# The Urogenital System

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## Overview

- Functionally:
  - Two separate systems → *Urinary system* & *Genital system*.
- Embryologically:
  - Common origin → Both develop from intermediate mesoderm (mesodermal ridge along posterior abdominal wall).
  - Initially, common outlet → *cloaca*.

### Kidney Systems in Development

- Three kidney systems develop cranio-caudally in sequence:

1. Pronephros → Rudimentary, non-functional.

2. Mesonephros → Temporary, may function briefly in early fetal life.

3. Metanephros → Becomes the *permanent kidney*.

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## Pronephros

- Timeline: Appears early 4th week.

- Structure:

  - 7–10 solid cell groups in cervical region.
  - Form vestigial nephrotomes (excretory units).

- Fate:

  - Rapid regression before caudal systems form.
  - By end of 4th week, completely disappears.

- Exam Tip: Often asked → "Which embryonic kidney system is *non-functional* in humans?" → Pronephros.

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## Mesonephros

- Origin: From intermediate mesoderm (upper thoracic → L3).

- Development (early 4th week):

  - Excretory tubules appear during pronephros regression.
  - Tubules elongate → S-shaped loop.
  - Medial end: forms glomerulus (capillary tuft).
  - Surrounding capsule: Bowman's capsule.
  - Together = Renal corpuscle.
  - Lateral end: connects to mesonephric (Wolffian) duct.

- Structure in 2nd month:

- Large ovoid organ on each side of midline.
- Along with developing gonad → forms urogenital ridge.

- Regression:

- Caudal tubules still differentiating → cranial ones start degenerating.
- By end of 2nd month, most mesonephric structures degenerate.

- Sex-specific fate:

- Male → Some caudal tubules + mesonephric duct persist → contribute to genital system (e.g., epididymis, vas deferens).
- Female → Mostly disappear.

Clinical/Exam Correlations

- Pronephros → vestigial, disappears (non-functional).

- Mesonephros → Important temporary kidney; remnants persist in males as genital ducts.

- High-yield MCQ: "The Wolffian duct persists in which sex, and what does it form?" → *Male; parts of genital tract.*

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## Metanephros – The Definitive Kidney

### Introduction

- Permanent kidney = *Metanephros.*

- Appears: 5th week of development.

- Becomes functional: by 10th week (urine formation starts).

- Origin:

- Excretory units (nephrons) → from metanephric mesoderm.
- Collecting system → from ureteric bud (outgrowth of mesonephric duct near cloaca).

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## Collecting System

- Derives entirely from the ureteric bud.

- Development:

1. Ureteric bud grows into metanephric tissue, which caps over its distal end.

2. Bud dilates → forms primitive renal pelvis.

3. Splits into cranial & caudal portions → future major calyces.

4. Each calyx sprouts new buds → keep branching until ~12 generations form.

5. Tubules of 2nd order enlarge → absorb 3rd & 4th order tubules → form minor calyces.

6. Collecting tubules of later generations elongate & converge → form renal pyramids.

- Structures derived from ureteric bud:

  - Ureter
  - Renal pelvis
  - Major calyces
  - Minor calyces
  - Collecting tubules (1–3 million)

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## Excretory System (Nephron Formation)

- Steps:

1. Each collecting tubule induces a metanephric tissue cap.

2. Cap cells form renal vesicles → elongate into S-shaped tubules.

3. Capillaries invade medial pocket → form glomerulus.

4. Together with Bowman's capsule → forms renal corpuscle.

5. Distal end of S-shaped tubule joins collecting tubule → continuity established.

6. Tubule elongates → differentiates into:

- Proximal convoluted tubule
- Loop of Henle
- Distal convoluted tubule

- Hence, kidney forms from two sources:

  - Metanephric mesoderm → nephron/excretory units.
  - Ureteric bud → collecting system.

## Timeline & Numbers

- Nephron formation continues until birth (~1 million per kidney).
- Urine formation starts → soon after glomerular capillaries develop (≈10th week).
- At birth:
  - Kidney has a lobulated surface (due to separate developing lobes).
  - Lobulation disappears during infancy (nephrons grow in size, but no new nephrons form after birth).

