

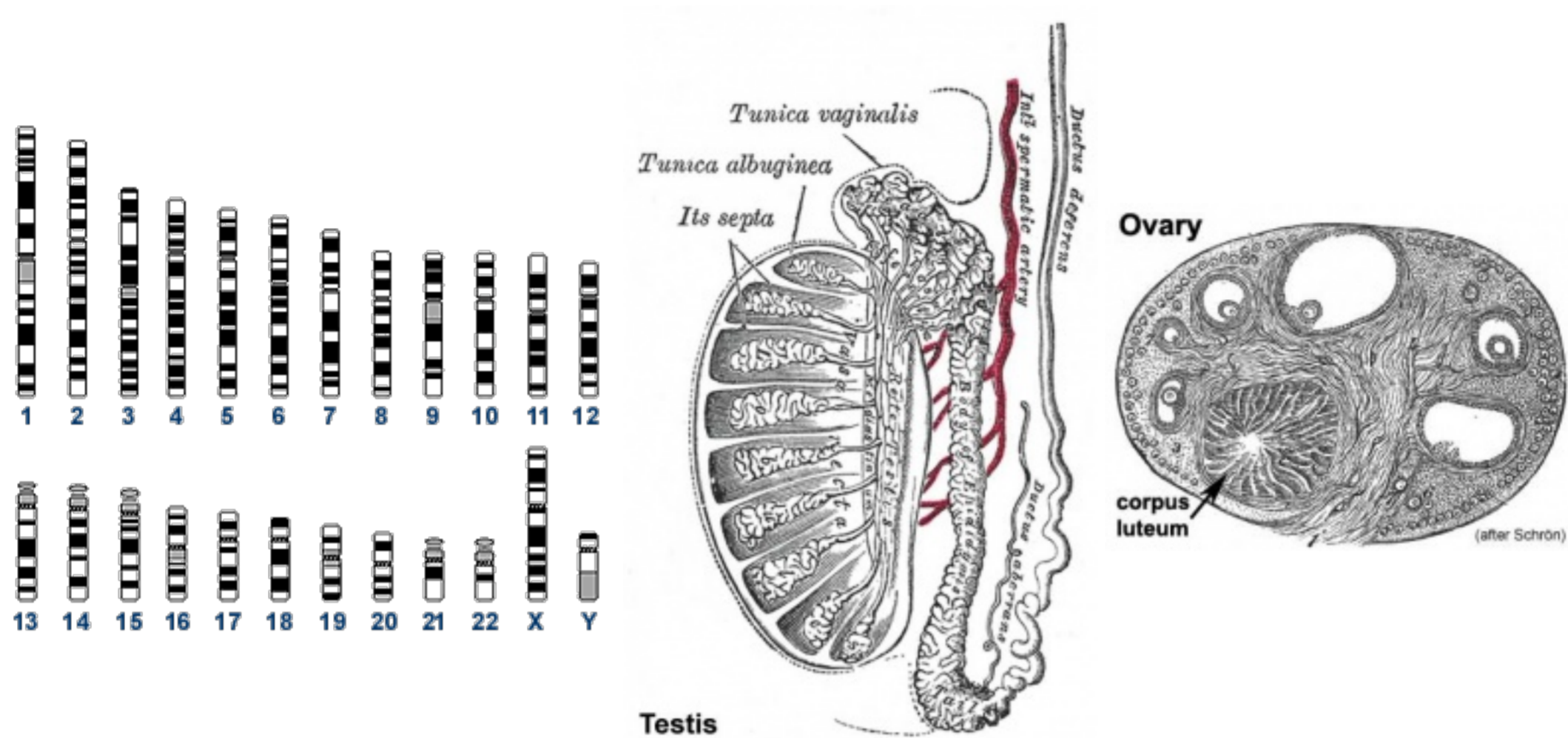
Lecture - Genital Development

From Embryology

Introduction

This lecture covers embryonic sexual differentiation covering gonad, internal and external genital development. Differences in development are dependent on a protein product of the Y chromosome SRY gene. The paired **mesonephric ducts** (Wolffian ducts) and **paramesonephric ducts** (Müllerian ducts) contribute the majority of male and female internal genital tract respectively. I will also introduce some abnormalities of development, that will be covered in the associated practical class. This is one system that continues to develop and change postnatally with puberty and menopause.

♂ Male ♀ Female



Objectives

- Understand the development of the gonads in males and females
- Understand the chromosomal basis of sex determination
- Understand the differences in male/female internal duct development.
- Understand the origins of the external genitalia
- Understand the developmental abnormalities in male and female development.

Lecture Resources

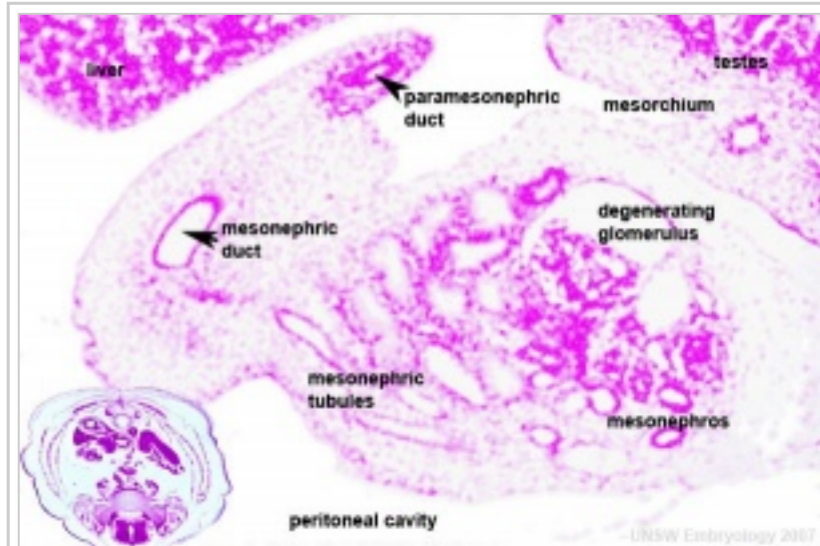
Movies[Expand]

References[Expand]

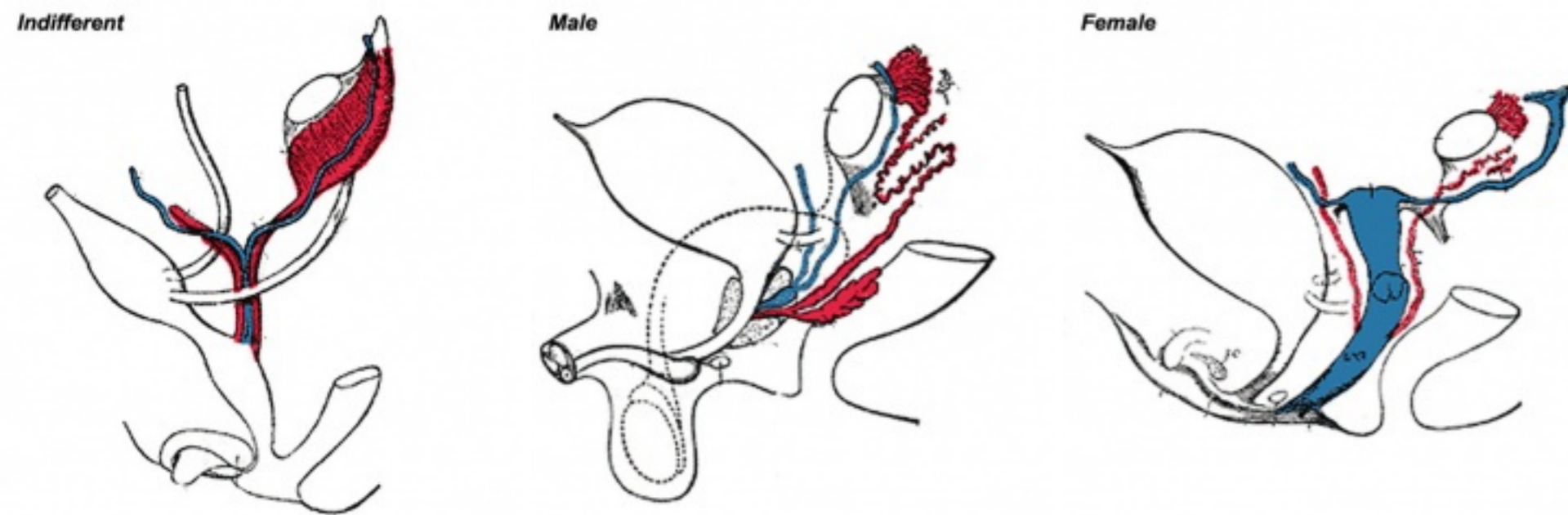
ECHO360 Recording[Expand]

Stages of Sexual Differentiation

1. Development of the **indifferent gonad** - (genital ridge) early embryo
2. Differentiation of gonad - (**testis or ovary**) late embryo, defining event in sexual differentiation
3. Differentiation of **internal genital organs** and ducts - late embryo to fetal
4. Differentiation of **external genitalia** - fetal
5. Development of **secondary sexual characteristics** - puberty



