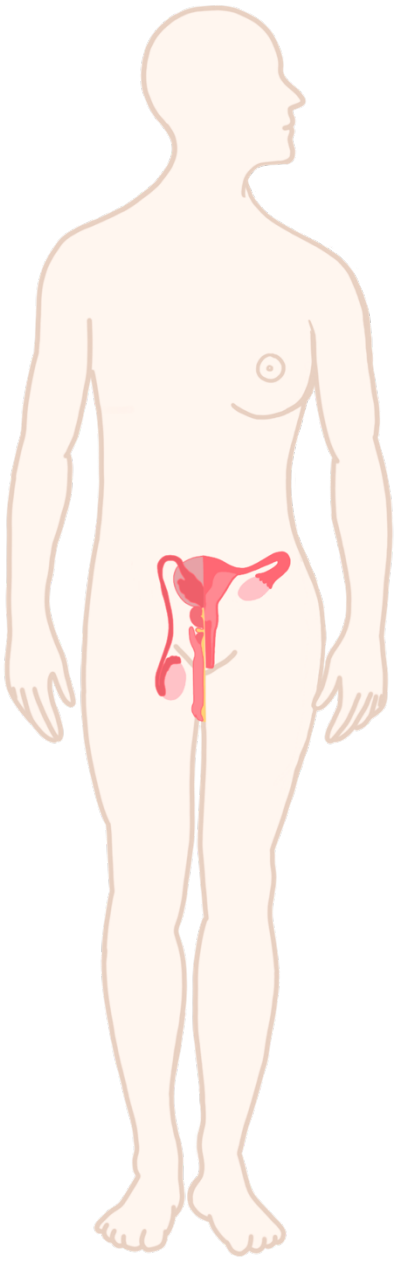

Reproductive Physiology

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It is available as a PDF and is available for printing.

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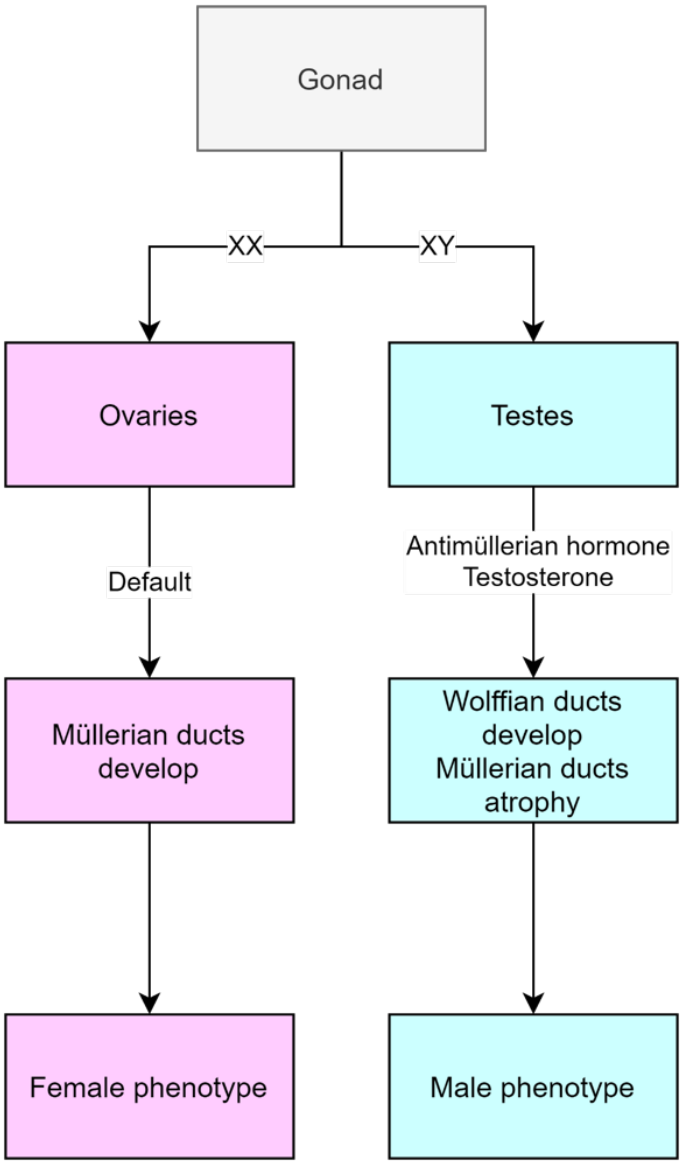
Section 1 – Sexual Differentiation and Puberty

1.1 – Sexual Differentiation

I. Definitions

Genetic sex	The chromosomal make-up Male - Chromosome 23: XY Female - Chromosome 23: XX
Gonadal sex	The primary reproductive organs Male - Testes female - Ovaries
Phenotypic sex	The physical characteristics of internal and external genitalia Male - Internal: Prostate, seminal vesicles, vas deferens, epididymis - External: scrotum and the penis Female - Internal: fallopian tubes, uterus, and upper one third of the vagina - External: clitoris, labia majora, labia minora, and lower two thirds of the vagina

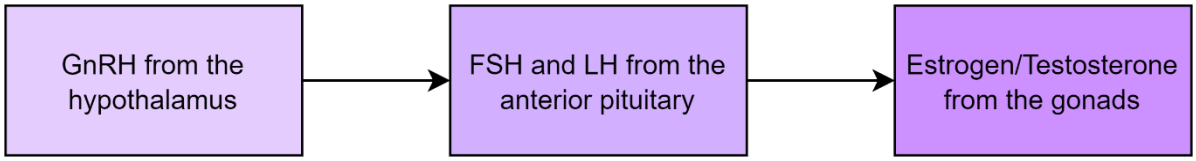
II. Process of sexual differentiation



1.2 – Puberty

I. Overview

- Puberty is initiated by the pulsatile release of hormones
- During puberty gonadotropin-releasing hormone (GnRH) upregulates its own receptor in the anterior pituitary to maximize its effect
- Levels of luteinizing hormone (LH) are higher than follicle-stimulating hormone (FSH) during puberty and reproductive age
- During childhood and senescence (older age) levels of FSH are higher than LH



