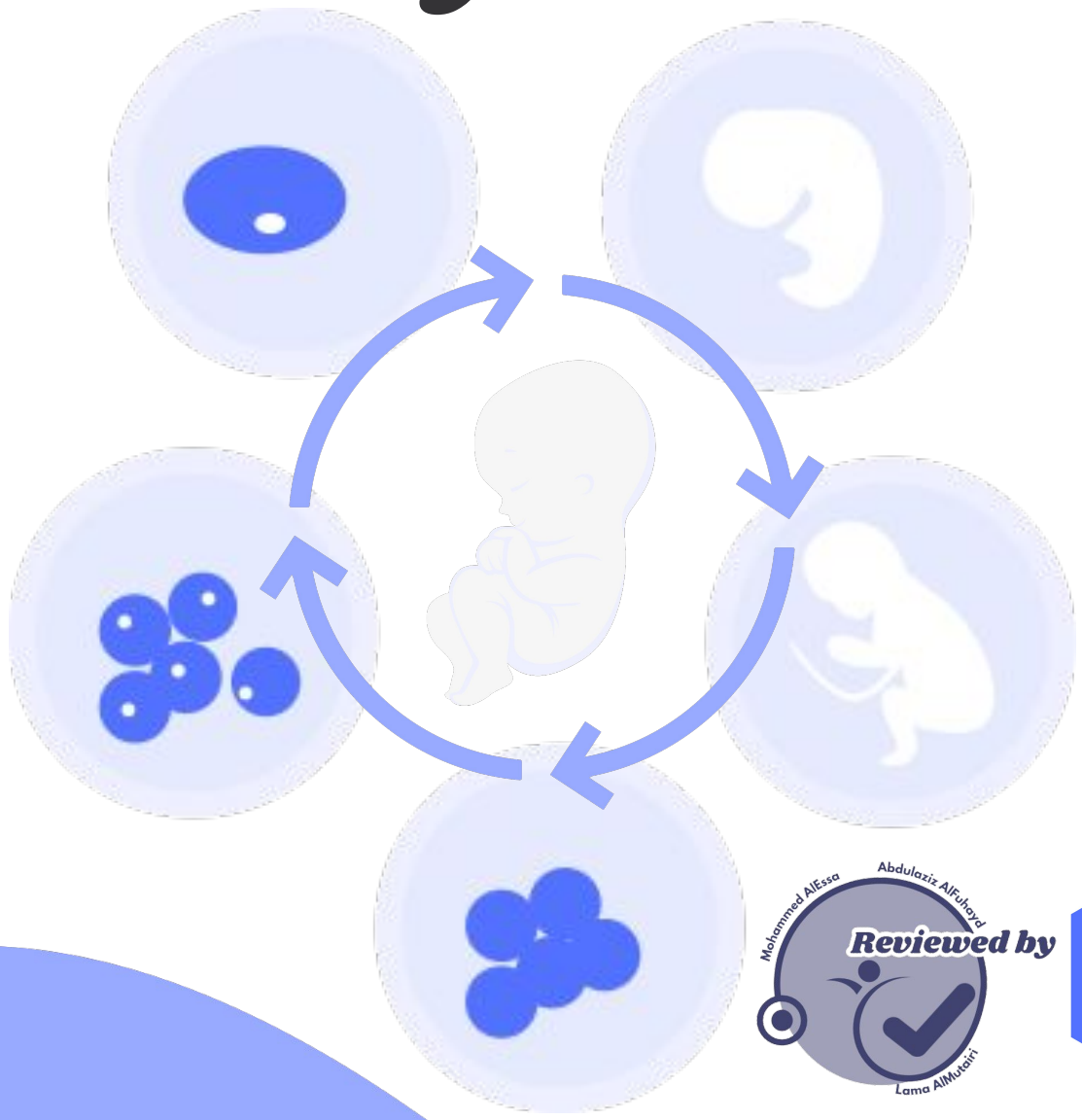
L1

Development of the female Reproductive system



MED 443
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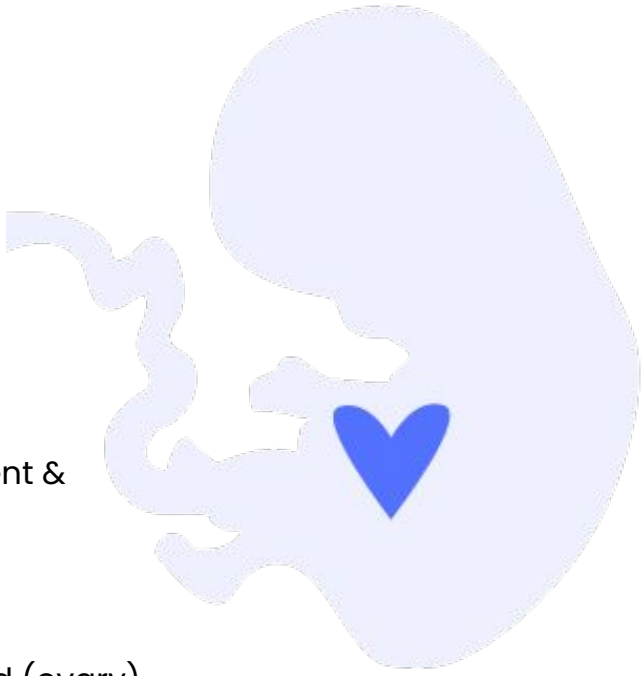
Reviewed by
Lama AlMutairi

Embryology
Team 443
Reproductive

Objectives



- Describe the development of gonads (indifferent & different stages)
- Describe the development of the female gonad (ovary).
- Describe the development of the internal genital organs (uterine tubes, uterus & vagina).
- Describe the development of the external genitalia.
- List the main congenital anomalies.