Stage 22 mesonephros



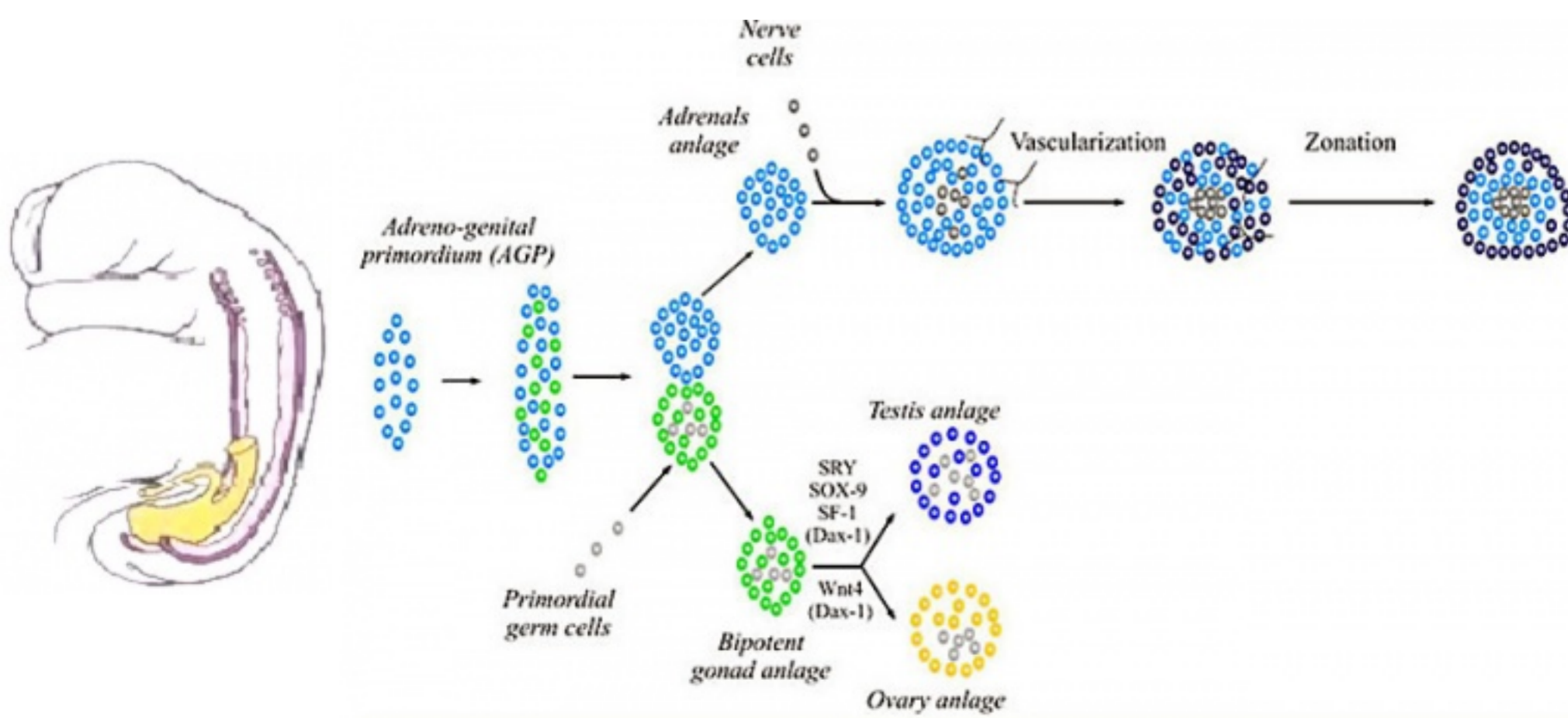
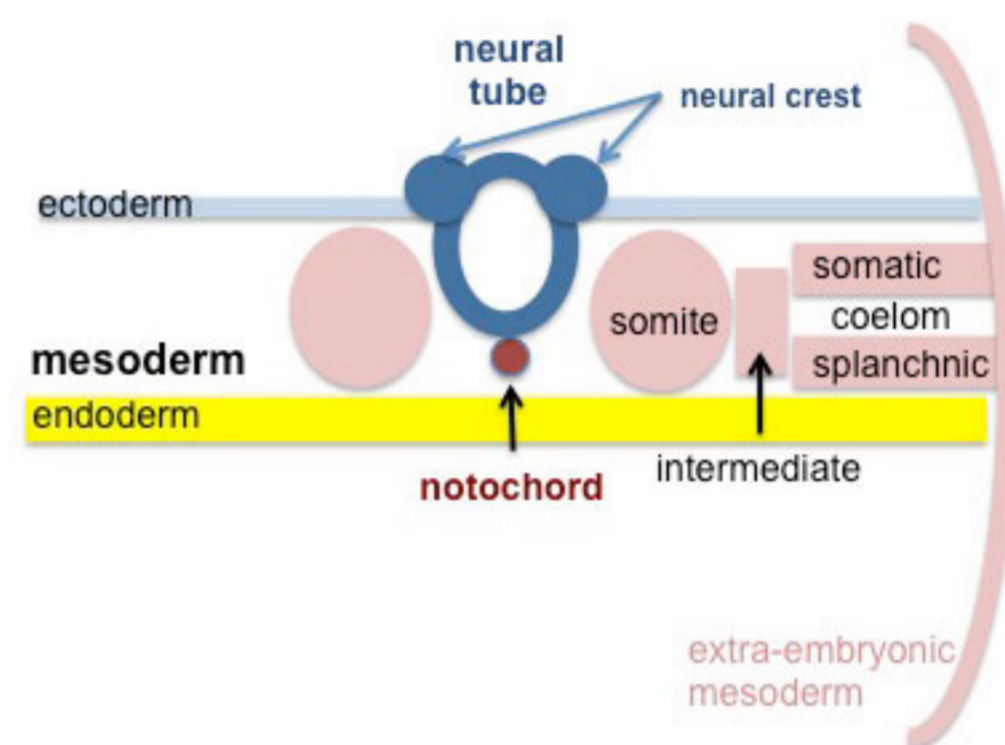
Human Timeline

- **Week 3-4** - primordial germ cells migrate during gastrulation
- **Week 4** - (24 days) intermediate mesoderm, pronephros primordium
- **Week 5** - (28 days) mesonephros and mesonephric duct
- **Week 6** - (35 days) ureteric bud, metanephros, genital ridge
- **Week 7** - (42 days) cloacal division, gonadal primordium - indifferent to first appearance of testis cords
- **Week 8** - (49 days) paramesonephric duct, clear gonadal differentiation
- **Week 9** - (56 days) paramesonephric duct fusion (female)
- **Week 15** - (100 days) primary follicles (ovary)



1. Development of the indifferent gonad

- **intermediate mesoderm** - (between somites and lateral plate mesoderm) kidneys and genital ridge develop.
- **kidney multiple stages** - occur in a rostrocaudal sequence
 - **pronephros** > **mesonephros** > **metanephros** (true adult kidney)
- **pronephros** (week 4) earliest structure to form featuring a pronephric duct with associated nephrogenic mesenchyme.
 - pronephros degenerates - leaving only the duct system running down to the cloaca (**mesonephric duct** = Wolffian duct).
- **mesonephros** - next stage a series of mesonephric tubules in the mesenchyme that are induced by the mesonephric duct.
 - mesonephros degenerates - in mammals (In fish and amphibians it is the functioning adult kidney).
 - In mammals it serves mainly as the site for gonadal development.



Gonad and adrenal early development (not required to know molecular information)

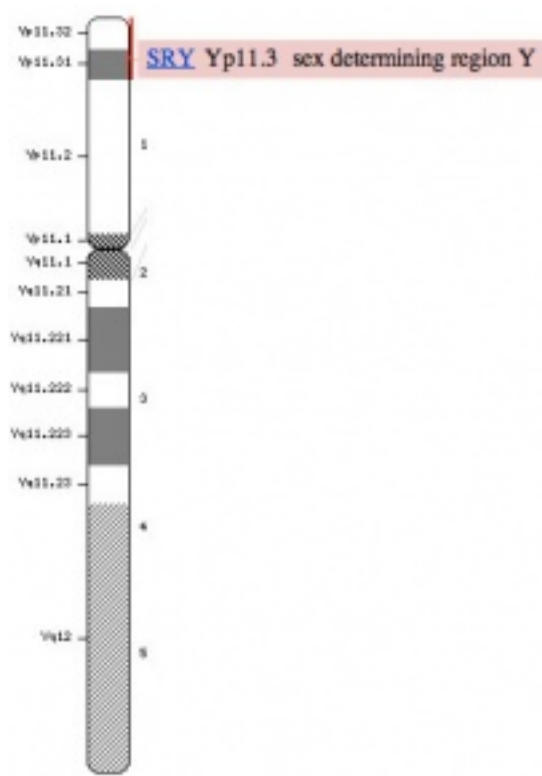
2. Differentiation of gonad into testis or ovary

Chromosomal Sex Determination

| Males | Females |
|---------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------|
| Y Chromosome | X Chromosome |
| <ul style="list-style-type: none"> ■ 59 million base pairs, hypervariable in length, mostly non-functional | <ul style="list-style-type: none"> ■ 155 million base pairs, contains about |

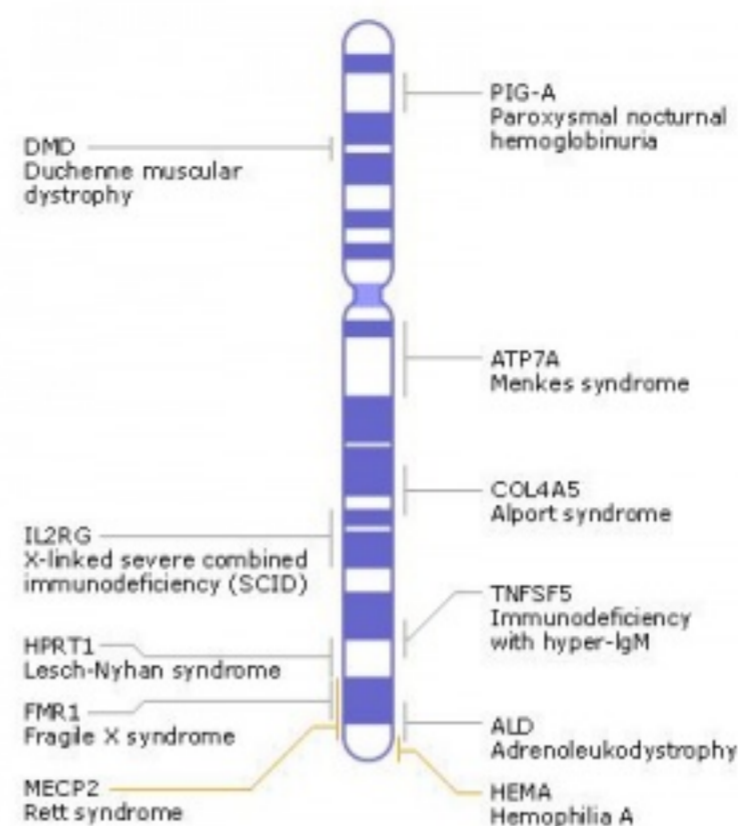
repeats

- Current known protein-coding genes = 48 including *SRY*
- *SRY* encodes a 204 amino acid protein (TDF) that is a member of the HMG (High mobility group) box class of DNA-binding proteins. Transcription factors bind to specific sites of DNA and regulates the transcription (expression) of other genes.