## Exam/Clinical Correlations

- MCQ: "Which structure induces nephron formation?" → Collecting tubules (ureteric bud).
- MCQ: "Source of nephron vs collecting system?"

- Nephrons → Metanephric mesoderm.
- Collecting system → Ureteric bud.

- Congenital anomalies: Abnormal ureteric bud branching → renal agenesis, hypoplasia, or duplication.

- Clinical: Fetal urine forms a major part of amniotic fluid → essential for lung development (important in Potter sequence).

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## Clinical Correlates of Kidney Development

1. Wilms' Tumor

- Definition: Kidney cancer, usually in children <5 years (may even occur in fetus).

- Genetics: Mutation in WT1 gene (11p13).

- Associated syndromes:

  - WAGR syndrome:
    - W = Wilms' tumor
    - A = Aniridia (absence of iris; due to PAX6 deletion)
    - G = Gonadoblastomas
    - R = Retardation (intellectual disability)
    - Cause → Microdeletion on chromosome 11 including WT1 + PAX6 (only 700 kb apart).
  - Denys-Drash syndrome:
    - Triad: Renal failure, Ambiguous genitalia, Wilms' tumor.

2. Renal Dysplasias & Agenesis

- Multicystic dysplastic kidney:

  - Numerous ducts + undifferentiated cells.
  - Nephrons fail to develop, ureteric bud fails to branch → no collecting ducts.

- Renal agenesis:

- Due to failed interaction between ureteric bud & metanephric mesoderm.
- Mechanism: GDNF (Glial cell-Derived Neurotrophic Factor) normally induces ureteric bud branching → failure causes agenesis.
- Gene mutations:
    - SALL1 → Townes-Brocks syndrome.
    - PAX2 → Renal coloboma syndrome.
    - EYA1 → Branchio-oto-renal syndrome.

Bilateral Renal Agenesis

- Incidence: 1/10,000 births.

- Clinical:

- Renal failure, anuria.
- Potter sequence:
    - Oligohydramnios → hypoplastic lungs.
    - Potter facies → flattened face, low-set ears.
    - Club feet.
- Associated anomalies (85% cases):

- Genital anomalies (uterus/vagina, vas deferens, seminal vesicles absent/abnormal).
- Cardiac defects.
- GI atresias (tracheal, duodenal).
- Cleft lip/palate.
- Brain abnormalities.

3. Congenital Polycystic Kidney Disease (PKD)

- Autosomal Recessive PKD (ARPKD)

  - Incidence: 1/5,000 births.
  - Origin: Cysts from collecting ducts.
  - Clinical: Enlarged kidneys → renal failure in infancy/childhood.
  - Progressive & severe.

- Autosomal Dominant PKD (ADPKD)

  - Incidence: 1/500–1,000 births (more common).
  - Cysts in all nephron segments.
  - Renal failure delayed until adulthood.
  - Less severe than ARPKD.

- Genetics/Pathogenesis:

  - Both linked to mutations in cilia-related proteins.
  - Belong to Ciliopathies.

- Examples of ciliopathies:

  - Bardet-Biedl syndrome → renal cysts, obesity, ID, limb defects.
  - Meckel-Gruber syndrome → renal cysts, hydrocephalus, microphthalmia, cleft palate, absent olfactory tract, polydactyly.

4. Duplication of Ureter

- Cause: Early splitting of ureteric bud.

- Variants:

  - Partial duplication.
  - Complete duplication (two ureters).

- Outcomes:

  - Both ureters may drain into bladder.
  - Ectopic ureter: One ureter enters vagina, urethra, or vestibule.
    - Mechanism → Abnormal ureteric bud migrates with mesonephric duct, opening ectopically.

## Exam High-Yield Points

- Wilms' tumor → WT1 gene mutation (11p13).

- WAGR syndrome → Wilms', Aniridia, Gonadoblastoma, Retardation.

- Denys-Drash → Renal failure + Ambiguous genitalia + Wilms.