- No objectives were found in male slides -

This lecture was presented by : Prof.Musaad Al Fayez & DR.Samira Shaheen

Editing File

Ninja Nerd's helpful Explanation

Click here for Ninja Nerd's board

Color index :
Main text (black)
Female Slides (Pink)
Male Slides (Blue)
Important (Red)
Dr's note (Green)
Extra Info (Grey)

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Overview by Lama Alotaibi

IMPORTANT

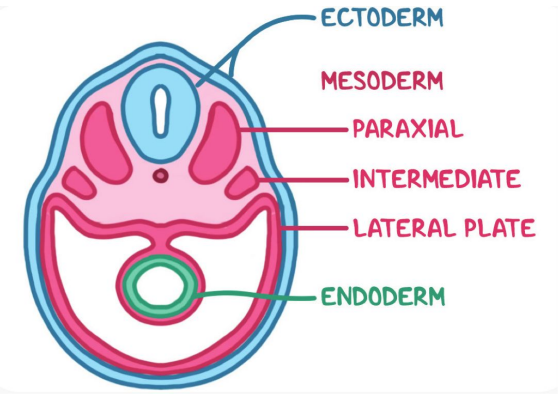
Extra

The alien from pathology took a trip to embryology to tell you a story

Step 1

Embryo Has 3 Layers

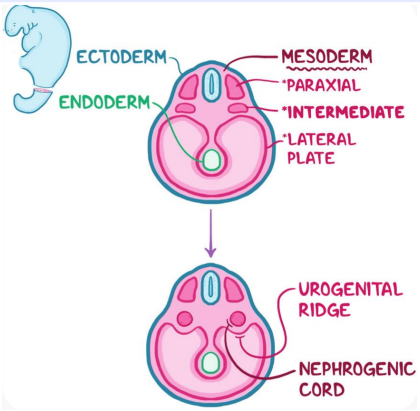
- Ectoderm
- Mesoderm
  - Paraxial
  - Intermediate
  - Lateral plate
- Endoderm



Step 2

A. Intermediate mesoderm form urogenital ridge
B. Urogenital Ridge Become nephrogenic cord
C. Nephrogenic cord gives gonadal ridge
D. Gonadal Ridge gives gonads

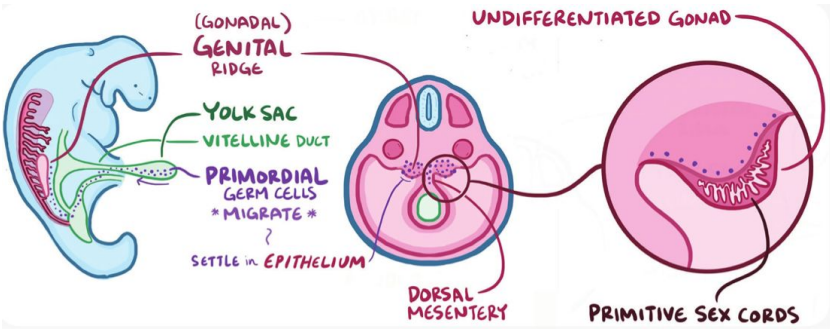
Week 5



Step 3

Gonads Development Start at yolk sac :
Primordial germ cells migrate to gonads
Note : **primordial germ cell form at yolk sac in W4 & migrate in W5**

Week 5

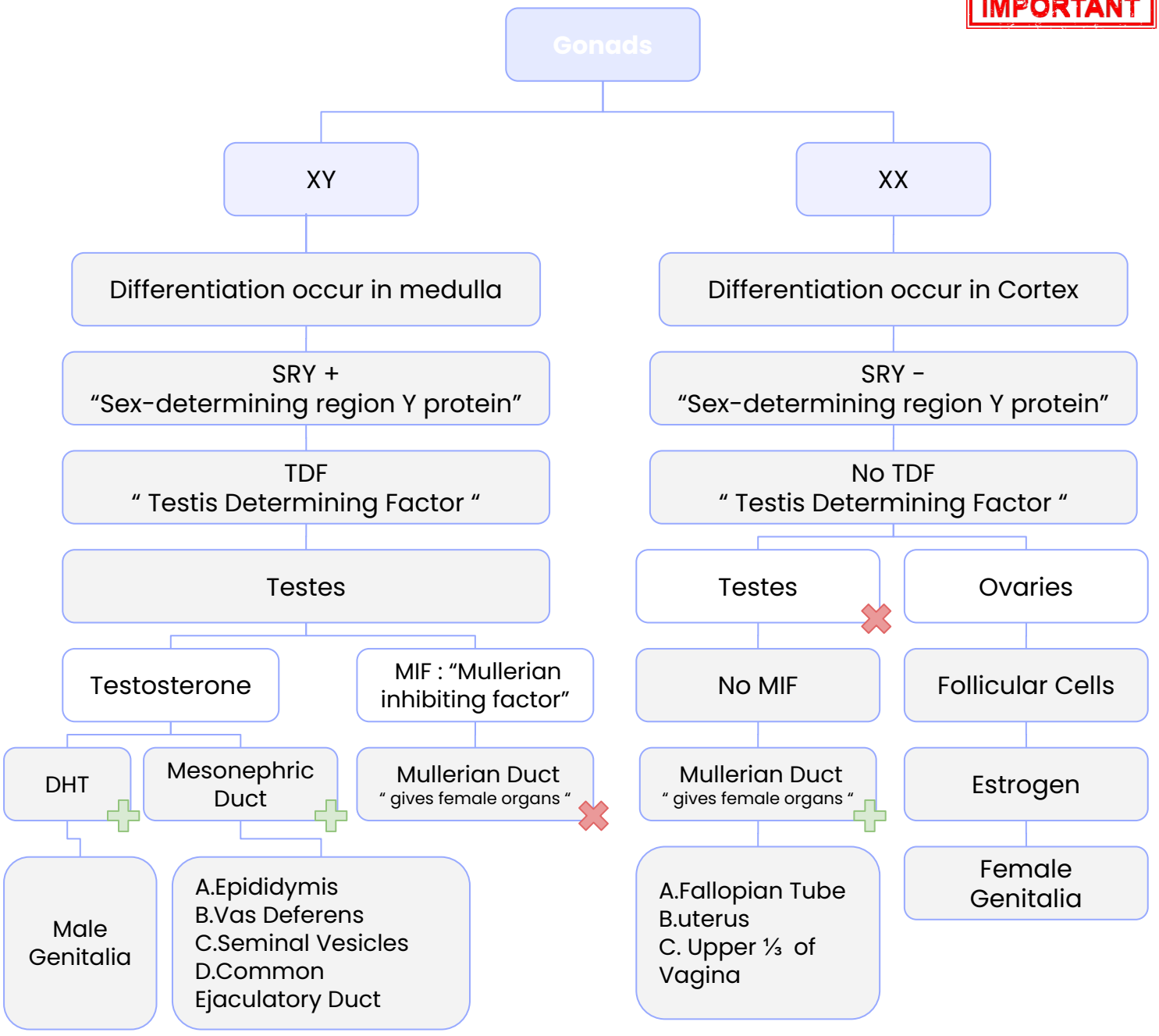


Step 4

Sex chromosomes express genes determine gonadal differentiation

Overview

IMPORTANT



IMPORTANT

Extra

Step 5

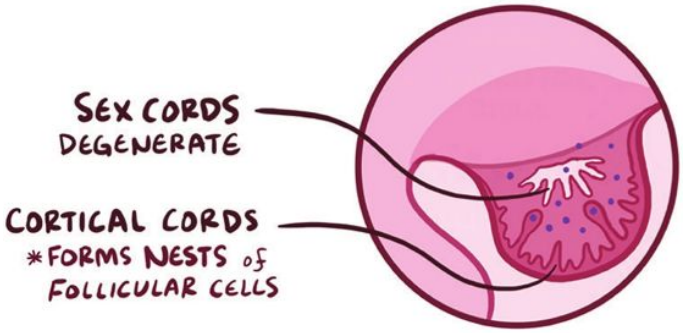
A. No TDF : gonads become ovaries
1. In Female : cortex gives ovaries & medulla regress
2. In males : medulla gives Testes & cortex regress