II. Stages of female and male puberty

Puberty → Activation of the hypothalamic-pituitary axis	
Female *- Starts approximately at age 10*	**Male** *- Starts approximately at age 12*
Ovaries secrete estradiol ↓ Breast development begins ↓ Pubic and axillary hair growth ↓ Menarche ↓ Growth spurt	Leydig cells secrete testosterone ↓ Pubic and axillary hair growth ↓ Growth of the penis and accessory sex organs ↓ Growth spurt

1.3 – Test Yourself

1) Describe in your own words the difference between gonadal sex and phenotypic sex

_____

_____

_____

2) What is responsible for the development of the male phenotype?

a) androstenedione
b) antimüllerian hormone
c) testosterone
d) b and c
e) all

3) Fill in the blanks

Puberty is initiated by the _____ release of hormones.
During puberty _____ upregulates its own receptor in the _____ to maximize its effect.

4) Arrange the stages of female puberty in the correct order.

Menarche, pubic and axillary hair growth, growth spurt, breast development begins, ovaries secrete estradiol

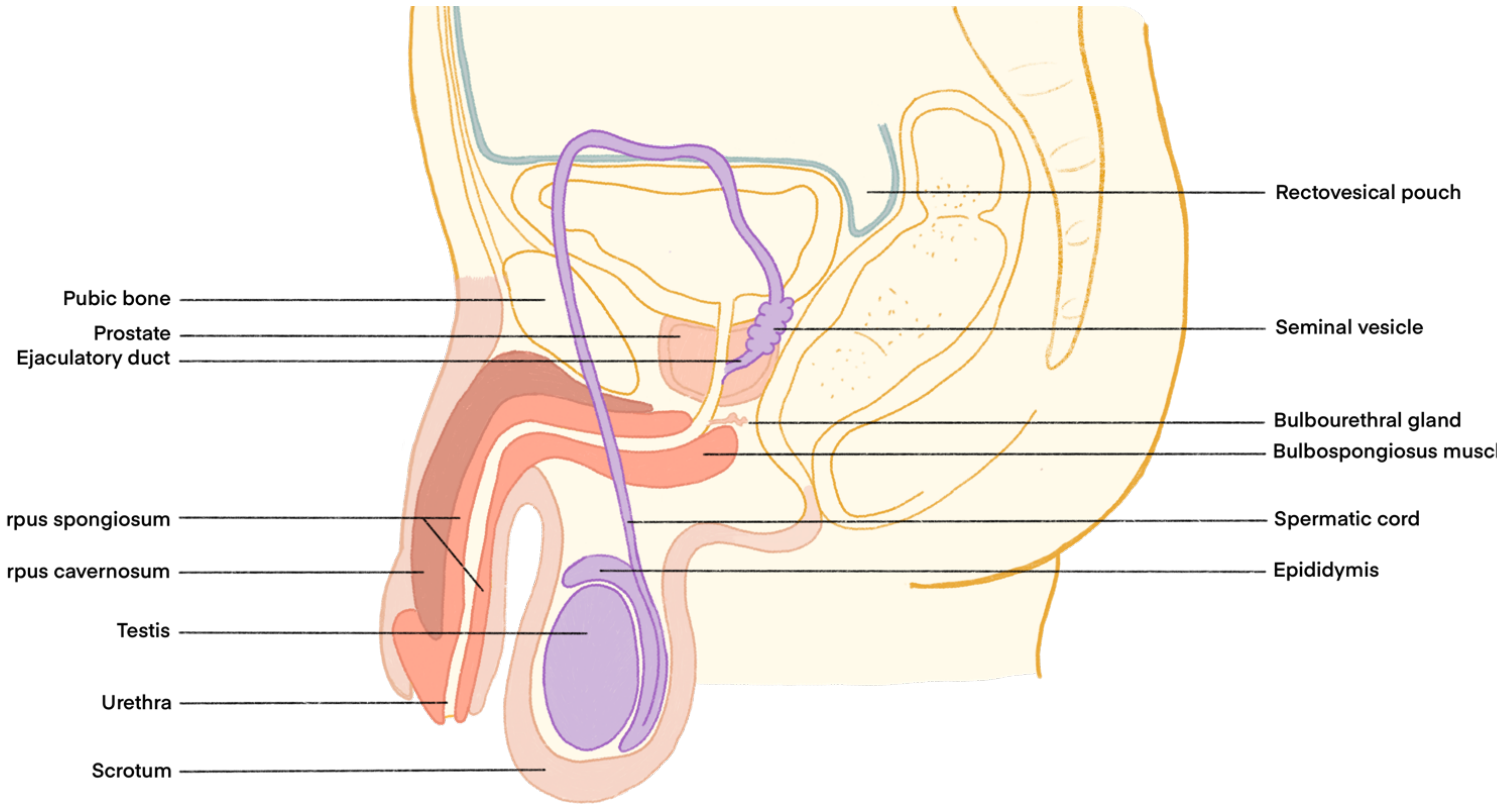
1.
2.
3.
4.
5.