- Bilateral renal agenesis → Potter sequence.

- PKD:

  - AR → Collecting ducts, infancy renal failure.

- AD → All nephron parts, adult renal failure.

- Ectopic ureter → continuous dribbling of urine in girls (enters vagina/vestibule).

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## Position & Ascent of the Kidney

Normal Development

- Initial position:

- Kidneys develop in the pelvic region.

- Ascent:

- Kidneys ascend to lumbar region (abdomen).
- Mechanism:
    - Straightening of body curvature.
    - Growth of lumbar & sacral regions.

- Blood supply changes during ascent:

- In pelvis → supplied by pelvic branch of aorta.
- During ascent → new arteries arise from progressively higher levels of the aorta.
- Lower vessels usually degenerate, but sometimes persist → accessory renal arteries.

## Clinical Correlates of Kidney Position

### 1. Pelvic Kidney

- Cause: Kidney fails to pass arterial fork formed by umbilical arteries.
- Location: Remains in pelvis, near common iliac artery.
- Clinical: Usually asymptomatic but may cause pelvic mass or obstruction.

### 2. Horseshoe Kidney

- Cause:

- During ascent, lower poles of kidneys fuse.
- Fusion occurs due to crowding at umbilical artery fork.

- Location:

- Remains low in abdomen → ascent blocked by inferior mesenteric artery (IMA).
- Typically at level of lower lumbar vertebrae.

- Features:

- Ureters arise from anterior surface → pass ventral to isthmus.
- Incidence: 1 in 600 people.

- Clinical:

- Often asymptomatic.
- May cause hydronephrosis, stones, or infection.
- Important in surgery (anomalous blood supply).

3. Accessory Renal Arteries

- Cause: Persistence of embryonic arteries that normally should regress.
- Origin: Usually arise from aorta.
- Course: Enter superior or inferior poles of kidneys.
- Clinical relevance:
  - Important surgically (risk of accidental ligation → infarction).
  - May compress ureter → cause obstruction/hydronephrosis.

Exam High-Yield Points

- Normal ascent: Pelvis → abdomen; blood supply shifts upwards.
- Pelvic kidney: Failure to ascend past umbilical arteries.

- Horseshoe kidney: Fusion of lower poles; ascent blocked by IMA.

- Accessory arteries: Persistence of embryonic vessels.

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## Function of the Kidney & Development of Bladder and Urethra

### Function of the Kidney in Fetal Life

- Onset of function: Around 12th week (when metanephros is functional).

- Urine formation:

  - Fetal kidney produces urine → excreted into amniotic cavity.
  - Urine mixes with amniotic fluid → swallowed by fetus → recycled.

- Excretion of wastes:

  - NOT by fetal kidneys.
  - Placenta removes waste products from fetal blood.

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## Development of Bladder and Urethra

### Cloacal Division (4th–7th weeks)

- Cloaca: Common cavity for urinary + digestive tracts.

- Divides into:

1. Urogenital sinus (anterior).
2. Anal canal (posterior).

- Division occurs by urorectal septum (mesodermal structure).

- Tip of septum → perineal body (important for pelvic floor integrity).

## Parts of the Urogenital Sinus

1. Upper & largest part → Urinary bladder

- Initially continuous with allantois.
- Lumen of allantois obliterates → forms urachus.
- Adult remnant: Median umbilical ligament.

2. Pelvic part of urogenital sinus

- Male → forms prostatic urethra + membranous urethra.
- Female → contributes to entire urethra.

3. Phallic part of urogenital sinus

- Flattened structure, pulled ventrally by growth of genital tubercle.
- Sexual dimorphism develops here (male vs female urethra).

## Incorporation of Mesonephric Ducts

- Caudal ends of mesonephric ducts absorbed into bladder wall.

- Consequences:

  - Ureters, initially outgrowths of mesonephric ducts, now enter bladder separately.
  - Ureteric orifices move cranially (due to kidney ascent).
  - Mesonephric duct openings move close together → in males, form ejaculatory ducts (opening into prostatic urethra).