Remember **M**edulla = **M**ale

Step 6

A. Sex cord form retro ovali then degenerate
B. Surface Epithelium proliferate
C. And form cortical cords that form nests
D. of follicle cells to support the primordial cells

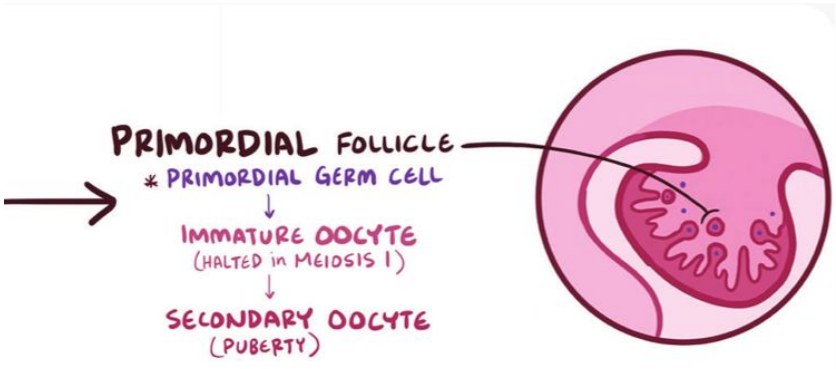
Remember that primordial cells is from yolk sac



Week 7

Step 7

A.Primordial germ cell + follicular cells = primordial ovarian follicles (W16)
B. Inside it primordial germ cell is differentiated to immature oocyte (Stopped In Meiosis 1) till puberty
No oocyte formation postnatally
After puberty it become secondary oocyte

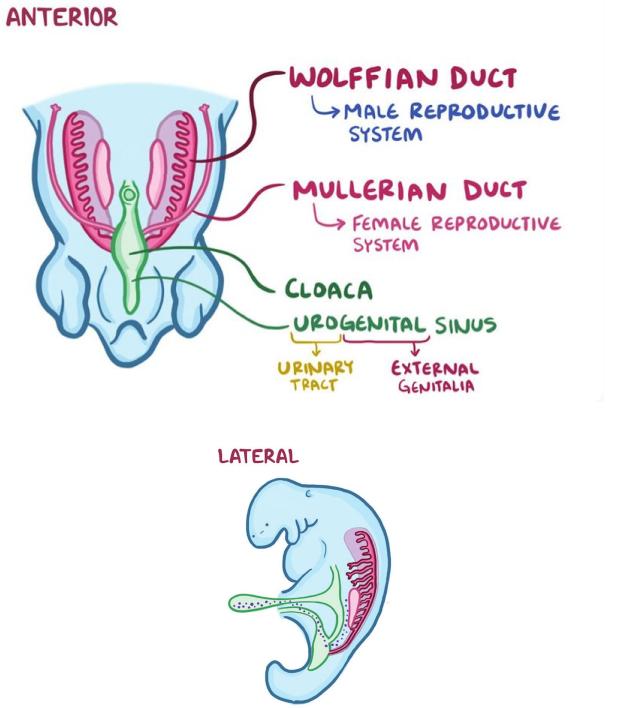


Step 8

Gonads differentiation turns on other female organs differentiation

Step 9

A.paramesonephric duct “Mullerian Duct” gives female reproductive system
B. Ovaries doesn’t make testosterone
> When there is no testosterone > wolffian duct degenerate (the duct that gives male reproductive System)
C.Ovaries doesn’t make MIF (Mullerian inhibiting factor) > paramesonephric duct “Mullerian Duct Persist (remember that MIF was produced in males by testes & causes “Mullerian Duct” degeneration)

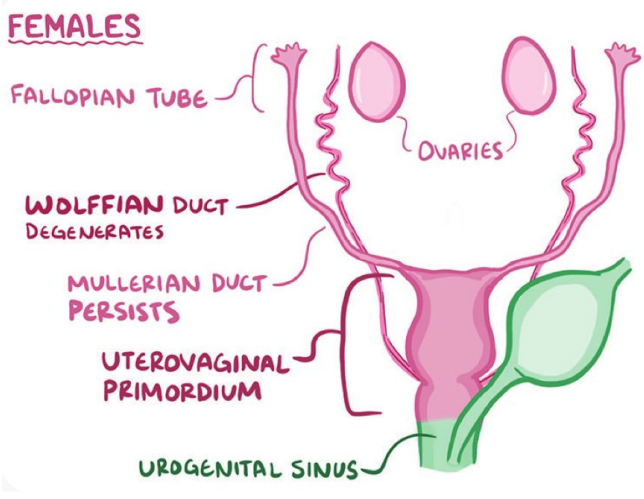


Step 10

A.paramesonephric duct “Mullerian Duct” gives :

Upper part	Lower part
Fallopian Tube	Uterovaginal Primordium
Cervix	Uterus
Vagina upper 1/3	

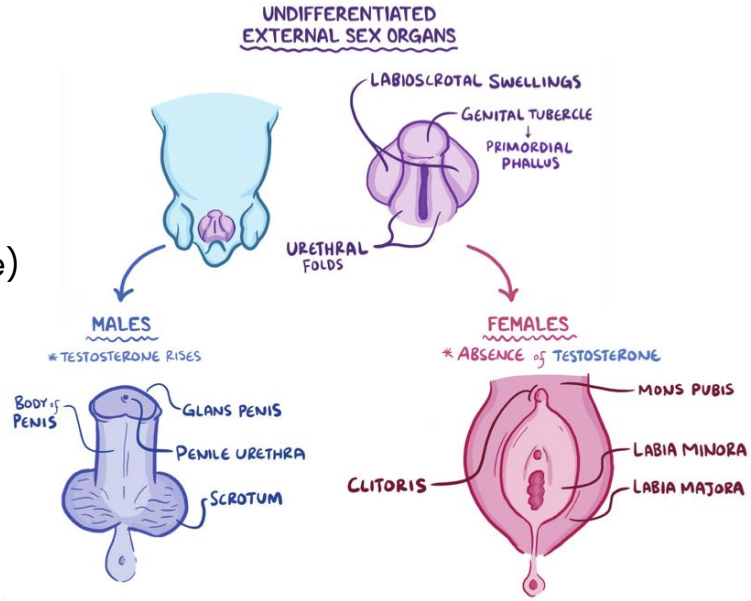
Endometrial & myometrium are derived from the splanchnic mesoderm.