5) At what age approximately does male puberty begin?

a) 10
b) 12
c) 14
d) 16

Section 2 – Male Reproductive System

2.1 – Male Reproductive Anatomy



2.1.1 – Structure of the Testes

- The epithelial lining consists of three cell types: spermatogonia (stem cells), spermatocytes (immature sperm), and Sertoli cells
- Sertoli cells aid spermatogenesis
    1. Provide nutrients to developing sperm
    2. Form blood-testes barrier
    3. Secrete fluid into seminiferous tubule to help sperm transport

	Seminiferous tubule		Leydig cells
% of testes	80		20
	Lobule	**Epithelial lining**	
Function	Spermatogenesis[1]	Support the developing sperm	Synthesis and secretion of testosterone
Location	Loops arranged in lobules surrounded by connective tissue	Lining of the seminiferous tubule	Cells surrounding the seminiferous tubule

[1]Production of sperm

2.1.2 – Reproductive Organs Contributing to Semen Content

- Accessory reproductive organs accounts for 90% of the semen volume, and sperm the remaining 10%
- The main function of the fluid secreted together with the sperm is to promote sperm survival
- The milky solution produced by the prostate gland is slightly alkaline and functions to neutralize the acidic secretions from the vagina, and it subsequently aids in fertilization.
- Prostaglandins in secreted by the seminal vesicle contribute to fertilization by
    1. Making the cervical mucous more permeable to sperm
    2. Increasing uterine contractions to move sperm up the female genital tract

	Prostate	Seminal vesicle
Composition of fluid secreted	Citrate, calcium and enzymes	Fructose, citrate, prostaglandins and fibrinogen
Function of fluid secreted	Increase sperm motility	- Nourishment of ejaculated sperm - Prostaglandin secretion

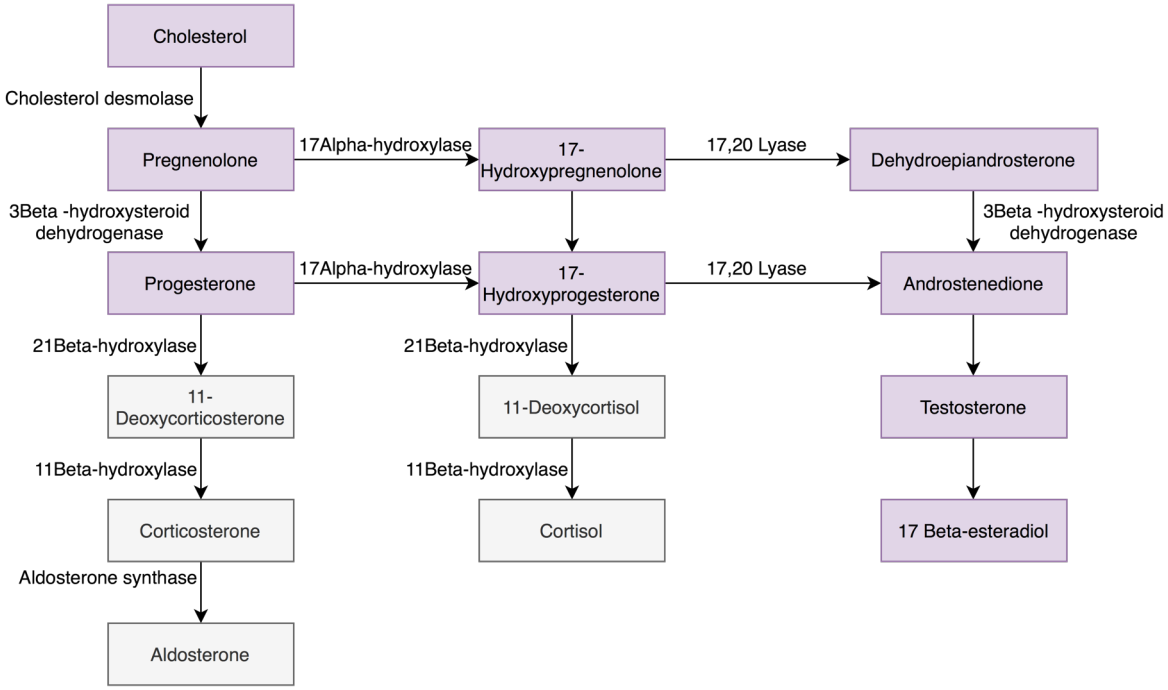
2.1.3 – Testosterone Synthesis and Secretion

- The Leydig cells in the testes produce testosterone similar to the adrenal gland pathway with two exceptions
    1. The tests do not have the two hydroxylases needed to synthesize glucocorticoids and mineralocorticoids
    2. The testes use the enzyme *17-beta-hydroxysteroid dehydrogenase* that converts androstenedione → testosterone
- Testosterone circulates in the blood bound to albumin and sex steroid-binding globulin

RECALL

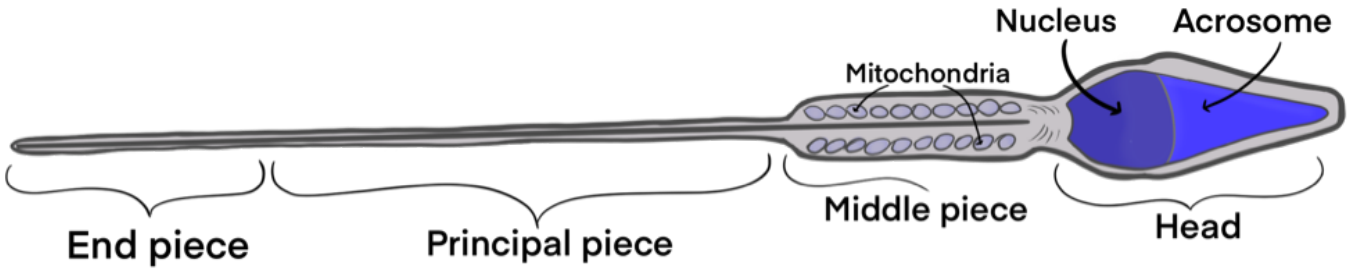
Synthesis of Androgens

Synthesis of androstenedione, the testosterone precursor, in the adrenal cortex occurs through a series of steps with cholesterol as the first substrate