5% of the haploid genome and encodes house-keeping and specialized functions.

- Genes such as Wnt-4 and DAX-1 necessary for initiation of female pathway ovary development



X inactivation

- one X chromosome randomly inactivated throughout the female embryo.
- mosaic of maternal and paternally derived X chromosome activity in all tissues and organs.

Links: MBoC - Figure 20-18. Influence of Sry on gonad development (<http://www.ncbi.nlm.nih.gov/books/NBK26940/figure/A3716>) | image (<http://www.ncbi.nlm.nih.gov/books/NBK26940/bin/ch20f18.jpg>) (image provides a good overview of the anatomy of sex determination, I will refer to this in the lecture and practical class)

Supporting Cells

- So called because they "support" the germ cells

Males

Sertoli cells

- SRY is expressed in the primordia of the supporting cells, transforming them into Sertoli cells that surround the germ cells and form testis cords
 - SRY is not expressed in the other cell types of the gonad
- Sertoli cells instruct the germ cells and the steroid secreting cells to take the male path of development

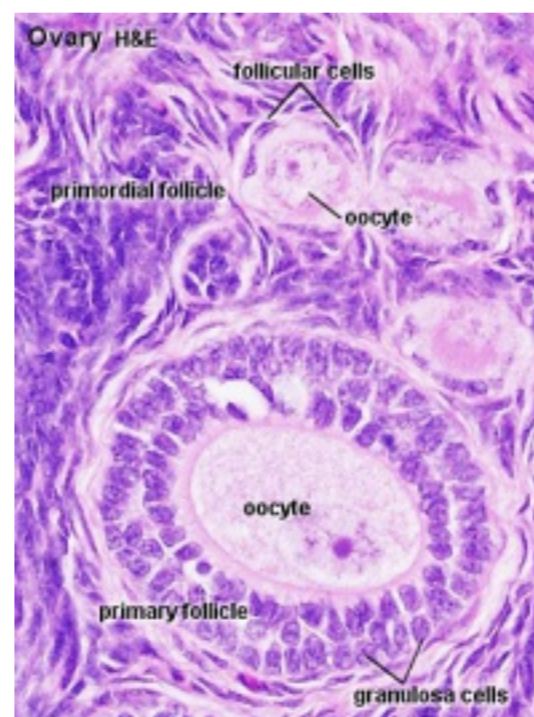


- embryonic cells - secrete anti-Mullerian hormone (AMH)
- adult cells - line the inside of the seminiferous tubules and support spermatogenesis.

Females

Granulosa cells

- Follicle cells surround and nurture the developing oocytes



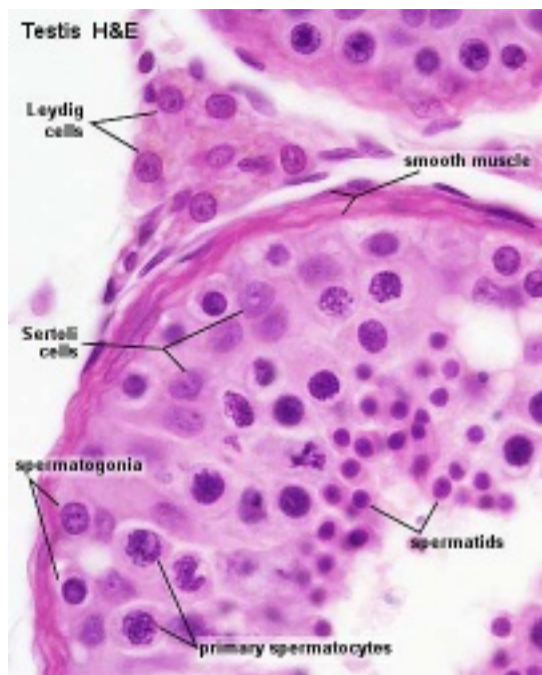
- adult cells - in response to FSH, follicle cells proliferate
 - After ovulation, these cells become luteal cells of the corpus luteum secreting progesterone and estrogen

Steroid secreting cell lineage

Males

Leydig cells

- (interstitial cells) that sit outside the seminiferous tubules
- Secrete **testosterone** in response to luteinizing hormone from the pituitary



Females

Theca cells

- that sit outside the follicle granulosa cells
- Secrete **androstenedione** that can be converted by the follicle cells into estrogens



Primordial Germ Cells

- Primordial germ cells (PGCs) are thought to be the first population of cells to migrate through the primitive streak in early gastrulation (week 3)
- cells then lie at the hindgut yolk sac junctional region
- later migrate into the genital ridge (germinal ridge) in early embryonic development.

Mouse Primordial Germ Cell Migration

Germ Cell E9.0

Page | Play

Germ Cell E9.5

Page | Play

Germ Cell E10.5

Page | Play

- **Not the primordial germ cells which respond to SRY** presence or absence, but the supporting cells within the developing gonad.
 - Germ cells occasionally migrate by mistake into the developing adrenal gland and in the absence of sertoli cells telling them what to do, abnormally begin to develop as oocytes, even in males

Links: Germ cell migration pathway (<http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=dbio&part=A4665&rendertype=figure&id=A4669>)

Gametogenesis

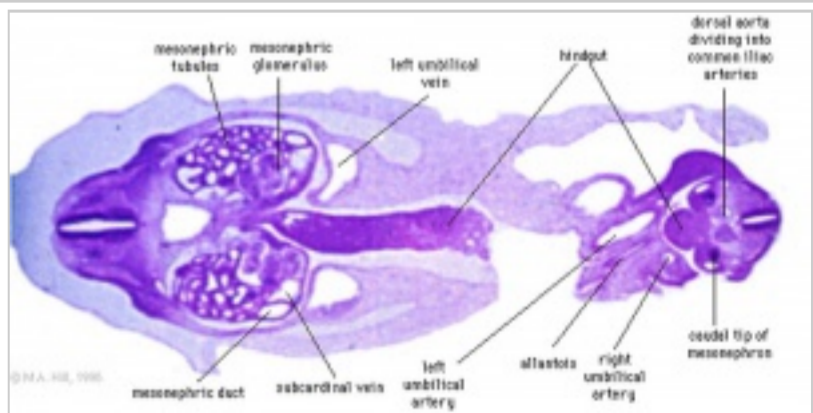
- forming PGCs as a small population of migratory cells
- enter the gonad where they undergo several rounds of mitotic cell division
- female - the germ cells enter meiosis and become arrested at the dictyate (diplotene) stage of meiotic prophase 1. All oocytes are at this stage at birth
- male - the germ cells are enclosed by the developing Sertoli cells and are induced to arrest differentiation and cell division as T1 prospermatogonia until after birth.

Links: Image - Spermatogenesis (<http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=mboc4&part=A3729&rendertype=figure&id=A3735>) | Image -Oogenesis (<http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=dbio&part=A4695&rendertype=figure&id=A4715>)