Origin of Bladder Tissues

- Trigone of bladder:

  - Initially mesodermal (from absorbed mesonephric ducts).
  - Later overgrown by endodermal epithelium → entire bladder epithelium = endodermal.

- Urethra epithelium: Endodermal origin (both sexes).

- Connective tissue + smooth muscle: Derived from splanchnic (visceral) mesoderm.

## Glandular Development

- At end of 3rd month: Prostatic urethra epithelium proliferates → buds into mesenchyme.

  - Male: Forms prostate gland.
  - Female: Cranial urethra forms urethral & paraurethral glands (homologous to prostate).

## Exam High-Yield Pointers

- Kidney function starts 12th week, but placenta handles waste.

- Cloaca → divided by urorectal septum into urogenital sinus + anal canal.

- Three parts of urogenital sinus: bladder, pelvic part, phallic part.
- Allantois → urachus → median umbilical ligament.
- Trigone origin = mesoderm, later replaced by endoderm.
- Male: Prostatic & membranous urethra + prostate (from buds).
- Female: Entire urethra + paraurethral glands.

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## Clinical Correlates: Bladder Defects

1. Urachal Anomalies (Allantois remnants)

- Normally → allantois lumen obliterates → fibrous cord (urachus) → adult median umbilical ligament.
- Persistence leads to defects:

- Urachal fistula: Entire lumen patent → urine drains from umbilicus.
- Urachal cyst: Only a local area persists → cystic dilation, secretes fluid.
- Urachal sinus: Persistence of upper lumen → sinus continuous with bladder.

2. Exstrophy of the Bladder

- Definition: Ventral body wall defect → bladder mucosa exposed.
- Associated feature: Epispadias (urethral opening on dorsal penis).
- Cause: Failure of lateral body wall folds to close in pelvic midline.
- Extent: Urinary tract may be open from bladder → umbilicus.
- Incidence: Rare (2/100,000 live births).

3. Exstrophy of the Cloaca

- More severe than bladder exstrophy.
- Cause: Major failure of lateral body wall closure + abnormal urorectal septum development.
- Associated defects:
  - Imperforate anus, anal canal malformations.
  - Widely spaced genital swellings → external genital anomalies.
- Incidence: Very rare (1/30,000).

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## Genital System – Introduction

### Sex Differentiation

- Controlled genetically, but morphologic differences appear 7th week.

- Key gene: SRY gene (Sex-determining Region on Y, Yp11).

- Produces SRY protein = Testis-Determining Factor (TDF).

  - Presence → male development.
  - Absence → female pathway (default).

- Other autosomal genes also contribute (e.g., SOX9, WNT4).

## Gonadal Development

### Origin

- Gonads appear as genital (gonadal) ridges (longitudinal ridges on posterior abdominal wall).

- Formed by:

1. Proliferation of coelomic epithelium.

2. Condensation of underlying mesenchyme.

Primordial Germ Cells (PGCs)

- Origin: Epiblast.

- Migration pathway:

1. Epiblast → primitive streak.

2. By 3rd week → yolk sac wall near allantois.

3. 4th week → migrate by amoeboid movement through dorsal mesentery of hindgut.

4. 5th–6th week → invade genital ridges.

- Failure of migration → gonads fail to develop (streak gonads/agenesis).

Exam High-Yield Pointers

- Urachal anomalies (fistula, cyst, sinus) – draw simple bladder diagram.
- Bladder exstrophy = ventral defect + epispadias.
- Cloacal exstrophy = more severe, includes anal + genital malformations.
- Gonads don't differentiate until 7th week, though sex is determined at fertilization.
- PGC migration pathway is a favorite question (trace epiblast → yolk sac → dorsal mesentery → gonadal ridge).

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## Development of Gonads and Genital Ducts

### Indifferent Gonad Stage

- Primordial germ cells (PGCs) induce gonadal development.
- Genital ridge epithelium proliferates → penetrates mesenchyme → primitive sex cords.
- Present in both sexes (cannot distinguish yet).
- Gonad at this stage = indifferent gonad.

