the Uterine Corpus and Cervix

The upper vagina, cervix, uterine corpus, and fallopian tubes are formed from the paramesonephric (müllerian) ducts. **The absence of a Y chromosome and the resultant absence of müllerian inhibiting substance lead to the development of the paramesonephric system, with the regression of the mesonephric system.** The paramesonephric ducts first arise at 6 weeks lateral to the cranial pole of the mesonephric duct and expand caudally. By 9 to 10 weeks, they fuse in the midline at the urogenital septum to form the uterovaginal primordium. Later, dissolution of the septum between the fused paramesonephric ducts leads to the development of a single uterus and cervix.

The most common anomalies of the uterus result from either incomplete fusion of the paramesonephric ducts, incomplete dissolution of the midline fusion of those ducts, or formation failures. Figure 19-8 shows variations of the uterine and cervical development and demonstrates that communication between the dual systems can exist at several levels. Failure of fusion is most evident in **uterus didelphys,** which presents with two separate uterine bodies, each with its own cervix and attached fallopian tube and vagina. **A bicornuate uterus with a rudimentary horn** also represents a fusion failure. Less complete fusion failure is seen in the **bicornuate uterus with or without double cervices.** Incomplete dissolution of the midline fusion of the paramesonephria explains the **septate uterus.** Failure of formation can be seen in the **unicornuate uterus. In müllerian agenesis, there is complete lack of development of the paramesonephric system.** The affected woman generally has an incomplete development of the fallopian tubes associated with the absence of the uterus and most of the vagina. All of these conditions occur in normal karyotypic and phenotypic females, but can be associated with important anomalies of the urinary system such as a horseshoe or pelvic kidney.

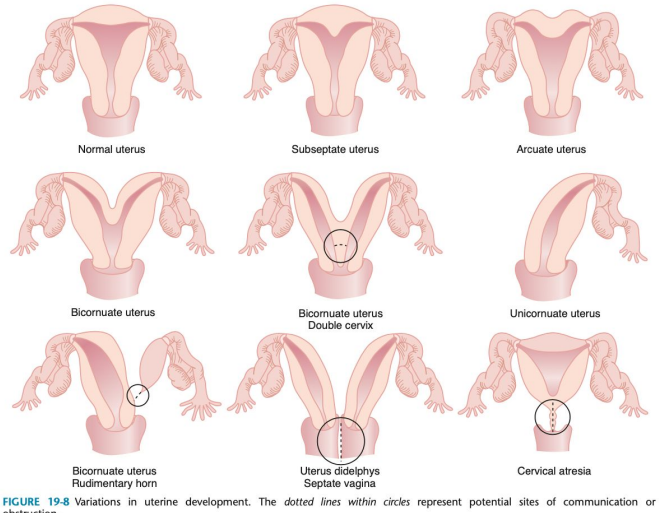

FIGURE 19-8 Variations in uterine development. The *dotted lines within circles* represent potential sites of communication or obstruction.

The most common congenital cervical anomalies are the result of malfusion of the paramesonephric (müllerian) ducts with varying degrees of separation, as seen in the didelphys cervix or septate cervix.

These different anatomies may have a significant effect on a woman's risk of infertility and early pregnancy loss, and may also cause dysmenorrhea and dyspareunia. Women with fusion anomalies may present with menstrual blood trapped in a noncommunicating uterine horn or vagina.

In addition to these macroscopic differences, subtle anomalies may exist within the uterine vascular system, such as an **arteriovenous malformation,** rupture of which may cause life-threatening hemorrhage.

Although all of these anomalies can occur spontaneously, they may also be caused by early maternal exposure to certain drugs. Historically, the most notable of these drugs is diethylstilbestrol (DES), which increases

Reference

the risk of a small T-shaped endometrial cavity or cervical deformity.

DIAGNOSIS AND TREATMENT OF CONGENITAL ANOMALIES

Certain congenital anomalies of the uterus may need to be treated, especially if they are thought to be interfering with normal function, fertility, or causing other symptoms. The diagnosis of intrauterine defects can be made by imaging studies such as HSG or MRI, and may be suspected at the time of laparoscopy because of visualized uterine distortion. Hysteroscopy may be performed to both diagnose and treat defects such as the resection of a uterine septum. A bicornuate uterus can be repaired laparoscopically by performing a metroplasty, thereby creating one functional uterine cavity (see Chapter 31).

Congenital Anomalies of the Ovaries

Abnormal embryologic development of the ovaries is uncommon. Congenital duplication or absence of ovarian tissue may occur, as may ectopic ovarian tissue and supernumerary ovaries. Although rare, the sexual bipotentiality noted in embryologic development can progress without the usual regression of one system, producing an ovotestis and subsequent intersex problems.

Genetic chromosomal disorders, such as **Turner syndrome (45 XO),** are associated with a lack of normal gonadal development, as evidenced by the rudimentary streaked ovaries that are a hallmark of the disorder. **Women with Turner syndrome usually progress through puberty and develop secondary sexual characteristics, but enter menopause shortly thereafter.** This provides evidence that two X chromosomes are required for normal ovarian development. Testicular predominance occurs with the addition of a single Y chromosome, even in the face of multiple X chromosomes. Such predominance is seen in **Klinefelter syndrome (47 XXY),** in which testicular development occurs embryologically. In **complete androgen insensitivity syndrome (46 XY), which is also known as testicular feminization,** the lack of androgen receptors produces a phenotypic female in the face of a Y chromosome. The gonads in these women (functioning testes) should be removed (usually after puberty) because of their significant malignant potential.

Congenital Anomalies of the Fallopian Tubes

Isolated anomalies of the fallopian tubes, the end result of abnormal development of the proximal unfused portions of the paramesonephric ducts, are rare. **Aplasia or atresia,** usually of the distal ampullary segment of the fallopian tube, is most commonly unilateral in the presence of otherwise normal development. Bilateral aplasia is noted in some cases of uterine and vaginal agenesis. **Complete duplication** of the fallopian tubes is rarely seen, but distal duplication and accessory ostia are relatively common.

In addition, women exposed in utero to certain drugs, such as diethylstilbestrol (DES), may have abnormalities in the architecture of the fallopian tubes; **with DES exposure, the tubes may be shortened, distorted, or clubbed.**

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