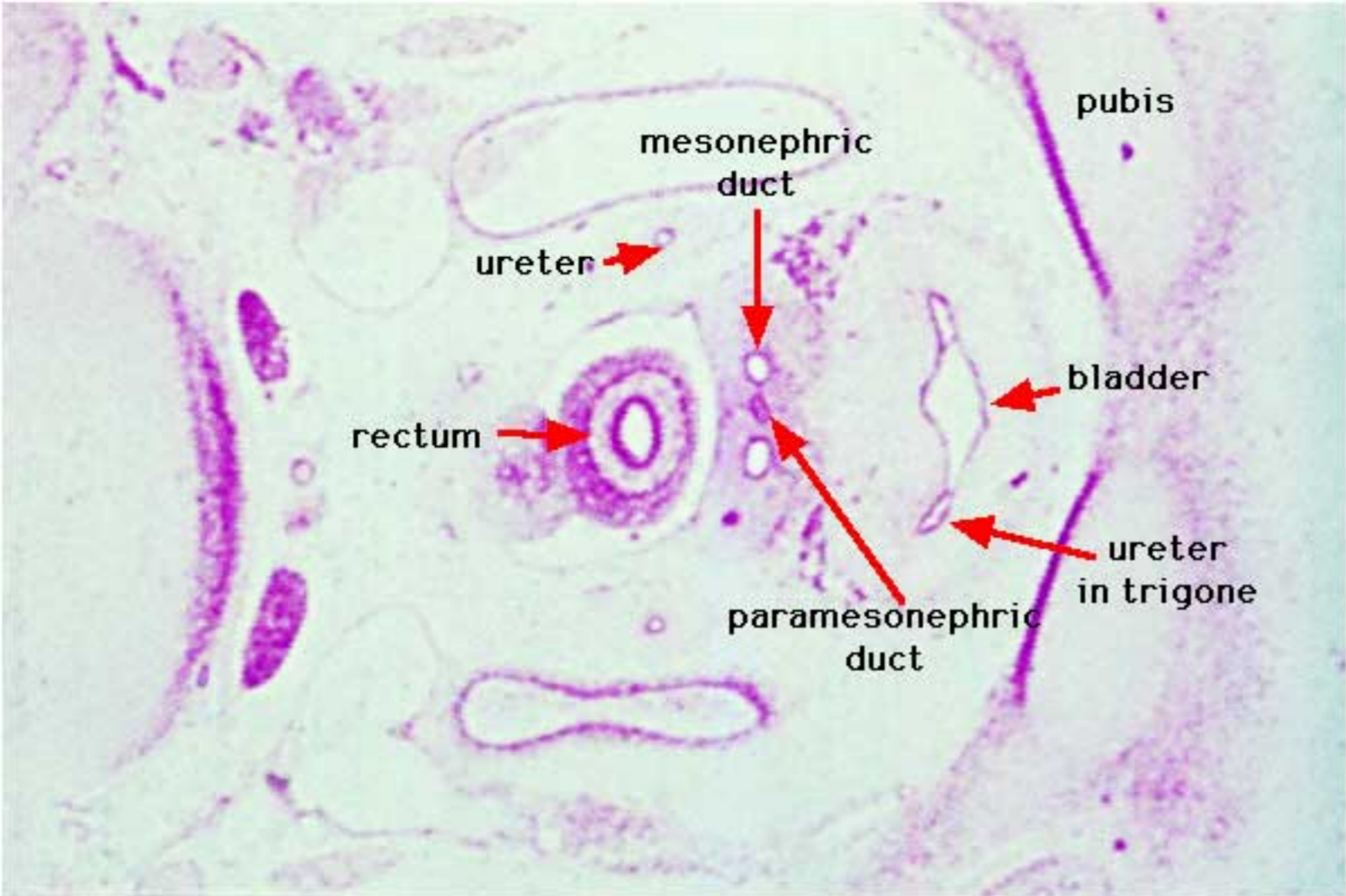
3. Differentiation of internal genital organs and ducts



Primordial germ cell region (Stage 9)



Genital Ridge (Stage 13)



Human embryo (Carnegie stage 22, week 8) pelvic level cross-section.

Male

This looped animation shows the development of the male gonad showing medullary sex cords.

- The paramesonephric duct (red, left) degenerates under the influence of anti-Mullerian hormone (AMH) secreted by sertoli cells.
- The mesonephric duct (purple) is maintained and differentiates under the influence of Testosterone secreted by Leydig cells. Within the testes these mesonephric tubules grow towards the testis cords and will form the rete testis. The mesonephric duct extending out of the gonad forms the ductus deferens.
- The testis cords (orange) containing the Sertoli cells and the germ cells (which are arrested as T1 prospermatogonia until after birth) later differentiate into seminiferous tubules which become hollow and actively produce spermatazoa during puberty.

The tunica albuginea (white) covers the testis and bands extend inward to form connective tissue septa.



Testis
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Anti-Mullerian Hormone

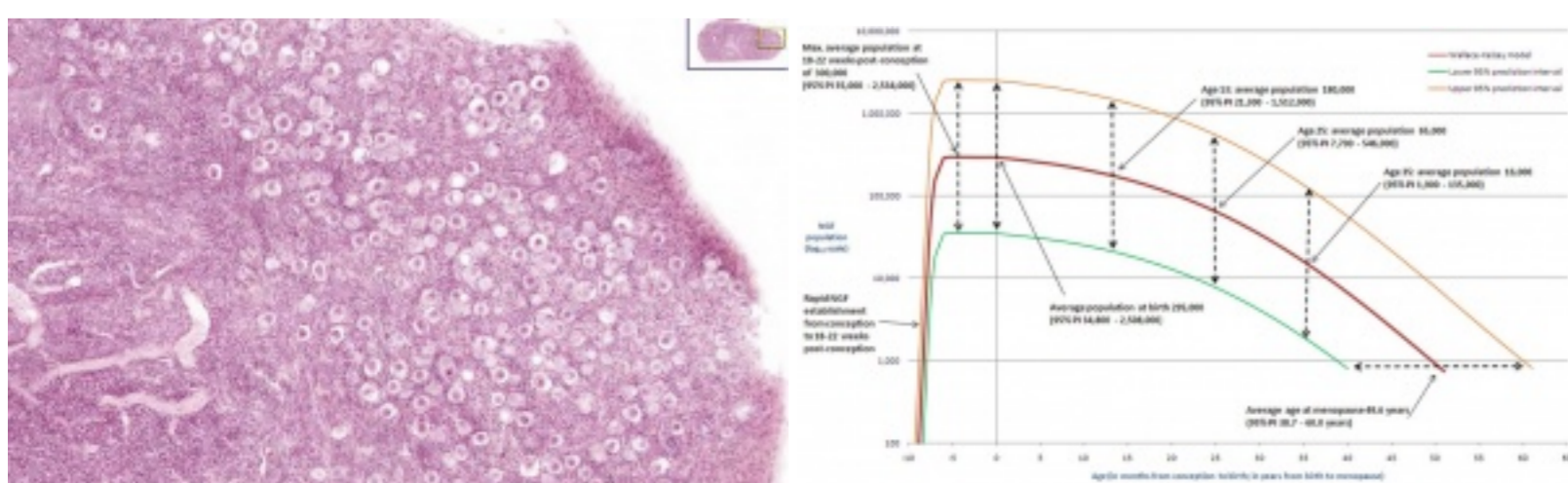
Anti-Mullerian hormone (AMH) or Mullerian Inhibiting Substance (MIS) hormone with at least two gonadal related functions:

- In males, it is produced by embryonic Sertoli cells and causes the loss of the paramesonephric (Mullerian) duct system that forms the internal female genital tract.
- In females, it is produced after puberty by follicle cells and suppresses the development of other primary follicles, thus restricting the number of follicles stimulated by FSH.

Female

This looped animation shows the development of the female gonad showing cortical sex cords.

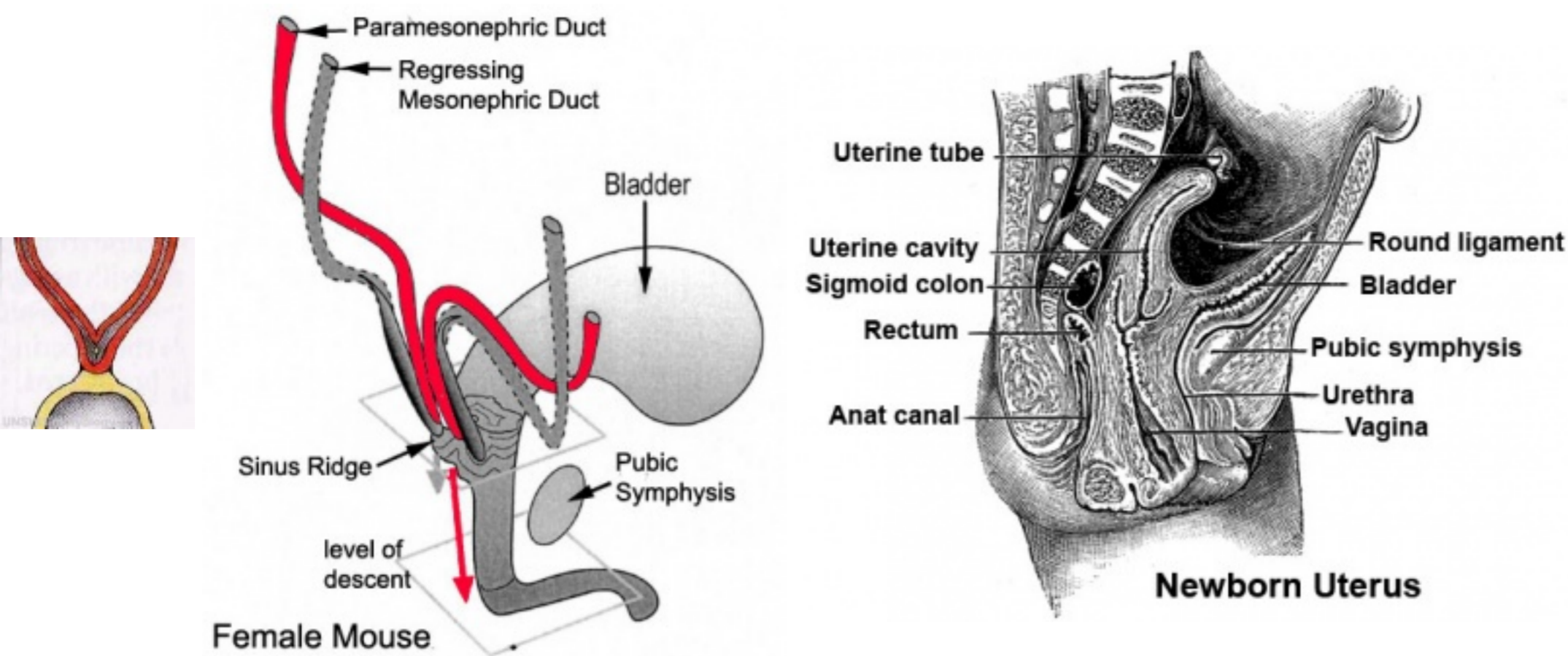
- The mesonephric duct (purple) degenerates, small remnants may remain as epoophoron and paroophoron (in the mesentery of the ovary) and Gartner's cysts (near vagina).
- The paramesonephric duct (red, left) grows forming the oviducts (fallopian tubes) and the end opens into the peritoneal cavity and terminates in fimbria (finger-like extensions). Away from the ovary, the two paramesonephric ducts fuse in the midline to form the uterus.
- After entry of the germ cell into meiosis they are called oocytes and they are surrounded by the derivatives of the supporting cell lineage - the follicle cells or granulosa cells.
- About 95% of the germ cells that entered meiosis in the female will be lost by a process called follicular atresia (see graph. Only about 400,000 remain at the time of puberty.