Lower ⅔ of vagina : (from sinovaginal bulbs), proliferate and form solid vaginal plate.
The Central cells of the vaginal plate break down to form the lumen of the vagina.
By the 5th month Vagina will be canalized. & By 5th week outgrowth is entirely canalized

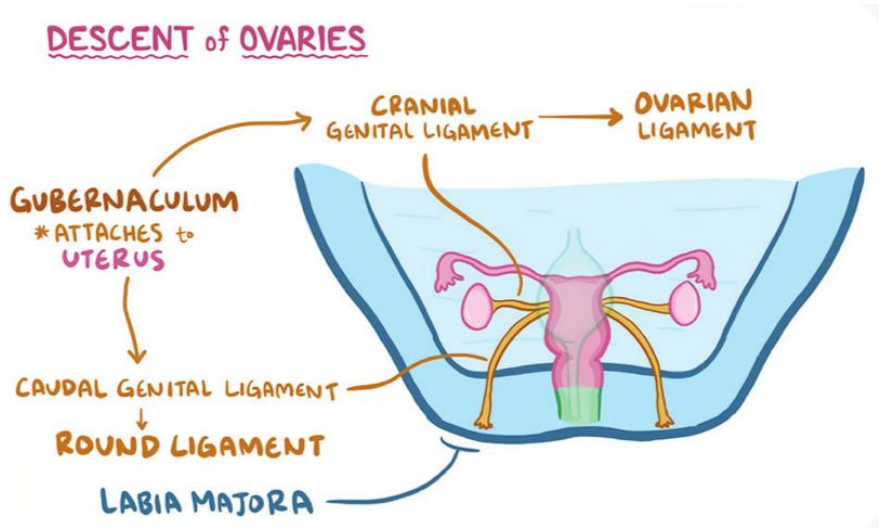
Step 12

The external Genitalia is formed from urogenital sinus
Absence of testosterone :
A.Urethral Doesn't fuse (unlike in male) :
Gives labia minora
B.Labioscrotal Folds form the Labia Majora
C.Primordial phallus(from gonadale tubercle) shrink & gives clitoris
D.urogenital groove is open & form vestibule
In external genitalia :
Are Similar in both sexes up to the
- 7th week (indifferent stage).
- 9th week Start to differentiate
- Fully differentiated by the 12th week.



Step 12 Extra

A.Gubernaculum is structure that attaches inferior part of ovaries to Labia Majora
B.After formation of uterus :
Gubernaculum attach to uterus & Gives :
1.cranial genetal ligament :
Gives Ovarian ligament
2.caudal cranial ligament :
Gives round ligament



Development of Genital system

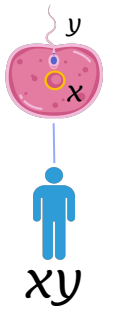
Sex Determination
(all in female slides except in blue)

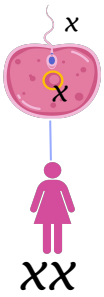
- Chromosomal and genetic sex of the embryo is determined /established genetically **at the time of fertilization** and depends upon the presence of Y(male)or X(female) chromosome of the sperm.(genetic sex) is the first stage of genetic determination.

- The **primary female sexual differentiation** is determined by the **presence** of the **X** chromosome , and the **absence** of **Y** chromosome and does **not** depend on **hormonal** effect. (Differentiation of the male gonad is determined by the hormonal effect, testosterone-> testis, no hormone-> ovaries (default pathway))
- Development of female **phenotype** requires **two X chromosomes.**

- The type of **sex chromosomes complex** established at fertilization determine the **type of gonad** differentiated from the indifferent gonad.(testis determining factor)differentiated means: I can differentiate if it's male or female, ovary or testicular. Indifferent gonad means: we can't differentiate female or male at this point .

- The **type of gonad** determines the type of **sexual differentiation** in the Sexual Ducts (give internal structures in female reproductive system) and External Genitalia.





male slides

Y chromosome have SRY

↓

SRY gives TDF

↓

TDF=male

↓

No TDF=female (no SRY)

Genetic sex

↓

Gonadal sex

↓

Phenotypic sex

↓

Internal genitalia | External genitalia

If we specify the genetic sex (X or Y chromosome) i can now know what is the gonadal sex (if it's ovary or testis) and this determining by the hormonal effect (if it's testis it will give testosterone, if it's ovary there's no testosterone and we call it " default pathway " . Meaning that all embryo are female unless there's Y chromosome that will produce testosterone and the embryo development will go to male direction

Development of gonads

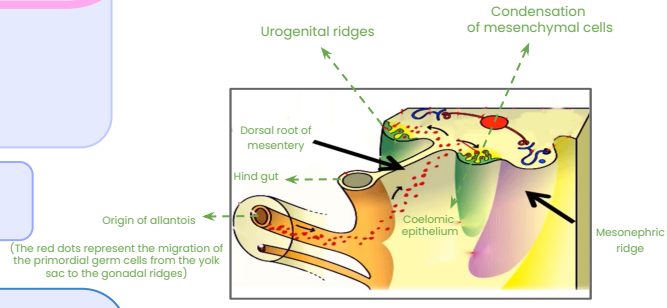
Female slides

1- Indifferent gonads
- Unspecialized gonads
- Can develop to either ways (testis or ovary)
- Present at 6th week

2- different gonads

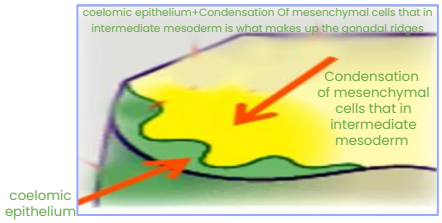
Indifferent Gonad: Genital (Gonadal) Ridge

First step in development of the reproductive system

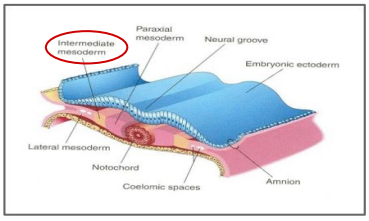


Genital system are developed from **two longitudinal ridges** of mesoderm which run down the entire length of the dorsal body wall. These ridges are called urogenital ridges. (Urinary ridge + genital ridge)

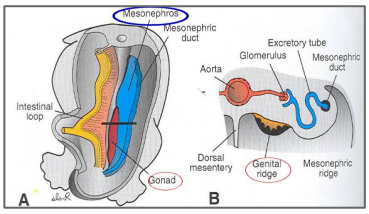
. The **medial region** of this ridge differentiates into the gential ridge where the gonads develop.



The gonads begin to develop during the fifth week in the genital ridge. The gonads are first **undifferentiated** and **have** only a cortex and a medulla.