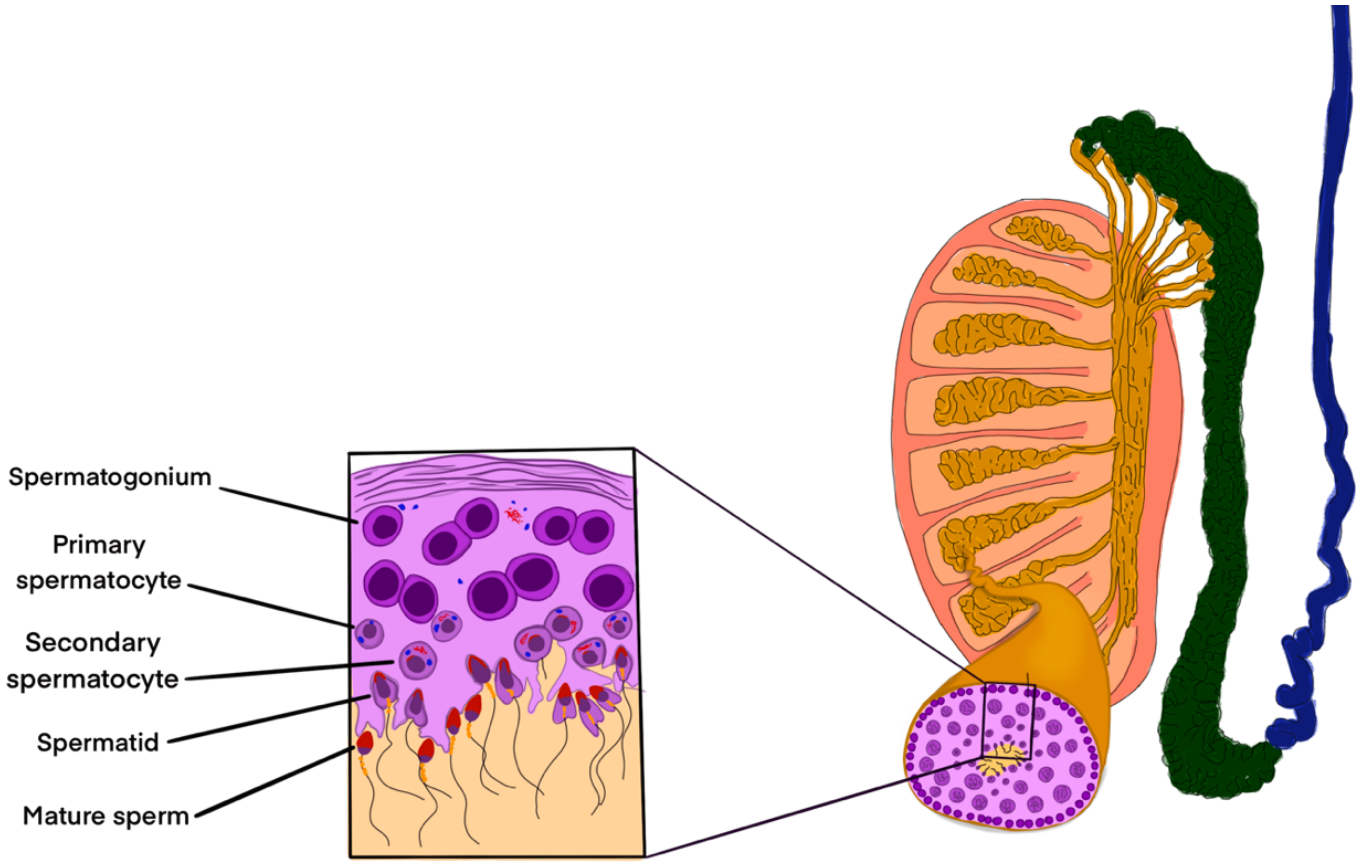
2.2 – Sperm

I. Sperm Structure



- The head contains the nucleus covered by the acrosome. The acrosome contains enzymes necessary for penetration of the ovum in the female.
- The tail is composed of a principal and an end piece. It is responsible for sperm motility.

II. Spermatogenesis



- Occur in the seminiferous tubule and take approximately 64 days
- There are three stages of spermatogenesis
  1. Mitotic division of spermatogonia to spermatocyte
  2. Meiotic division of spermatocyte to spermatids
  3. Maturation of spermatids into mature sperm

III. Sperm Storage and Ejaculation

- Sperm is stored and matured in the epididymis
- Sexual arousal activates the sympathetic nervous system → closure of bladder neck and contraction of reproductive glands and smooth muscle
- Sperm and secretions are transported through the epididymis → vas deferens → ejaculatory duct → internal urethra and is expelled