Ovary
Page | Play

Uterus Development

■ Week 7 – duct preservation or regression begins



Paramesonephric duct development

Vagina Development

- The embryonic origin of the vagina has been a historically hotly debated issue with several different contributions and origins described.
- Current molecular studies show the whole vagina is derived from the intermediate mesoderm-derived Müllerian duct (see review ^[1])
 - bone morphogenic protein 4 (BMP4) reshapes the duct into the vaginal primordium.
- exhibits different features from the uterus
 - stratified squamous epithelium
 - insensitivity to anti-Müllerian hormone

Links: Vagina Development

4. Differentiation of External Genitalia

Endocrinology - Diagram of the development of the external genitalia

(<http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=endocrin&part=A972&rendertype=box&id=A1026>) | image (<http://www.ncbi.nlm.nih.gov/books/NBK29/bin/ch6fb5.jpg>)

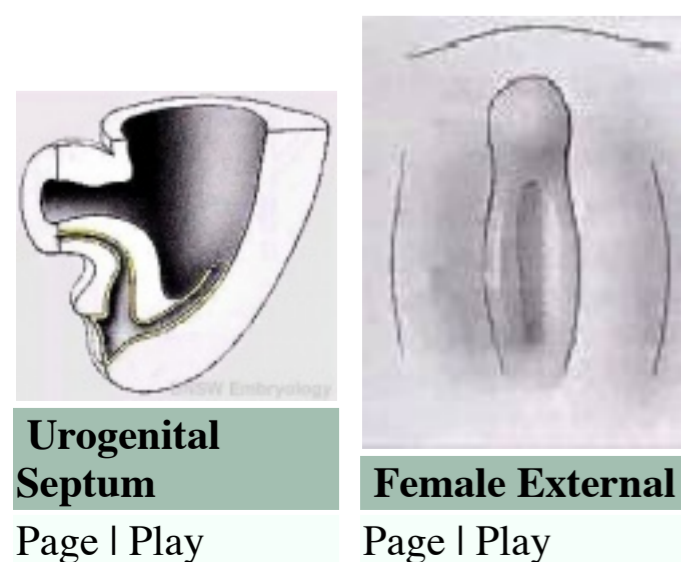
- external genitalia are initially identical and undergo male and female differentiation under the influence or absence of steroidal sex hormones.
- Indifferent stage – cloaca divided by proliferating mesenchyme forming the urorectal septum which separates the ventral urogenital sinus from the dorsal rectum.
- Difference stage – locally in this region the presence or absence of **dihydrotestosterone** (DHT), generated from testosterone, determines male/female development.

Dihydrotestosterone (DHT)

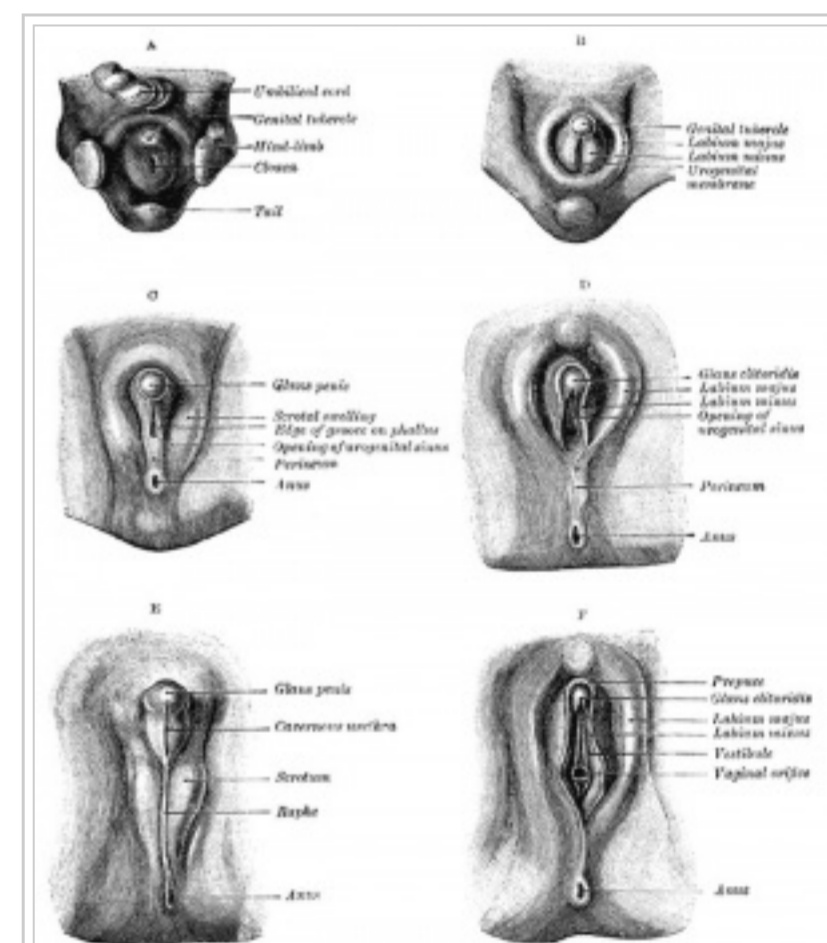
- Male presence of DHT
 - locally in this region leads to **genital tubercle** growth, form
 - **genital folds** (urethral) initial maintenance and then fusion, forming perineal and penile raphe.
 - **labioscrotal swellings** (lateral to urethral folds) become the scrotum.
- Female absence of DHT
 - genital tubercle remains small, bends caudally to form the clitoris.
 - genital folds (urethral) persist, do not fuse, and form labia minora.
 - open urogenital sinus forms a cleft into which urethra and vagina open.
 - labioscrotal swellings become the labia majora.

Female

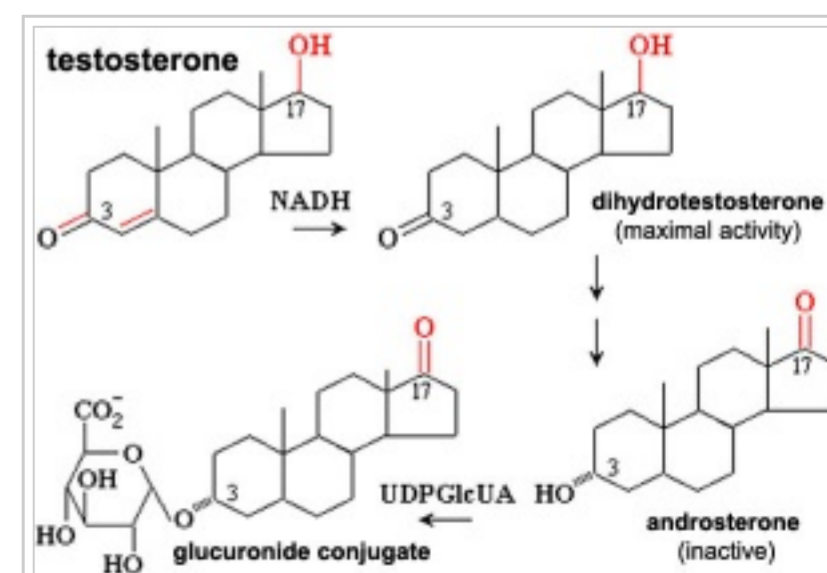
This looped animation shows the development of external female genitalia from the indifferent external structure, covering the approximate period of week 9 to 12.



Note the original cloacal membrane becomes separated into the urogenital membrane and anal membrane. The urogenital folds beneath the genital tubercle remain separate (unfused), forming the inner labia minora and second outer skin folds form the larger labia majora either side of the developing vestibule of the vagina. Note at the top of the animation, the changing relative size of the genital tubercle as it forms the glans of the clitoris.



Historic diagram of external development

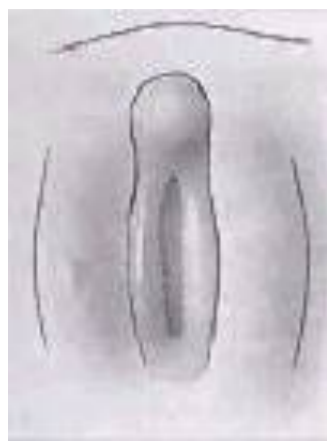


Testosterone metabolism

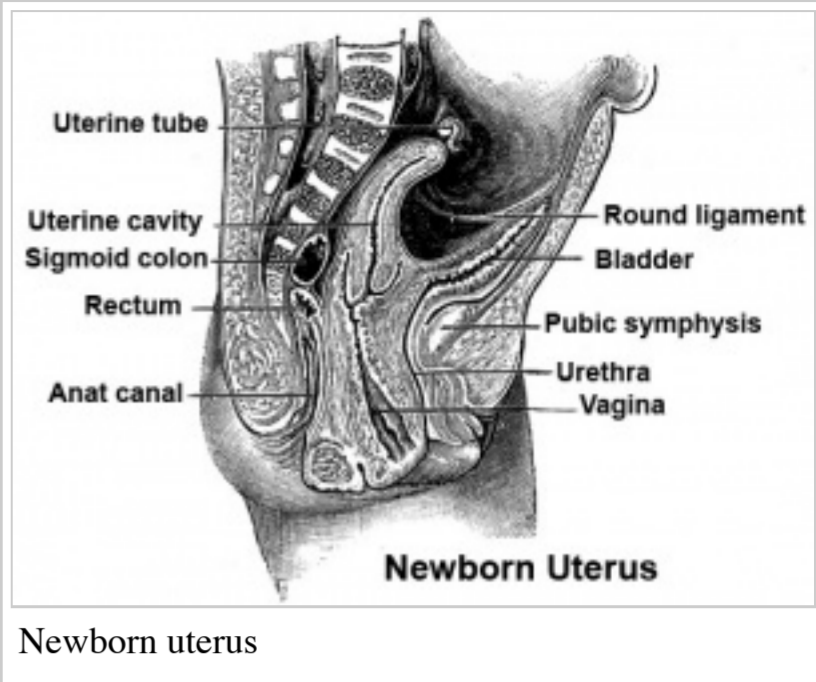
Male Genitalia Development

Endocrinology - Box 6.6 The roles of testosterone (T) and 5 α -dihydrotestosterone (DHT) (<http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=endocrin&part=A972&rendertype=box&id=A1027>)

This looped animation shows the development of external male genitalia from the indifferent external structure, covering the approximate period of week 9 to 12.