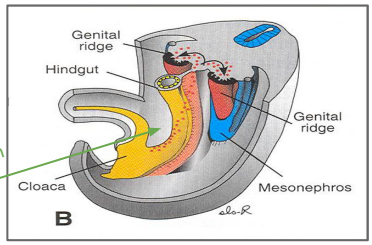


Appears during the 5th week as a pair of **longitudinal ridges** (from the intermediate mesoderm), on the **medial** side of the Mesonephros (nephrogenic cord).

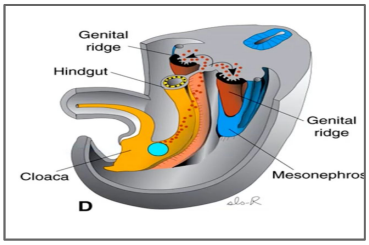


Lies on both sides of the midline between the nephrogenic cord (later it will develop the kidney) & the root of the dorsal mesentery.

In the 6th week, the **Primordial germ cells**(1) (**which appear early in the 4th week** among the Endodermal cells in the wall of the **yolk sac** near origin of the allantois(2)) migrate to the Gonadal Ridges. Primordial germ cells appear as "red dots " in the last two pictures, it will appear in the 4th week but it will migrate to genital ridge in the 6th week .



The **primordial germ cells** have an Inductive Influence on the **differentiation** of the gonad into ovary or testis (PGC is the foundation of the gonads to differentiate, appears 4th week and migrate 6th week)



If they fail to reach the genital ridges, the gonad remains **Indifferent** or **Absent**.

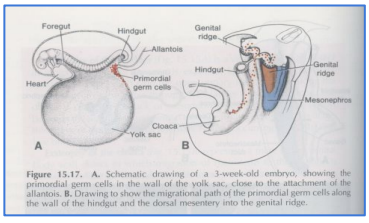


Figure 15.17. A. Schematic drawing of a 3-week-old embryo, showing the primordial germ cells in the wall of the yolk sac, close to the attachment of the allantois. B. Drawing to show the migrational path of the primordial germ cells along the wall of the hindgut and the dorsal mesentery into the genital ridge.

1-Primordial germ cells :the primary undifferentiated stem cell type that will differentiate towards gametes: spermatozoa or oocytes.
2-allantois :is the embryonic precursor of the umbilical cord in mammals

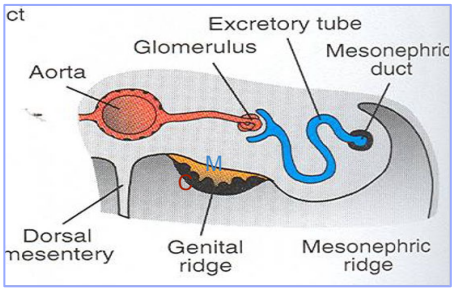
Development of gonads

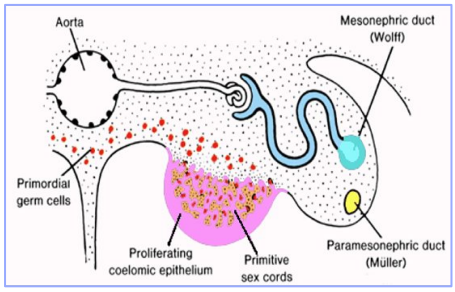
IMPORTANT

Structure of Indifferent Gonad

Structure of Indifferent Gonad

The indifferent gonad	The indifferent gonad consists of an **External Cortex** (colored black) and **Internal Medulla** (colored yellow)
primordial sex cells	It's Large primitive cells, **form in the yolk sac during the fourth week**. They migrate along the dorsal mesentery of the hindgut to the genital ridges where they become incorporated into the developing gonads
Embryos	Female : XX chromosomes, the Cortex differentiates into the Ovary and the medulla regresses تختفي Male: XY chromosomes, the Medulla differentiates into Testis and the cortex regresses
Times & changes	**At 5th week:** Male slides **EXCEPT** 7th week - Germ Cells **arriving** - During arrival of Germ cells, the **epithelium** of the genital ridge **proliferates**, and **epithelial cells penetrate** the underlying mesenchyme - **Forming irregular shaped cord** primitive sex cord(indifferent gonad) **At 6th week:** - the germ cell **invading** genital ridge **At 7th week :** The gonad acquires the Female or Male **morphological characteristics**/Gonads do not acquire male or female morphological characteristics until 7th week of development.





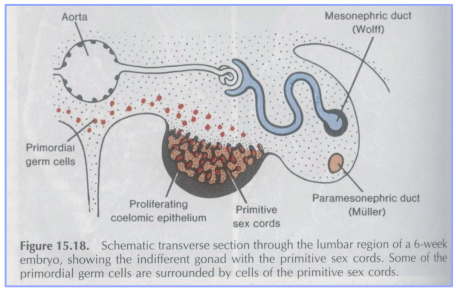


Figure 15.18. Schematic transverse section through the lumbar region of a 6-week embryo, showing the indifferent gonad with the primitive sex cords. Some of the primordial germ cells are surrounded by cells of the primitive sex cords.

Development of Ovary

male slides

OVARY

- medullary cords will be degenerated (see picture)(1)

- **Primitive sex cords dissociate** into irregular cell cluster. Later they will disappear and are **replaced** by vascular stroma **forming** ovarian medulla.

- Surface **epithelium** of the female gonad **proliferate**.

- In 7th week give rise to **2nd generation of cords, cortical cords**(2)

- **Penetrate** the underlying mesenchyme

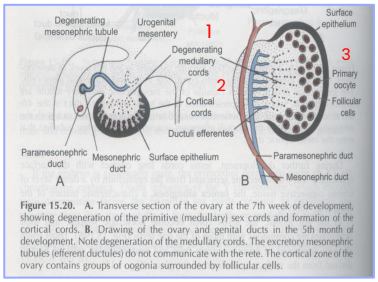
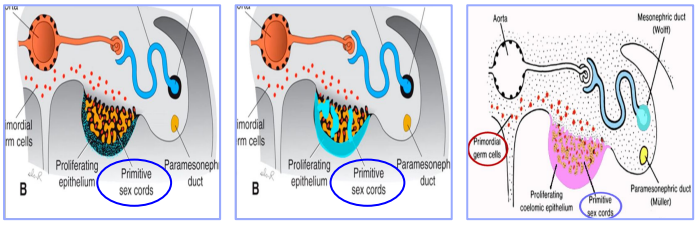
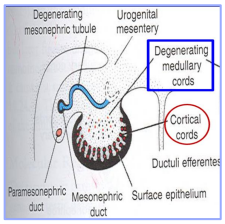


Figure 15.20. A. Transverse section of the ovary at the 7th week of development, showing degeneration of the primitive (medullary) sex cords and formation of the cortical cords. B. Drawing of the ovary and genital ducts in the 5th month of development. Note degeneration of the medullary cords. The excretory mesonephric tubules (efferent ductules) do not communicate with the rete. The cortical zone of the ovary contains groups of oogonia surrounded by follicular cells.