Testis Development (XY embryo)

- Controlled by SRY gene → Testis-Determining Factor (TDF).
- Primitive sex cords → proliferate & extend deep → testis/medullary cords.
- Near hilum → cords break into rete testis (future tubular network).
- Tunica albuginea (fibrous capsule) forms → separates cords from epithelium.

By 4th month

- Testis cords horseshoe-shaped, connected with rete testis.

- Contain:

  - PGCs (future spermatogonia).
  - Sertoli cells (from surface epithelium, supporting cells).

Leydig cells

- From mesenchyme between cords.

- Differentiate by 8th week → secrete testosterone → drives development of male ducts & external genitalia.

Puberty

- Testis cords canalize → form seminiferous tubules.

- Seminiferous tubules connect → rete testis → ductuli efferentes (remnants of mesonephric tubules) → mesonephric/Wolffian duct (future ductus deferens).

Ovary Development (XX embryo)

- Primitive sex cords → dissociate into cell clusters in medulla → regress, replaced by vascular stroma (ovarian medulla).

- 7th week: surface epithelium proliferates → cortical cords.

- 3rd month: cortical cords → isolated clusters → cells surround oogonia with epithelial cells (follicular cells) → primordial follicles.

Key Difference

- XY (male): medullary cords → testis cords; cortical cords regress.

- XX (female): medullary cords regress; cortical cords → primordial follicles.

📌 Exam one-liner:

- Testis = medullary origin.
- Ovary = cortical origin.

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## Genital Duct Development

### Indifferent Stage

- Both sexes initially have:

1. Mesonephric (Wolffian) ducts.
2. Paramesonephric (Müllerian) ducts.

### Paramesonephric (Müllerian) duct formation

- Arises as longitudinal invagination of coelomic epithelium on anterolateral urogenital ridge.
- Cranial end: funnel-shaped opening into abdominal cavity.
- Course: runs lateral to mesonephric duct → crosses ventrally → grows caudomedially.
- Fusion of both sides → uterine canal.
- Caudal end projects into posterior wall of urogenital sinus → Müllerian tubercle.
- Mesonephric ducts open into urogenital sinus on either side of the tubercle.

Exam-Oriented Pointers

- SRY gene → testis cords + Leydig testosterone production by 8th week = very high-yield.

- Seminiferous tubules connection pathway (seminiferous → rete → efferent ductules → mesonephric duct) is a must-remember.
- Ovary cortical cords → primordial follicles is another favorite short note.
- Paramesonephric duct course & fusion → uterine canal formation = classic diagram question.

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## Development of Genital Ducts

Male (XY, with SRY gene)

Mesonephric (Wolffian) Duct Derivatives

- Efferent ductules: from epigenital tubules connecting rete testis to mesonephric duct.
- Paradidymis: from paragenital tubules (caudal excretory tubules that don't connect to rete testis).

- Mesonephric duct proper:

  - Cranial remnant → appendix epididymis.
  - Highly convoluted part → epididymis.
  - Straight portion with muscular coat → ductus deferens.
  - Beyond seminal vesicle → ejaculatory duct.

Paramesonephric (Müllerian) Duct Fate

- Suppressed by Anti-Müllerian Hormone (AMH) from Sertoli cells.

- Only remnant: Appendix testis.

Hormonal Control (Male)

- Sertoli cells → AMH → regression of Müllerian ducts.

- Leydig cells → Testosterone → stimulates mesonephric duct → epididymis, vas deferens, seminal vesicle.

- Leydig cells → Dihydrotestosterone (DHT) → development of external genitalia (penis, scrotum, prostate).

Female (XX, no SRY gene)

Paramesonephric (Müllerian) Duct Derivatives

- Each duct has 3 parts:

1. Cranial vertical part → opens into peritoneal cavity → uterine tube opening.

2. Horizontal part → uterine tube proper.

3. Caudal vertical part → fuses with opposite side → uterine canal (uterus + cervix).

- Broad ligament: formed as ducts fuse and move mediocaudally → divides pelvic cavity into uterorectal & uterovesical pouches.

- Mesenchyme around fused ducts → myometrium & perimetrium.