Male External
Page | Play



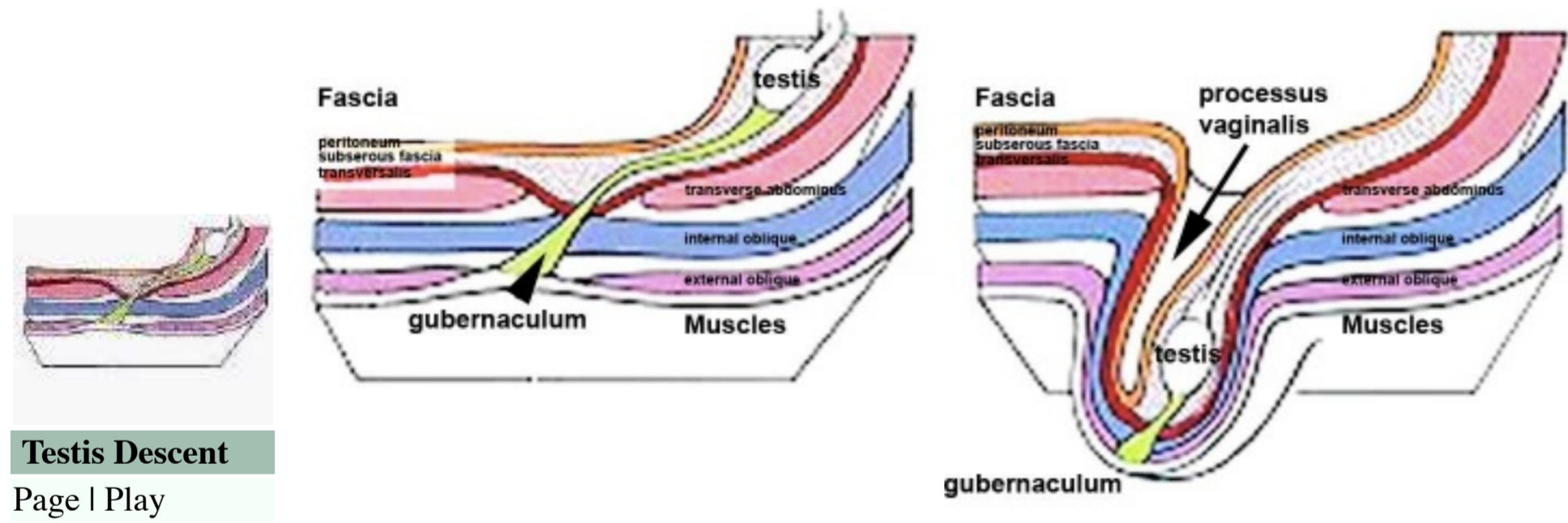
Note the original cloacal membrane becomes separated into the urogenital membrane and anal membrane (identical to female). The urogenital folds beneath the genital tubercle begin to fuse in the midline. The skin folds either side for the scrotum, which too has a midline fusion, the raphe. The scrotal sac is initially empty and is an attachment site for the gubernaculum, descent of the testes begins generally during week 26 and may take several days.

Gonad Descent

- Both kidney and gonads develop retroperitoneally, with the gonads moving into the abdomen or eventually into the scrotal sacs.
- During fetal development the gubernaculum and fetal growth in both male and female, changes the gonads' relative positions finally reaching their adult locations.

Both female and male gonads undergo anatomical descent.

- Ovaries** – undergo caudal and lateral shifts to be suspended in the broad ligament of the uterus, gubernaculum does not shorten, it attaches to paramesonephric ducts, causing medial movement into the pelvis.
- Testes** – two anatomical phases in descent, transabdominal and transinguinal, under the influence of the shortening gubernaculum.



Testis Descent
Page | Play

The testis (white) lies in the subserous fascia (spotted) a cavity processus vaginalis evaginates into the scrotum, and the gubernaculum (green) attached to the testis shortens drawing it into the scrotal sac. As it descends it passes through the inguinal canal which extends from the deep ring (transversalis fascia) to the superficial ring (external oblique muscle). Descent of the testes into the scrotal sac begins generally during week 26 and may take several days. The animation shows the path of a single testis.

Data from a recent study of male human fetal (between 10 and 35 weeks) gonad position.

- 10 to 23 weeks - (9.45%) had migrated from the abdomen and were situated in the inguinal canal
- 24 to 26 weeks - (57.9%) had migrated from the abdomen
- 27 to 29 weeks - (16.7%) had not descended to the scrotum

Incomplete or failed descent can occur unilaterally or bilaterally, is more common in premature births, and can be completed postnatally.

5. Postnatal - Puberty

Puberty can occur over a broad range of time and differently for each sex:

- girls (age 7 to 13)
- boys (age 9 to 15)

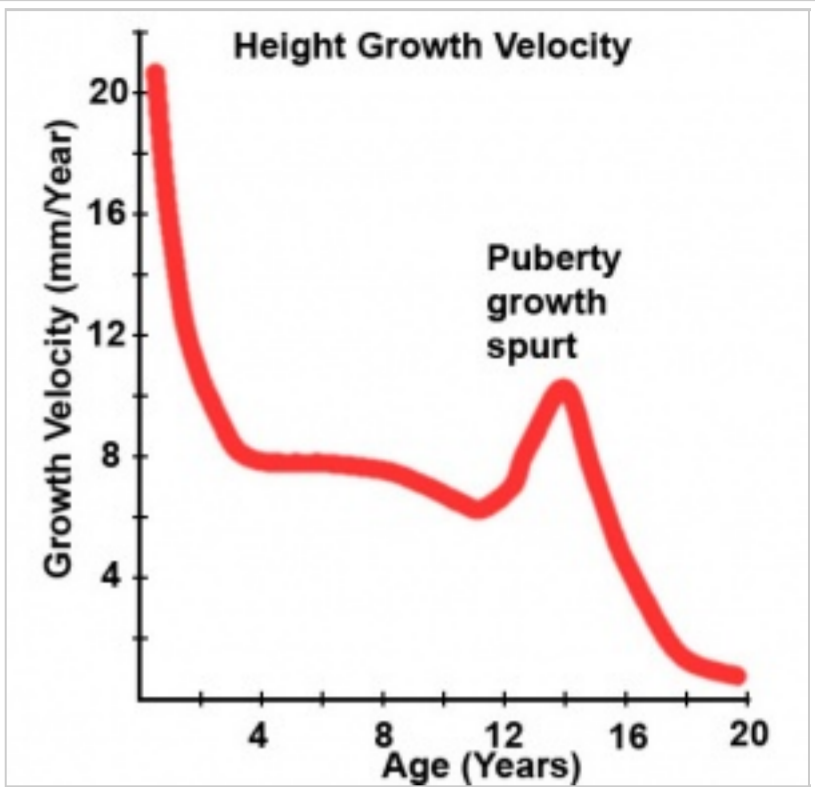
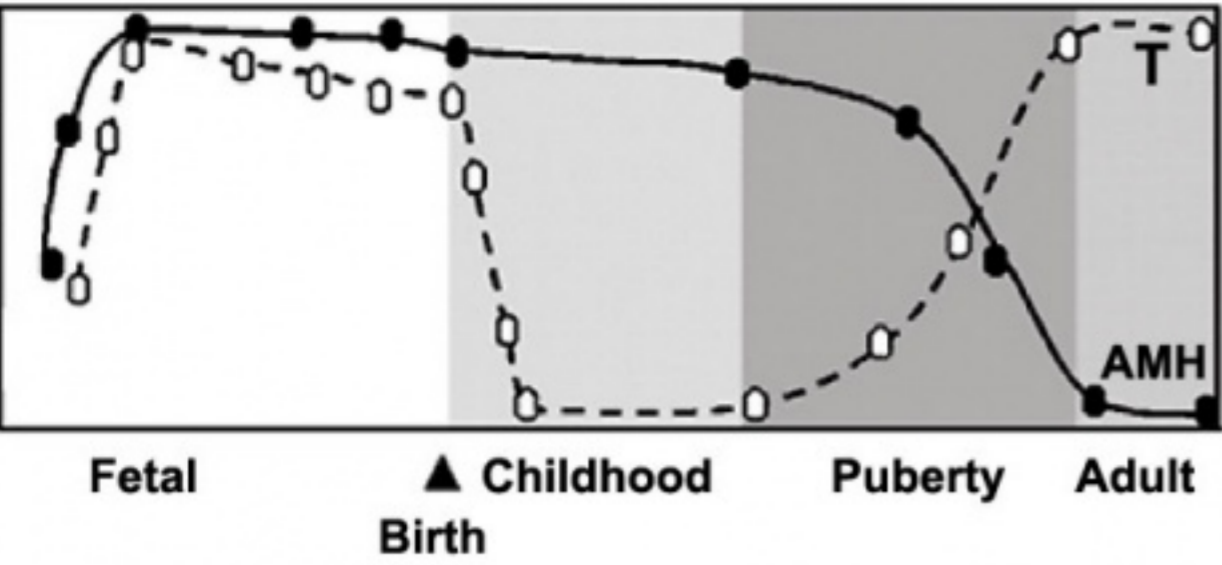
The physical characteristics that can be generally measured are: genital stage, pubic hair, axillary hair, menarche, breast, voice change and facial hair.