- In **4th month** these cords split into **isolated cell clusters** which **surrounding** one or more **primitive germ cells.**
- GC will develop into **oogonia** and **surrounding** epithelial cells form **follicular cells.**(3)

Female slides

Primitive (primary) sex cord It's the first stage of different stage	**Cortical (Secondary) Sex Cords** Cortical because it's close to the cortex, appears after the degeneration of the primitive sex cord and rete ovarii
Fingerlike epithelial cords grow from cortex of the indifferent gonad and extend into the medulla.(primitive sex cord originates from the cortex which is a proliferation of the coelomic epithelium)	They extend from the surface epithelium into the underlying mesenchyme to replace the primary cords.
The Primary sex cords dissociate (disconnect) into (Rete ovarii).	The primordial germ cells are incorporated into them
Both the primary sex cords and rete ovarii degenerate and disappear.during the fertile development of the embryo .	- The ovary is identifiable histologically at the 10th week. - At the 16 weeks 4 months , the **cortical cords** break up into **isolated cell clusters**: Primordial Follicles containing (Primary Oocytes).
	

Development of Ovary

Female slides

Primordial Follicles/ Primary Oocyte

- Composed of :

- **Oogonium** derived from the **Primitive Germ Cell**
- **Surrounded by** a single layer of flattened **Follicular Cells**

derived from the surface epithelium (Sex Cord).

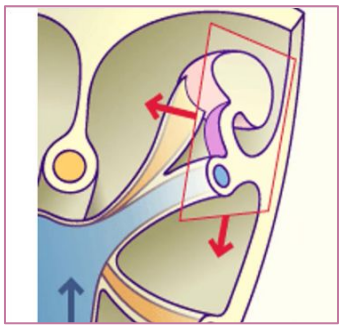
- Active Mitosis of Oogonia occurs during fetal period producing thousands of primordial follicles. the female fetus inside the uterus it will go through a lot of mitosis and divisions , so at birth the female is already lost some of her ovum/eggs.
- (No New Oogonia Are Formed Postnatally)
- Two million oogonia (or so) enlarge to become Primary Oocytes (Before Birth)

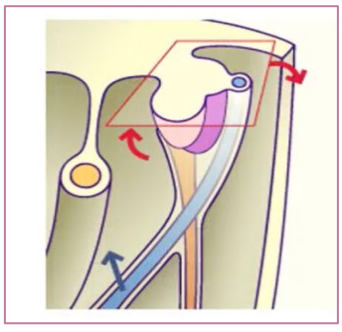
Postnatal Changes of the Ovary

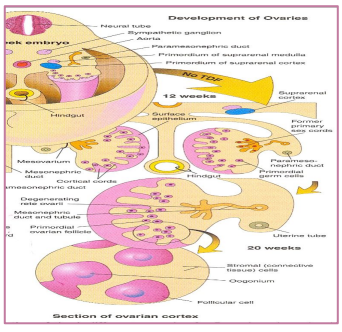
1-Surface Epithelium:
Flattened into a single layer and **separated from follicles** in the cortex by a thin **tunica albuginea.**

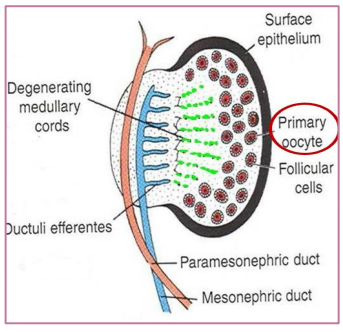
2-The ovaries **descend** from the posterior abdominal wall into the pelvis: just **inferior to the pelvic brim.**ovaries at the beginning will be in the abdomen, after that it will descend by the help of the ligaments as fetus grows, opposite to the direction of kidneys ascend from the pelvis to the abdomen

Summary in female slides click here









Development of Genital Ducts

Two pairs of genital ducts develop in both sexes:

Click here

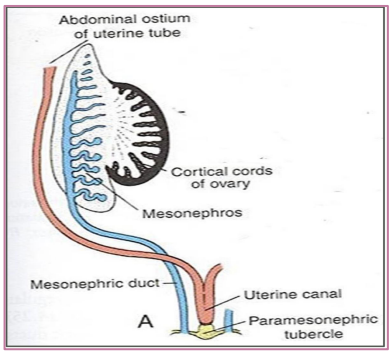
Mesonephric (Wolffian) Ducts:
In female embryos, the mesonephric ducts regress due to absence of the testosterone hormone

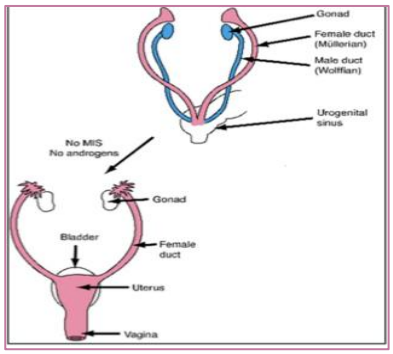
Paramesonephric (Mullerian) Ducts:
Müllerian ducts develop due to absence of MIS or MIF (Müllerian Inhibiting Substance) into fallopian tubes, uterus, cervix and upper vagina. (upper third of vagina only)

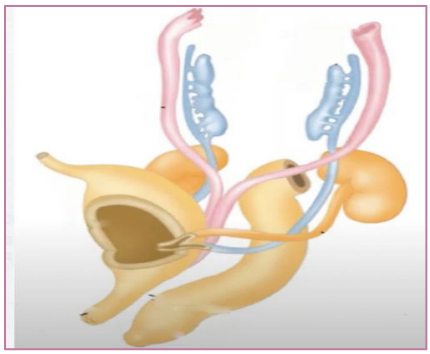
The Paramesonephric Ducts:

Female slides

1. They form most of the female genital tract./Develop into the main genetal ducts of the female
2. They develop lateral to the gonads and mesonephric ducts.
3. Their funnel-shaped cranial ends open into the peritoneal cavity.
4. They pass caudally parallel to mesonephric ducts to reach the future pelvic region.
5. They Cross ventral to the mesonephric ducts & approach each other in the median plane and fuse to form the Y shaped Uterovaginal Primordial.
6. (which opens into the dorsal wall of the urogenital sinus and produces Paramesonephric(mülleria n) Tubercle.)