Vagina (Dual Origin)

- Upper vagina → uterine canal (paramesonephric duct).
- Lower vagina → from sinovaginal bulbs (endodermal evaginations of urogenital sinus).
- Vaginal plate forms → canalizes by 5th month.
- Vaginal fornices → paramesonephric origin.
- Hymen: thin tissue plate (sinus epithelium + vaginal cells); normally perforates at birth.

Mesonephric (Wolffian) Duct Fate

- Mostly regresses, but remnants may persist:
  - Epoophoron & paroophoron (in mesovarium).

- Gartner's duct cysts (if mesonephric remnants persist in uterus/vagina wall).

## Hormonal Control (Female)

- No AMH → paramesonephric ducts persist → uterus, uterine tubes, upper vagina.
- Estrogens (placental + maternal + fetal) → stimulate external genitalia (labia, clitoris, lower vagina).

## Comparison: Male vs Female Genital Ducts

| Feature | Male (XY) | Female (XX) |
|---|---|---|
| Mesonephric duct | Epididymis, vas deferens, seminal vesicle, ejaculatory duct | Mostly regresses; remnants → epoophoron, paroophoron, Gartner's cyst |
| Paramesonephric duct | Regresses (AMH action); remnant = appendix testis | Persists → uterine tubes, uterus, cervix, upper vagina |
| Excretory tubules | Epigenital → efferent ductules; Paragenital → paradidymis | Cranial/caudal remnants → epoophoron & paroophoron |

| | | |
|---|---|---|
| Hormones | AMH (Sertoli), Testosterone & DHT (Leydig) | Estrogen (placental, maternal, fetal) |
| External genitalia | Penis, scrotum, prostate (via DHT) | Labia, clitoris, lower vagina (via estrogen) |

### Exam-Oriented Pointers

- Vagina dual origin (upper from Müllerian, lower from sinus) is *very frequently asked*.

- Clinical correlations:

  - Persistent Müllerian duct syndrome (due to AMH defect in male).
  - Gartner's cyst (mesonephric remnant in female).
  - Imperforate hymen (failure of canalization).

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## Clinical Correlates of Genital Duct & External Genital Development

# 🔹 Uterine & Vaginal Defects (Paramesonephric anomalies)

Result from abnormal fusion or canalization of paramesonephric ducts.

Types of Uterine Anomalies

- Uterus didelphys → complete failure of fusion → double uterus (sometimes with double vagina).
- Uterus arcuatus → least severe → slight midline indentation at fundus.
- Uterus bicornis → partial fusion failure → 2 uterine horns opening into a common vagina.
- Uterus bicornis unicollis with rudimentary horn → unilateral duct atresia → one normal uterus + rudimentary non-communicating horn → may cause pain/hematometra.

- Cervical atresia → if both ducts fail → no cervical canal.
- Double vagina → failure of sinovaginal bulbs to fuse.
- Vaginal atresia → failure of sinovaginal bulb development → small paramesonephric pouch around cervix.

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## Development of External Genitalia

Indifferent Stage (up to 6th week, same in both sexes)

- Cloacal folds → form around cloacal membrane.
- Genital tubercle → cranial fusion of cloacal folds.
- Subdivision caudally → urethral folds (ventral) + anal folds (dorsal).

- Genital swellings → lateral to urethral folds → scrotal swellings (male) / labia majora (female).

- At end of 6th week, sexes are indistinguishable.

Male External Genitalia Development (Androgen-dependent)

- Genital tubercle elongates → phallus (future penis).

- Urethral folds pulled forward → form walls of urethral groove.

- Urethral plate → endodermal epithelial lining of groove.

- By 3rd month → urethral folds fuse over plate → penile urethra (till shaft).

- Glans portion: ectodermal ingrowth → epithelial cord → canalizes → external urethral meatus.

- Scrotal swellings → migrate caudally → fuse in midline → scrotal septum formed.