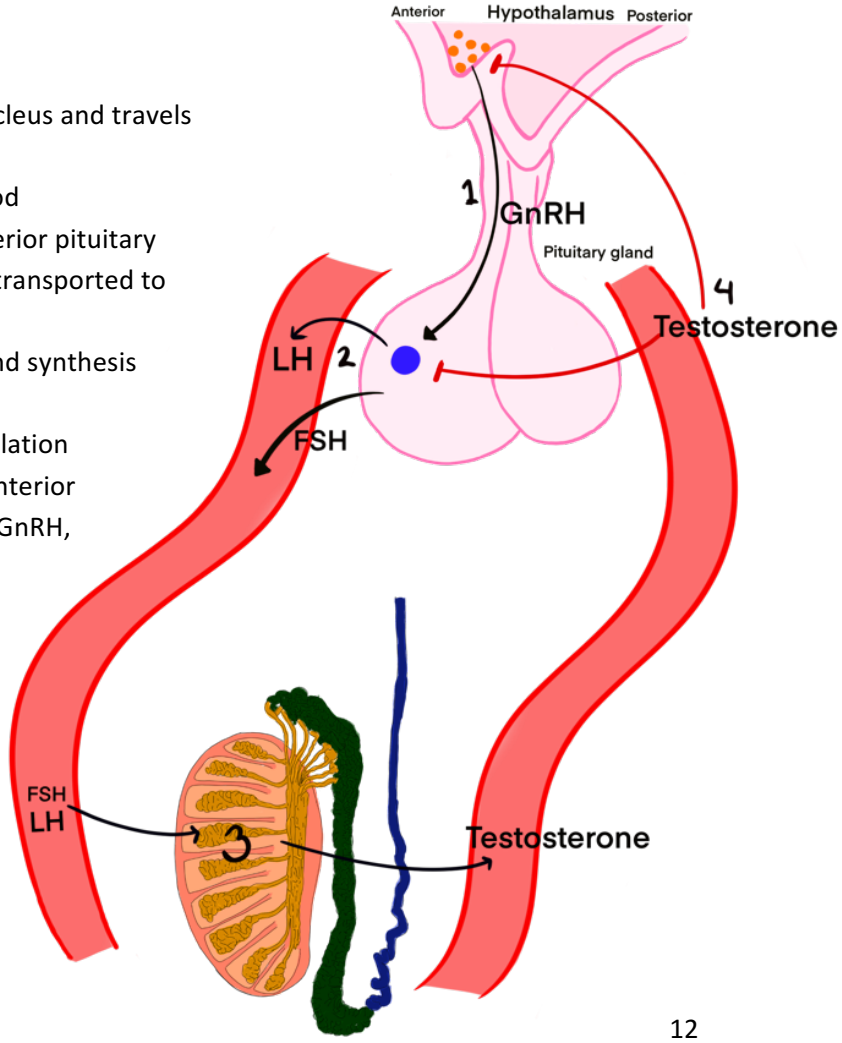
2.3 – Regulation of Testes

2.3.1 – Male Reproductive Hormone Functions

Hormone	Secreted from	Acts on	Physiological effect
GnRH	Hypothalamus	Pituitary	Stimulate secretion of LH and FSH
LH	Pituitary	Testes	Stimulates Leydig cells to synthesize testosterone
FSH	Pituitary	Testes	Stimulate spermatogenesis and Sertoli cells to aid in spermatogenesis

Hypothalamus-pituitary-testes axis

1. GnRH is secreted from the arcuate nucleus and travels to the anterior pituitary through the hypothalamic-hypophyseal portal blood
2. LH and FSH are secreted from the anterior pituitary in response to GnRH release, and are transported to the testes
3. FSH and stimulate spermatogenesis and synthesis of testosterone
4. Testosterone is secreted into the circulation and elicits negative feedback on the anterior pituitary downregulating secretion of GnRH, LH and FSH.



2.3.2 – Androgens

	Testosterone	Dihydrotestosterone (DHEA)
Precursor	Androstenedione	Testosterone
Enzyme	17-beta-hydroxysteroid dehydrogenase	5-alpha-reductase
Function	Biologically active androgen	Fetal development of male reproductive system

2.4 – Test Yourself

1) Fill in the blanks about the function of components of the tests

	Seminiferous tubule		Leydig cells
% of testes	80		20
	Lobule	**Epithelial lining**	
Function		Support the _____	
Location	Loops arranged in lobules surrounded by connective tissue	Lining of the seminiferous tubule	Cells surrounding the seminiferous tubule

2) What is the physiological effect of LH and FSH?

_____

_____

3) What is the main regulatory mechanism of the testes?

a) LH levels in blood
b) Positive feedback
c) FSH levels in blood
d) Negative Feedback

4) Fill in the blanks

	Prostate	Seminal vesicle
Composition of fluid secreted	Citrate, calcium and enzymes	
Function of fluid secreted		- Nourishment of ejaculated sperm - Prostaglandin secretion