Male

- Testosterone - adult testes produce about 6-10 mg /day in males (~0.5 mg / day in females) carried in circulation by a specific carrier globulin.

- masculinizing androgen - also at puberty, spermatogenesis in males
- development of secondary sexual characteristics - body and facial hair growth (male pattern baldness)
- anabolic effect - metabolism towards conservation of amino acids, promoting protein synthesis, muscle development
- neural - libido in both sexes, male pattern behaviour
- Sustentacular (Sertoli) cells - produce anti-mullerian hormone (AMH) to puberty.
 - **AMH** - anti-Müllerian hormone (Müllerian inhibiting factor (MIF), Müllerian-inhibiting hormone (MIH), and Müllerian-inhibiting substance (MIS)).

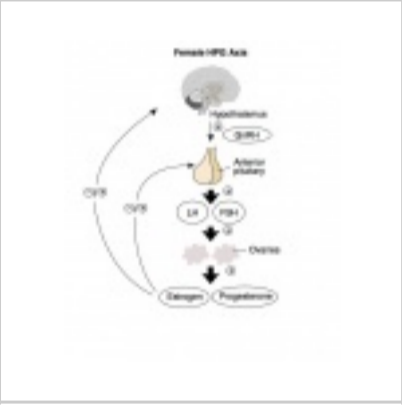
Human Serum Relative Levels



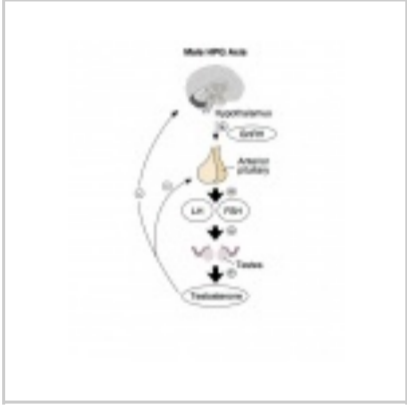
Puberty growth

- **GnRH** = Gonadotropin-releasing hormone (GnRH). This peptide hormone is a decapeptide (10 amino acids) with a short half life (<15 minutes).
- **LH** = Luteinizing Hormone
- **FSH** = Follicle Stimulating Hormone

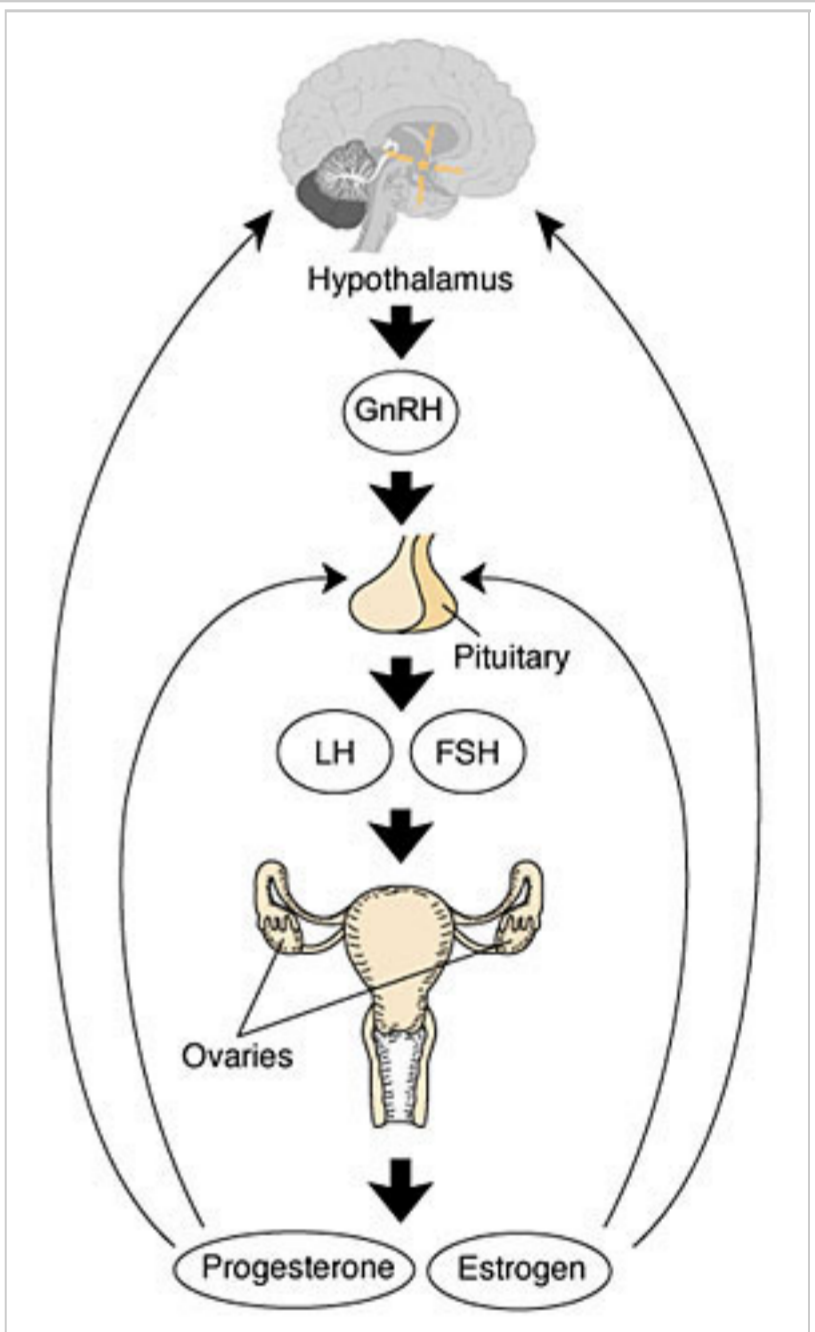
A similar endocrine axis is also found for regulation of the male gonad.



Hypothalamus - Pituitary - Gonad (female)



Hypothalamus - Pituitary - Gonad (male)



Female HPG Axis

Puberty Abnormalities

- **Precocious Puberty** - Premature development of the signs of puberty which can occur in both girls (before age 7 or 8) and in boys (before age 9).
- **Delayed Puberty** - Determined in boys by a lack of increase in testicular volume by the age of 14 years. In girls, no breast development by the age of 13.5 years and a lack of menstruation by the age of 16 years. There can also be a "pubertal arrest" where there is no progress in puberty over 2 year period.

Sex Differences in Adult and Developing Brains

Brains of males and females differ

- in regions specialized for reproduction
- in other regions (controlling cognition, etc) where sex differences are not necessarily expected
- differentially susceptible to neurological and psychiatric disease

2 sources of sexually dimorphic information

- complement of sex chromosome genes
- mix of gonadal hormones
- not known significance of brain sex differences
- transient sex differences in gene expression in developing brains may cause permanent differences in brain structure

Abnormalities

Human genital abnormalities are currently described as "**Disorders of Sex Development**" (DSD).

Include: chromosomal, gonadal dysfunction, tract abnormalities, external genitalia and gonadal descent.

Sex Reversal

- Where chromosomal sex does not match phenotypic sex i.e. XX males or XY females.

XX males - usually caused by a transfer of some Y chromosome DNA onto the X chromosome

- Gonads develop as testes, everything looks normal internally and externally but infertile due to a failure of spermatogenesis
- Similar to Klinefelters syndrome (XXY)

XY females - usually steroidal origin

- Main cause is Androgen Insensitivity Syndrome (AIS) Complete (CAIS) Partial (PAIS) and Mild (MAIS) usually caused by mutations of the gene encoding the androgen receptor *AR* gene located on the X chromosome
- 5-alpha-reductase deficiency - again leads to a lack of complete steroidal induction of external genitalia
- Rare mutations in key sex determining genes including deletion or mutations of *SRY*

Links: Genital System - Abnormalities

Congenital Adrenal Hyperplasia

- impairment of cortisol production by the adrenal cortex, is one of the most common causes of intersex genitalia at birth.
- genetically male (XY) infants born with undervirilized genitalia are often assigned and reared as girls.

Cryptorchidism

- abnormality of either unilateral or bilateral testicular descent, occurring in up to 30% premature and 3-4% term males.
- Descent may complete postnatally in the first year, failure to descend can result in sterility.

Testis descent is thought to have 2 phases:

1. transabdominal descent - dependent on insulin-like hormone 3 (INSL3).
2. inguinoscrotal descent - dependent on androgens.

Undescended Ovaries

- reasonably rare gonad abnormality, often detected following clinical assessment of fertility problems and may also be associated with other uterine malformations (unicornuate uterus).
- Due to the relative positions of the male (external) and female (internal) gonads and the pathways for their movement, failure of gonad descent is more apparent and common in male cryptorchidism than female undescended ovaries.