Development of Genital Ducts

Paramesonephros in Female/3 parts can be recognized in each duct :

IMPORTANT

1. **Cranial vertical part:** opens into coelomic/abdominal cavity
2. **Middle horizontal part:** crosses the mesonephric duct
3. **Caudal vertical part:** fuses with each other in midline/its partner from the opposite side

develop into uterine tubes

caudal fused parts give rise to the body of uterus, cervix and upper third of vagina

Differentiations of paramesonephric duct

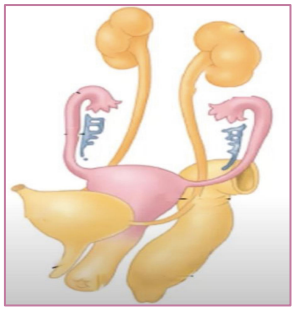
Uterine tubes:
Formed from the cranial unfused parts of the ducts.

Uterine canal:
formed from the fusion of the caudal vertical part

Utero-vaginal Primordium (fused lower parts):
It is divided into:
- Uterus (Body and Cervix)
- Superior Portion of the Vagina.

- The endometrial stroma and myometrium are derived from the splanchnic mesoderm.
- Mesenchyme will form muscular coat of the uterus myometrium & perimetrium

- If the embryo is to become a male, **the mesonephric duct system remains to form efferent ductules, epididymis, vas deferens and ejaculatory duct**.
- The seminal vesicle develops as a diverticulum from the developing vas.



Vagina & Lower Portion of Vagina

Lower portion of vagina is derived from the **urogenital sinus.**

The contact of the uterovaginal primordium /After solid tip of paramesonephric ducts reaches with the urogenital sinus induces formation of two evagination grow out (**sinovaginal bulbs**)which they proliferate cranially and form solid vaginal plate.

The Central cells of the vaginal plate break down to form the lumen of the vagina.

By the 5th month Vagina will be/entirely canalized.
(At first it was a solid block then it got canalized completely by the 5th month)

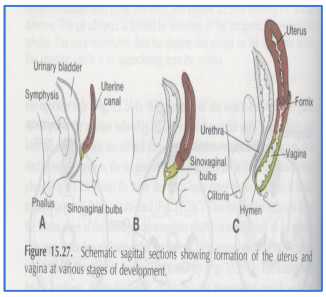
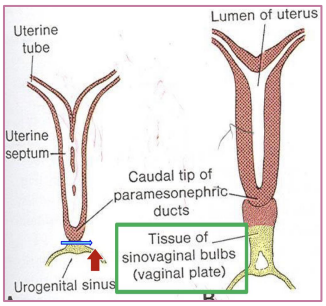
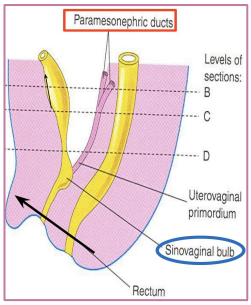


Figure 15.27. Schematic sagittal sections showing formation of the uterus and vagina at various stages of development.





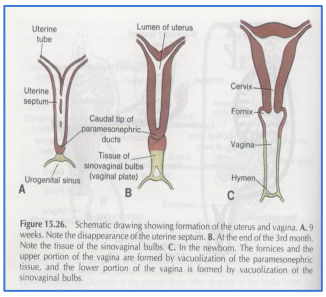


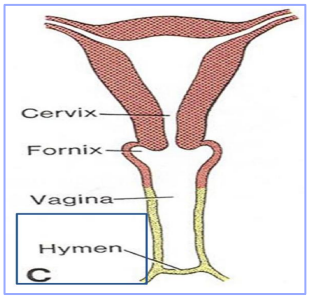
Figure 15.26. Schematic drawing showing formation of the uterus and vagina. A, 9 weeks. Note the disappearance of the uterine septum. B, At the end of the 3rd month. Note the tissue of the sinovaginal bulbs. C, In the newborn. The fornices and the upper portion of the vagina are formed by vacuolization of the paramesonephric tissue, and the lower portion of the vagina is formed by vacuolization of the sinovaginal bulbs.

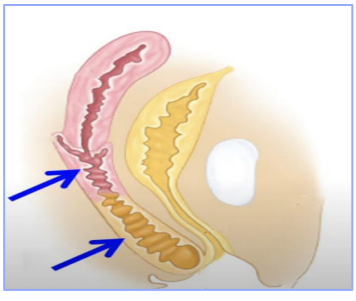
Female slides

Differentiation of vagina

- The lining of the entire vagina is derived from the vaginal plate (urogenital sinus).

- The lumen of vagina is separated from the urogenital sinus by the Hymen which remains as a thin fold of mucous membrane just within the vaginal orifice.





External Genitalia

male slides

3rd week:

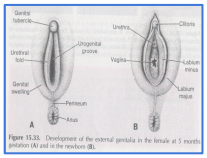
mesenchyme cells originated from primitive streak migrate around the cloacal membrane to form a pair of cloacal folds.

- Cranial to cloacal membrane the folds unite to form the genital tubercle.
- Caudally the folds are subdivided into urethral folds anterior & anal folds poste

In the meantime, another pair of elevation, genital swelling become visible on each side of the urethral folds These will form labia majora.

Estrogens stimulate development of the external genitalia of the female

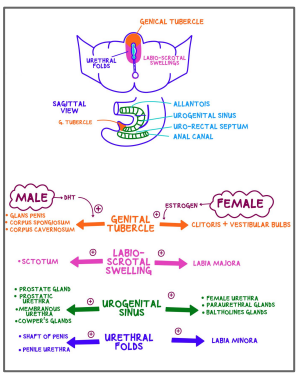
The genital tubercle elongates slightly to form clitoris



Urethral folds do not fuse to form labia minora

Urogenital groove is open and forms the vestibule.

The 2nd, 3rd and 4th points are found in both male and female slides



extra picture from ninja nerd

External Genitalia

Female slides

Are Similar in both sexes up to the 7th week indifferent stage

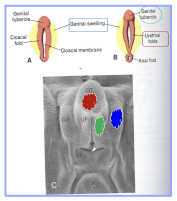
Start to differentiate in the 9th week

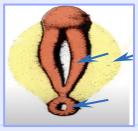
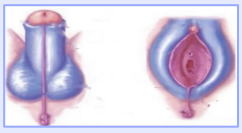
Fully differentiated by the 12th week

Development of female external genitalia:

Proliferation of Mesenchyme at the Cranial end and Sides of the Cloacal Membrane, forms :

1. **GenitalTubercle,** later will develop to be the clitiros in females.
2. **Urogenital Folds** (Urethral Fold).
3. **Labioscrotal Swellings** (GenitalSwellings).