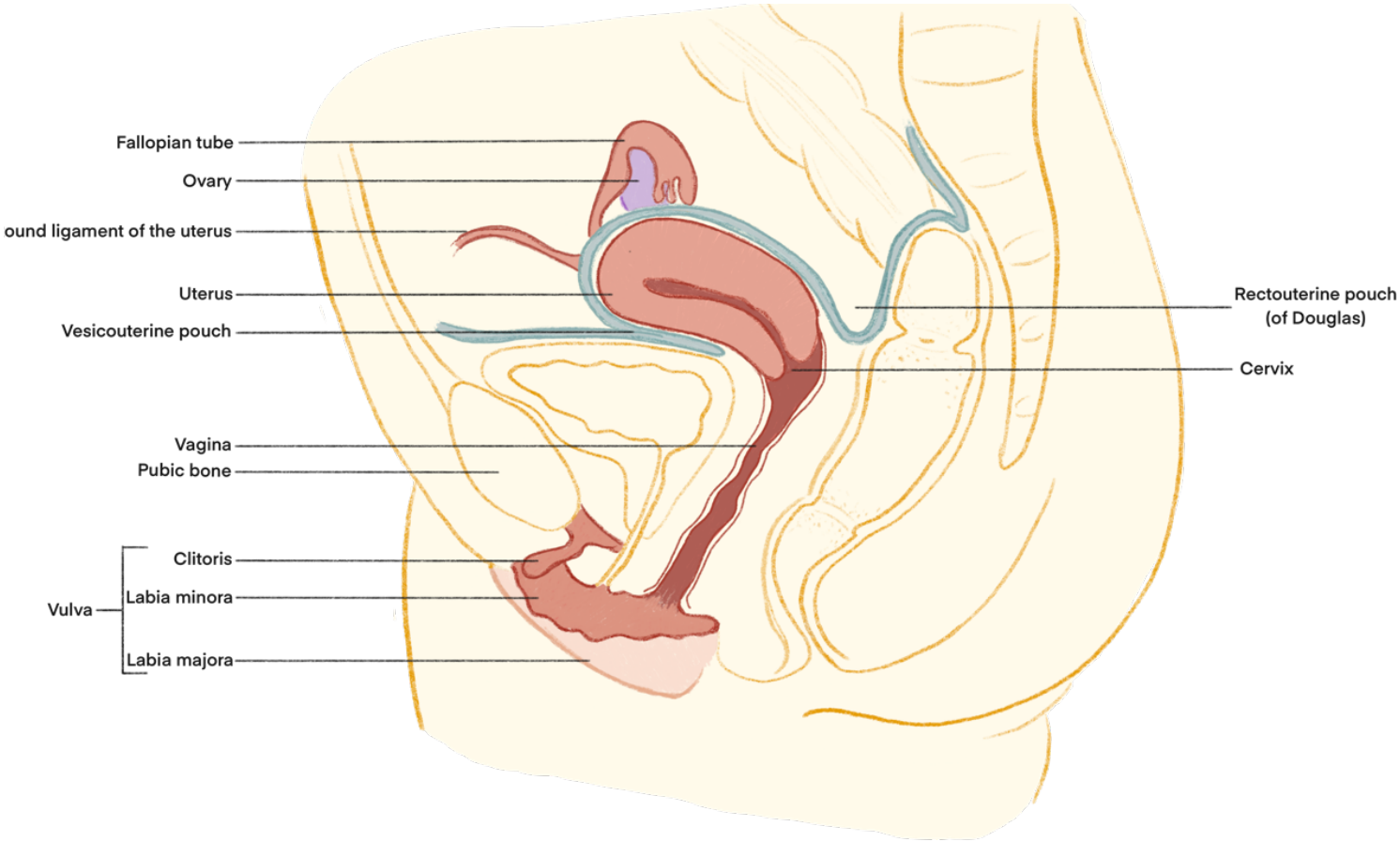
5) What is the function of the acrosome?

_____

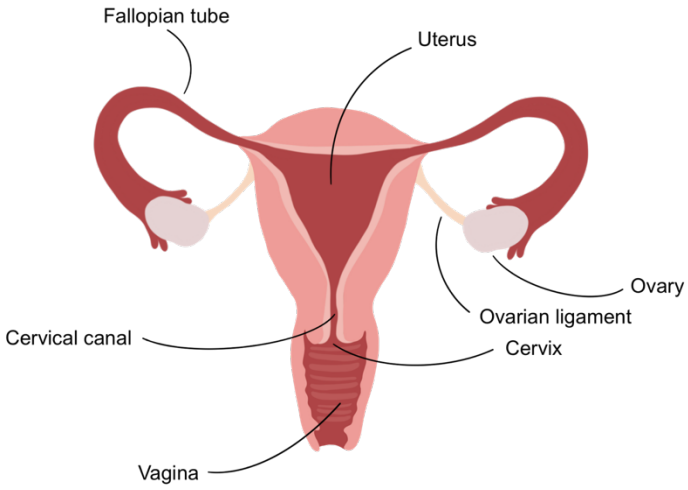
_____

Section 3 - Female Reproductive System

3.1 – Female Reproductive Anatomy



3.2 – Oogenesis



I. Function of the ovaries

- Oogenesis = development of the egg cell
- Secretion of sex steroid hormones: progesterone + estrogen.
- The ovarian hormones have both a *paracrine* and an *endocrine* function. Locally they help with the preparation of the oocyte. Systemically they target the uterus, breast and bone.

II. Oogenesis

- The development of the oocyte starts in the female fetus
- Unlike boys, who produce sperm cells throughout life, girls are born with a limited number of oocytes
- There will also be a continuous attrition (reduction) of oocytes, so the number is constantly decreasing throughout life

The development of the oocyte	
	**1. Primordial germ cell** - Develops in the fetus at the gestational age of 20-24 weeks. - It begins with about 7.000.000 cells
	*Mitotic division*
	**2. Oogonia**
	Meiotic division
	**3. Oocyte** - This stage is finished when a girl is 6 months old - The oocyte is in a suspended prophase - Now, there will be around 2.000.0000 cells

- When a girl reaches puberty the development of the ovarian follicle starts. This process will repeat itself until the woman reaches menopause.
- At the start of puberty, the girl will have around 400.000 oocytes in her ovaries. When she reaches menopause, there will only be a few, if any, left.

The development of the ovarian follicle		
Stage 1 	This stage takes 13-50 years[1]	**Primary follicle** – oocyte surrounded by granulosa cells producing nutrients and steroid hormones
Stage 2  [2-5 mm]	This stage takes 70-84 days	During each menstrual cycle, a few follicles enter this phase. A fluid is emerging into the oocyte, filled with steroid hormones, proteins and FSH. The follicle is now a **graafian follicle**.
Stage 3  [20 mm]	This stage takes 48 hrs	5-7 days after menses, a single graafian follicle takes dominance and the others will regress. This is called the **dominant follicle**, and it grows up to 20 mm in only 48 hrs.
Ovulation 	This occurs 14 days before menses	The dominant follicle releases its oocyte. First meiotic division is now completed.

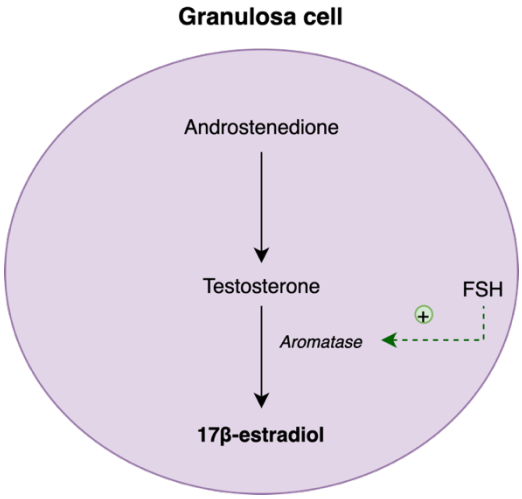
[1]This stage is so long because it is the waiting stage from birth until it enters the second stage in the menstrual cycle. This will happen to woman in the age between 13-50 years.