## Clinical Correlates: Male Genitalia Defects

Hypospadias (common, 3–5/1000 births; incidence rising)

- Cause: incomplete fusion of urethral folds → abnormal urethral opening on ventral (inferior) surface of penis.
- Types:
  - Glandular, penile shaft, penoscrotal, perineal.
- Severe form: wide sagittal slit; scrotal swellings resemble labia majora.
- Etiology note: possible link to increased environmental estrogens (endocrine disruptors).

Epispadias (rare, 1/30,000 births)

- Cause: defect in genital tubercle positioning + ventral body wall closure abnormality.
- Feature: urethral opening on dorsal surface of penis.
- Commonly associated with: bladder exstrophy.

Exam-Oriented Summary Table

| Defect | Cause | Key Feature | Clinical Importance |
|---|---|---|---|
| Uterus didelphys | Complete failure of duct fusion | Double uterus (± double vagina) | Infertility, miscarriage risk |
| Uterus bicornis | Partial fusion failure | Two uterine horns | Recurrent pregnancy loss |
| Uterus bicornis unicollis | One duct atretic | Rudimentary horn | Hematometra, dysmenorrhea |
| Vaginal atresia | Failure of sinovaginal bulbs | Absent vagina, pouch at cervix | Primary amenorrhea |

| | | | |
|---|---|---|---|
| Hypospadias | Urethral folds fail to fuse | Ventral urethral opening | MCQ favorite; ↑ incidence |
| Epispadias | Abnormal genital tubercle & ventral wall closure | Dorsal urethral opening | Associated with bladder exstroph |

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## Clinical Correlates

- Male External Genitalia

  - Micropenis

    - Cause → insufficient androgen stimulation.
    - Etiology: primary hypogonadism or hypothalamic/pituitary dysfunction.
    - Definition: penile length ≤ 2.5 SD below mean (measured dorsally from pubis → stretched tip).

- Bifid Penis / Double Penis

  - Due to abnormal splitting of genital tubercle.
  - Very rare anomaly.

🔹 External Genitalia in the Female

- Hormonal Influence → Estrogens stimulate development.

- Developmental Steps:

  - Genital tubercle → Clitoris (slight elongation).
  - Urethral folds → Labia minora (no fusion).
  - Genital swellings → Labia majora.
  - Urogenital groove → Vestibule.

🔑 Exam Point: Early in development, genital tubercle is larger in females than males → can cause sexing errors on ultrasound (3rd–4th month).

# Clinical Correlates – Disorders of Sexual Development (DSD)

## 1. Ambiguous Genitalia

- Spectrum: clitoral hypertrophy → small penis with hypospadias.
- May resemble both sexes → termed *hermaphroditism* (but true hermaphrodites not seen in humans).
- Instead → ovotestes (both ovarian & testicular tissue).
- 70% cases → karyotype 46,XX; usually have a uterus.

## 2. Congenital Adrenal Hyperplasia (CAH)

- Most common cause of ambiguous genitalia.

- Pathogenesis: ↓ steroid synthesis → ↑ ACTH → adrenal hyperplasia.

- Classic form: 21-hydroxylase deficiency.

  - Females → virilization (large clitoris → male appearance).

- Rare form: 17α-hydroxylase deficiency.

  - Females → normal internal/external genitalia, but no secondary sexual characters at puberty (no breasts, no pubic hair).
  - Males → inhibited virilization.

3. Androgen Insensitivity Syndrome (AIS)

- Genotype: 46,XY with testes.

- Pathogenesis: androgen receptor defect → no response to androgens.

- Effects:

- Male differentiation fails, despite testes + MIS (so no uterus/tubes).
- CAIS (Complete): female phenotype, short vagina, undescended testes. ↑ risk of testicular tumors (33% by age 50).
- PAIS (Partial): ambiguous genitalia (clitoromegaly / small penis with hypospadias).
- MAIS (Mild): varying virilization, usually infertility.

4. 5α-Reductase Deficiency (5-ARD)

- Defect: testosterone → dihydrotestosterone conversion blocked.

- Phenotype: ambiguous genitalia (female-like or underdeveloped male), hypospadias or clitoromegaly.

5. Other Syndromes

- Klinefelter Syndrome (47,XXY)

- Commonest sex chromosome disorder (1/1000 males).