	External genitalia
Indifferent stage 	- The cloacal membrane is surrounded by cloacal fold which meet anteriorly to form genital tubercle. - The urorectal septum divides it into urethral & anal folds. - A genital swelling is formed lateral to the urethral folds.
Different stage 	In male: - Genital tubercle: forms the penis - Urethral folds: fuse and form the urethra - Genital swelling: fuse and form the scrotum In Female: - It will be mentioned next in this lecture

Feminization of external genitalia	
	Estrogen produced by both the placenta and the fetal ovaries has a role in feminization of the external genitalia.
	The Genital Tubercle proliferates to form the Primordial Phallus. The phalls elongates slightly to form the Clitoris.
	The Urethral Folds do not fuse and form the Labia Minora.
	The Labioscrotal Folds form the Labia Majora , they fuse to form the Posterior & the Anterior Labial Commissures.

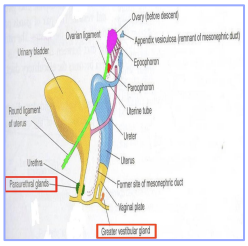
External Genitalia

Female slides

Female sex glands

Urethral & Paraurethral Glands: Grow as buds from the urethra, they are corresponding to the Prostate Gland of the male

Greater Vestibular Glands: Outgrowths the urogenital sinus, they are corresponding to the Bulbourethral Glands of the male



Congenital Anomalies

Various types of anomalies can result due to:

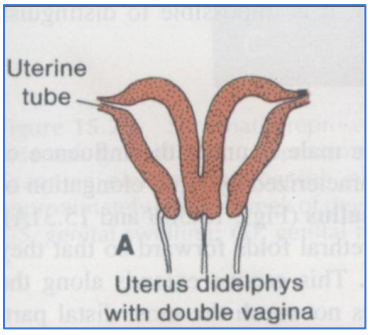
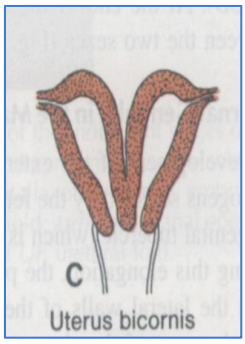
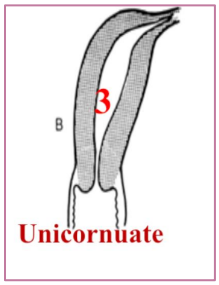
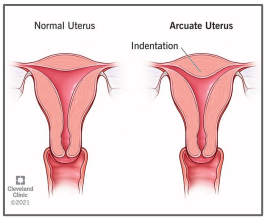
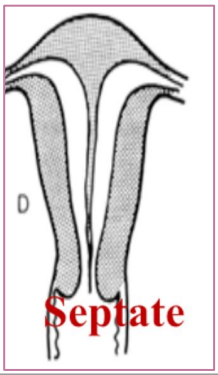
- *Arrest of development of the uterovaginal primordium during the 8th week.*
- *Incomplete development of the paramesonephric ducts.* (Didn't form the Y shape)
- *Incomplete fusion of the paramesonephric ducts.*
- *Failure of parts of one or both paramesonephric ducts to develop.*
- *Incomplete canalization.*

Congenital Anomalies

Female slides

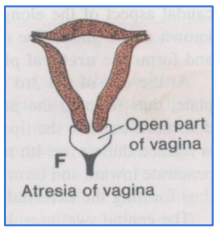
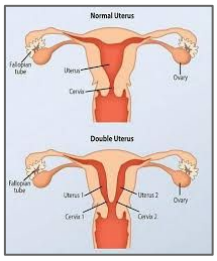
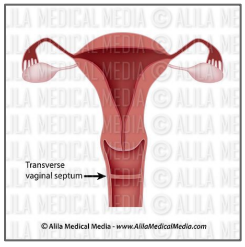
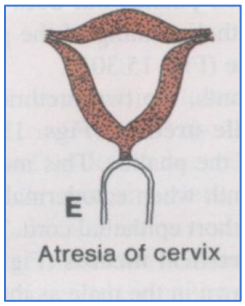
Extra

Uterine Malformations

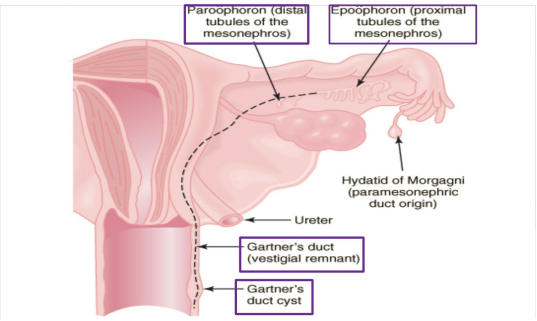
Double uterus (Uterus Didelphys):	Bicornuate Uterus:	Unicornuate Uterus:	Arcuate Uterus:	Septate Uterus:
• Due to failure of fusion of inferior parts of the paramesonephric ducts. • May be associated with a double or single vagina.	The duplication involves superior segment.	One paramesonephric duct fails to develop	A small dent at the top of the uterus, unlike a typical pear-shaped uterus	A membrane runs down the middle of the uterus, splitting it into two parts.
				

Congenital Anomalies

Female slides

Vaginal Anomalies	**Atresia:** birth defect in which the vagina is closed or absent	(Partial or Complete).	
	Double vagina:	May Be associated with double uterus.	
	Transversely septate Vagina:	Result from faulty canalization of the fused Müllerian Ducts.	
Cervical Anomalies	**Cervical Atresia**	It may be combined with incomplete development of the upper vagina or lower uterus.	

Remnants of the mesonephric (wolffian) ducts may persist in the anterolateral wall of vagina or adjacent to the uterus within the broad ligament or mesosalpinx.



MCQ

1

Uterus arise from which structure?

A Mesonephric duct

C Paramesonephric duct

B Mesonephros

D Metanephros

2

Which of the following anomalies arise Due to failure of fusion of inferior parts of the paramesonephric ducts.?

A Double uterus

C Bicornuate Uterus

B Septate Uterus

D Arcuate Uterus

3

When does the vagina get entirely canalized?

A 4th Month

C 5th Month

B 3rd month

D 6th Month

4

When does the primordial germ cells form ?

A 5th week

C 6th week

B 4th week

D 7th week

5

Which of the following part of the Paramesonephric duct give rise to the body of uterus, cervix and upper third of vagina?

A Cranial part

C Horizontal part

B Fusion of A + B

D Caudal fused parts

Answer key : 1-C 2-A 3- C 4-B 5- D

Embryology Team

Leader
سلطان البقمي

Leader
رهف الشويهي

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- ريوف الأحمري
- ريماز المحمود
- شادن الهزاني
- ريناد محمد الشهري
- لمى العتيبي
- ريم العمير

- أبو عويد
- عبدالله الكودري
- خالد العنزي
- فراس مازن
- زياد العتيبي
- فيصل الشويعر

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