3.3 – Female Reproductive Hormones

3.3.1 – Synthesis and Secretion

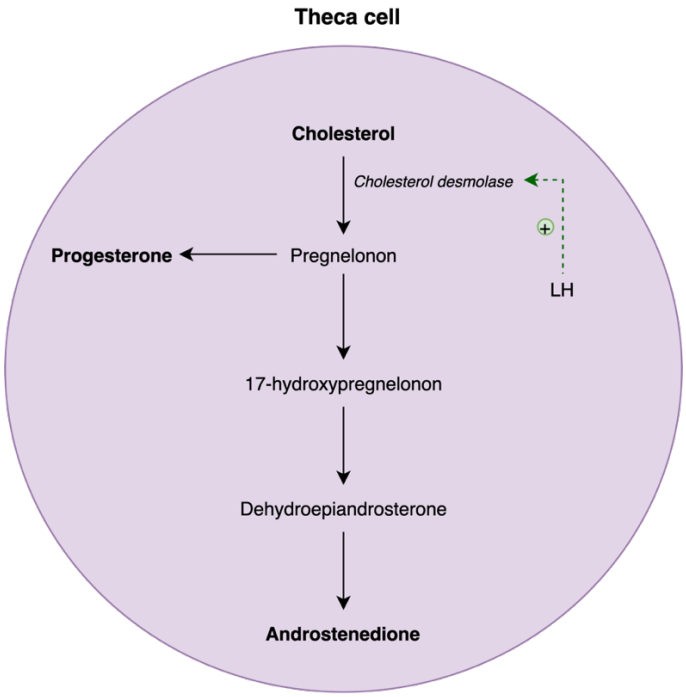
I. Granulosa cells

- Granulosa cells of the ovarian follicle produce *17β-estradiol*
- Stimulated by FSH and are found in especially high concentrations during ovulation (in the middle of the menstrual cycle).



II. Theca cells

- Theca cells produce *progesterone*
- Stimulated by LH and the production is especially high in the luteal phase (last phase) of the menstrual cycle.



3.3.2 – Estrogen and Progesterone Function

Estrogen

Prolactin

- Stimulates prolactin secretion → promoting breast development
- Blocks the action of prolactin on the breasts

Puberty and menses

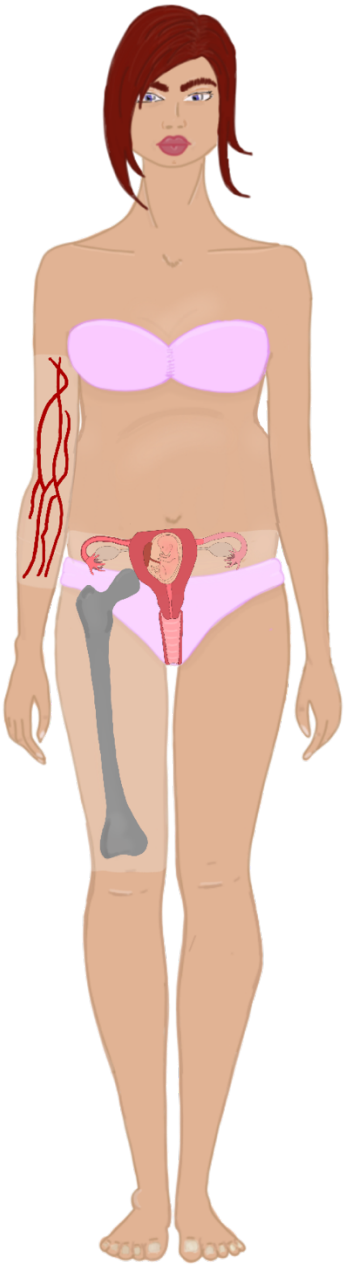
- Promotes development of secondary sex characteristics
- Proliferation and development of ovarian granulosa cells
- Participate in breast development

Pregnancy

- Maturation of the uterus
- Maintenance of pregnancy
- Lowers the uterine threshold for contractile stimuli during pregnancy

Other

- Reduce LDL cholesterol in the blood
- Anti-osteoporosis effect



Progesterone

Puberty and menses

- Participates in breast development
- Controls the luteal phase of the menstrual cycle

Pregnancy

- Maintenance of pregnancy
- Raises the uterine threshold for contractile stimuli during pregnancy

Other

- Increases body temperature

CLINICAL CORRELATION

Hormonal contraceptives

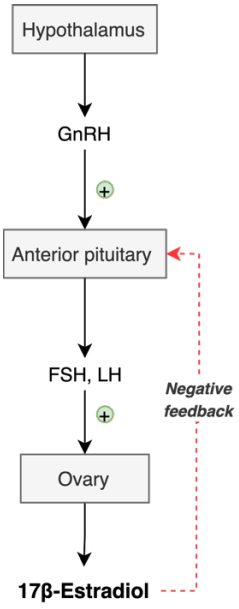
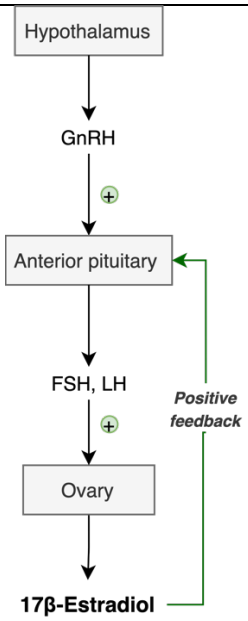
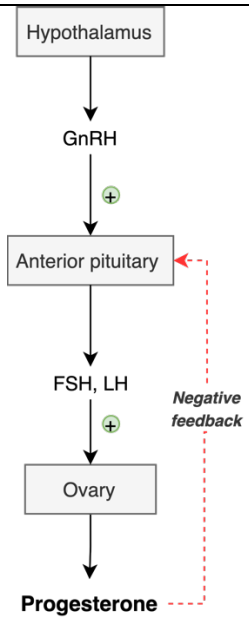
Oral contraceptives contain either progesterone or a mix of progesterone and estrogen.