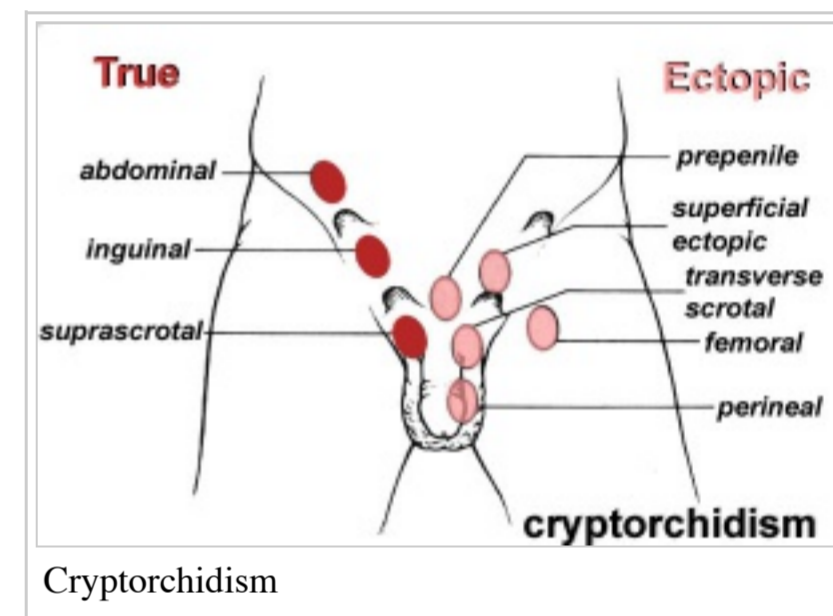
Hydrocele

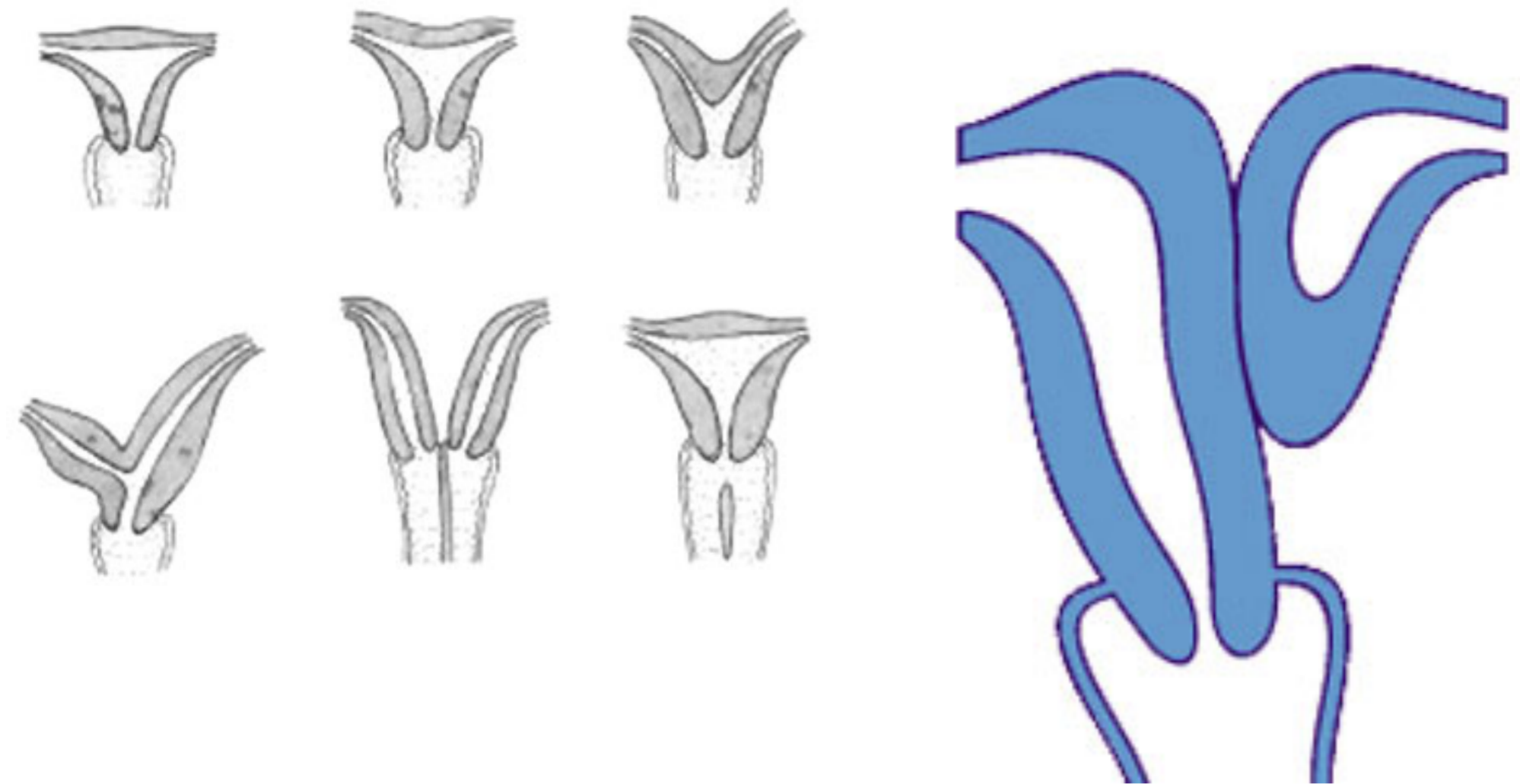
- **Male Hydrocele** is a fluid-filled cavity of either testis or spermatic cord, where peritoneal fluid passes into a patent processus vaginalis.
- **Female Hydrocele** is a similar, but rarer, fluid-filled cavity occurring in the female as a pouch of peritoneum extending into the labium majorum (canal of Nuck).

Tract Abnormalities

Many different forms

- Uterine: associated with other anomalies, unicornuate uterus
- Vagina: agenesis, atresia
- Ductus Deferens: Unilateral or bilateral absence, failure of mesonephric duct to differentiate





Uterine abnormalities

Unicornate uterus

Uterine Duplication (uterus didelphys, double uterus, uterus didelphis) A rare uterine developmental abnormality where the paramesonephric ducts (Mullerian ducts) completely fail to fuse generating two separate uterus parts each connected to the cervix and having an ovary each.

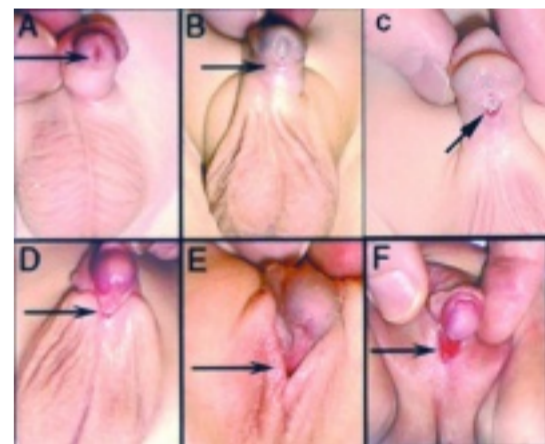
Septate Uterus

Cervical: cervical agenesis, cervical duplication

Vaginal: Mayer-Rokitansky syndrome (MRK anomaly, Rokitansky-Küster-Hauser syndrome, RKH syndrome, RKH) congenital absence of the vagina, dyspareunia, vaginal agenesis.

External Genitalia - Hypospadia

- most common penis abnormality (1 in 300) from a failure of male urogenital folds to fuse in various regions and resulting in a proximally displaced urethral meatus.
- The cause is unknown, but suggested to involve many factors either indivdually or in combination including: familial inheritance, low birth weight, assisted reproductive technology, advanced maternal age, paternal subfertility and endocrine-disrupting chemicals. Infants with hypospadias should not undergo circumcision.

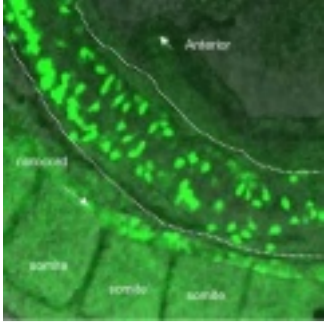


Hypospadia classifications

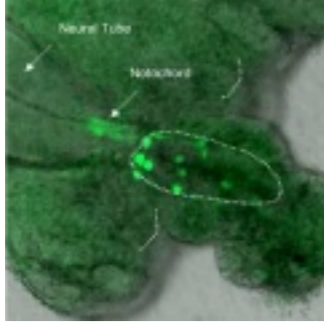
Movies

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|--------------|---------------|--------------------------|------------------------|----------------------|---------------|-----------------------|-----------------------|
| | | | | | | | |
| Ovary | Testis | Urogenital Septum | Female External | Male External | Uterus | Testis Descent | Gonad Vascular |
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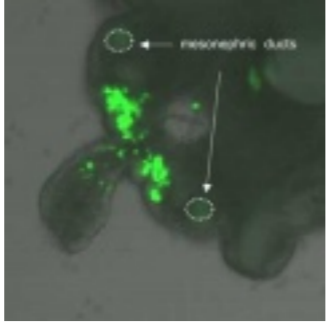
Mouse Primordial Germ Cell Migration



Germ Cell E9.0
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Germ Cell E9.5
Page | Play



Germ Cell E10.5
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References

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Yi Cai

Revisiting old vaginal topics: conversion of the Müllerian vagina and origin of the "sinus" vagina. Int. J. Dev. Biol.: 2009, 53(7);925-34
PubMed 19598112

Textbooks

- **Before We Are Born** (5th ed.) Moore and Persaud Chapter 14 p289-326
- **Essentials of Human Embryology**, Larson Chapter 10 p173-205
- **Human Embryology**, Fitzgerald and Fitzgerald Chapter 21-22 p134-152

Online Textbooks

- **Developmental Biology** (6th ed.) Gilbert Chapter 14 Intermediate Mesoderm (<http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=dbio.section.3498>)
- Historic - **Text-Book of Embryology**. Bailey, F.R. and Miller, A.M. (1921). New York: William Wood and Co. Chapter 15. The Genital Glands

Reviews

Dagmar Wilhelm, Stephen Palmer, Peter Koopman **Sex determination and gonadal development in mammals.** Physiol. Rev.: 2007, 87(1);1-28 PubMed 17237341

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- **Histology:** Male Reproductive System (<http://www.lab.anhb.uwa.edu.au/mb140/CorePages/MaleRepro/malerepro.htm>) | Female Reproductive System (<http://www.lab.anhb.uwa.edu.au/mb140/CorePages/FemaleRepro/femalerepro.htm>)

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