- Features: ↓ fertility, small testes, ↓ testosterone, gynecomastia (~33%).
- Cause: nondisjunction of XX homologues.

- Gonadal Dysgenesis

- Ovaries → streak gonads (no oocytes).
- Phenotypically female.
- Swyer syndrome (46,XY female): SRY gene deletion/mutation. → Female appearance, no menstruation, no secondary sexual characters.
- Turner syndrome (45,X):
    - Features: short stature, webbed neck, shield chest, cardiac/renal anomalies, inverted nipples.

✅ Exam Tips:

- Always link hormone deficiencies or receptor defects with the phenotype.

- Remember: SRY = Testis Determining Factor, MIS suppresses Müllerian system, and DHT (from

5α-reductase) drives external male genitalia development.

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## 🔹 Descent of the Testes

1. Early Attachments

- 2nd month: Testis + mesonephros attached to posterior abdominal wall by urogenital mesentery.
- With mesonephros degeneration → attachment persists as mesentery for gonad.
- Caudally → becomes caudal genital ligament.

2. Gubernaculum

- Mesenchymal condensation from caudal pole of testis → extends toward inguinal region.

- Later, extra-abdominal portion grows toward scrotal swellings.
- Guides descent of testes.
- In females → rudimentary gubernaculum (becomes ovarian & round ligament).

3. Factors Controlling Descent

- Not fully clear. Proposed factors:
  - Gubernaculum outgrowth → intra-abdominal migration.
  - Intra-abdominal pressure (organ growth) → passage through inguinal canal.
  - Regression of extra-abdominal gubernaculum → final scrotal descent.
  - Hormonal influence → Androgens & MIS (Müllerian Inhibiting Substance).

4. Timeline

- ~12 weeks → testis reaches inguinal region.
- ~28 weeks → passes inguinal canal.
- ~33 weeks → enters scrotum.
- 🔑 Clinical point: Normally present in scrotum before birth.

5. Vascular Supply

- Arterial supply: Aortic branches remain constant.

- Testicular vessels elongate during descent from lumbar origin.

6. Processus Vaginalis

- Evagination of peritoneum into scrotal swelling, guided by gubernaculum.

- Accompanied by fascial/muscular coverings → forms inguinal canal.

- After descent → processus vaginalis closes, leaving tunica vaginalis:

- Visceral layer → covers testes.
- Parietal layer → lines scrotal sac.

- Narrow connection with peritoneal cavity → obliterates at/soon after birth.

7. Layers of Spermatic Cord (from abdominal wall)

- Transversalis fascia → Internal spermatic fascia.

- Internal oblique muscle → Cremasteric fascia + muscle.

- External oblique aponeurosis → External spermatic fascia.

- ❌ Transversus abdominis → *No contribution* (arches over).

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## 🔹 Clinical Correlates (Testis Descent)

- Congenital Indirect Inguinal Hernia

  - If processus vaginalis remains patent → intestinal loops herniate into scrotum.

- Hydrocele

  - Partial obliteration → fluid-filled cysts in processus vaginalis/testis/spermatic cord.

- Cryptorchidism

  - Testis fails to descend (≤1% of males after 3 months).
  - Causes: often ↓ androgen (testosterone).
  - Effects:
    - No mature spermatozoa (infertility).
    - ↑ risk of malignancy (seminoma).
    - Associated with 3–5% renal anomalies.

## 🔹 Descent of the Ovaries

- Extent: Much less than testes → ovaries settle just below pelvic brim.

- Ligaments derived:

  - Cranial genital ligament → Suspensory ligament of ovary.
  - Caudal genital ligament →
    - Ligament of ovary proper.
    - Round ligament of uterus (passes into labia majora, via inguinal canal).

✅ Exam Pointers:

- Sequence of descent (12w → 28w → 33w).

- Coverings of testis = favorite MCQ.

- Difference in descent (testis vs ovary) – both guided by gubernaculum derivatives.

- Clinicals: *cryptorchidism, indirect hernia, hydrocele.*

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-> The End <-