Combination medication inhibit LH and FSH and therefore have a negative feedback effect on the anterior pituitary, preventing ovulation. They also change the character of the cervical mucus so that sperm cannot penetrate and fertilize the egg.

Progesterone only pills have their main contraceptive effect on the cervical mucus consistency and the fallopian tube motility, inhibiting fertilization.

Higher-dose preparations of estrogen and progesterone can interfere with implantation. These may be taken after intercourse and are known as the "morning after" pills.

3.4 – Menstrual Cycle

The menstrual cycle			
Time	**Follicular phase**	**Ovulation**	**Luteal phase**
	Day 0-14[1]	Day 14	Day 14-28[2]
The hypothalamus-pituitary-ovarian axis			
Effect on ovaries	- FSH and LH receptor up-regulation - Steadily increase of 17β-estradiol.	- Burst of 17β-estradiol[3] - FSH and LH surge cause ovulation of the mature ovum.	- The remaining granulosa cells + theca cells continue to supply hormones. - The once a follicle is now called a Corpus luteum. - If no fertilization occurred, the corpus luteum will turned into a scar called corpus albicans.
Effect on uterus and cervix	***Preparation for possible fertilization*** - ↑ Endometrial lining of uterus - Elongation of spiral arteries supplying endometrium.	***Fertilization can occur*** - Cervical mucus turns waterier. This helps for easier swimming of the sperm.	***The implantation of the fertilized egg*** - Progesterone secretion increases vascularization of the endometrium - Cervical mucus is now thick, making it harder for the sperm to mobilize. If they arrive now, they were simply too late.

[1]This example uses a regular mensural cycle consisting of 28 days. This phase may vary.

[2]This phase is always 14 days

[3]> 200 picogram/mL

I. The follicular phase

- Day 0-14 in a regular 28-day cycle. This phase may vary in length.
- LH and FSH receptors are up regulated in theca and granulosa cells
- Estradiol levels increase**,** preparing the endometrium for possible fertilization
- FSH and LH is suppressed by negative feedback of estradiol on the anterior pituitary

II. Ovulation

- Day 14
- A burst of estradiol gives a positive feedback on the anterior pituitary. This causes a burst in production of FSH and LH, called the "LH surge".
- The LH surge triggers the release of the ovum from the dominant follicle.

III. The luteal phase

- Day 14-28, this phase is always 14 days
- Progesterone levels increase to help prepare the endometrium for implantation of a fertilized ovum
- Progesterone stimulates the hypothalamic thermoregulatory system, increasing the body temperature.
- In this phase, 1 of the 2 following happens:

1. Fertilization	The oocyte is fertilized by the sperm cell in the fallopian tubes. The second meiotic division is complete – creating a haploid ovum with 23 chromosomes. The remaining granulosa cells and theca cells supply hormones important for maintenance of the zygote. This once a follicle is now called a corpus luteum.
2. No fertilization	There is no need for the hormone production of the corpus luteum, and this will be replaced by a scar called corpus albicans.

IV. Menses

- At the end of the luteal phase, if there has not been a successful fertilization
- The corpus luteum will regress. This regression causes decreased levels of estradiol and progesterone.
- The endometrial lining of the uterus will shred
- The endometrial shredding will be flushed out with blood, resulting in the menstrual bleeding.
- It will on *average* last for 3-5 days and contain 30-40 mL of menses (2-3 tablespoons).
- The menstrual bleeding marks the *beginning* of the next follicular phase, hence a circle.

3.5 – Pregnancy

I. Fertilization

- The oocyte is fertilized by the sperm cell in the fallopian tubes
- This usually happens 12-24 hrs after ovulation, around day 15-16 of the menstrual cycle
- The second meiotic division is complete, creating a haploid ovum with 23 chromosomes
- The fertilized ovum will divide itself as it migrates to the uterine wall. This journey takes around 4 days, and when it arrives, the fertilized ovum has turned into a blastocyst.

II. Implantation

- The blastocyst sticks to the uterine wall on day 5
- It is dependent on the high levels of progesterone produced in the luteal phase to attach correctly
- At this point, the blastocyst consists of an inner mass of cells which will become the fetus, and an outer layer of cells called the trophoblasts

III. Secretion of Human chorionic gonadotropin (hCG)

- The trophoblasts will start to produce hCG on day 8
- The hCG tells the corpus luteum that fertilization has occurred stimulating continuation of estrogen and progesterone secretion maintaining the corpus luteum for the implanted blastocyst.
- This trophoblast-to-corpus-luteum communication is called the "corpus luteum rescue", as the surge of hCG rescues the corpus luteum from turning into an corpus albicans scar
- The secretion of hCG increases dramatically during the first week of pregnancy

Clinical correlation

"The peeing on a stick"
Pregnancy tests detect high levels of hCG in the urine.
hCG levels are detectable as early as 9 days after ovulation – even before the next expected menses.

First trimester	The corpus luteum produces progesterone and estradiol
Second and third trimester	The placenta takes over as the main producer of progesterone
Parturition	1. Progesterone increases the threshold for uterine contractions and are found in high concentrations throughout pregnancy 2. At the end of the pregnancy, estradiol increases in concentration. Estradiol decreases the threshold for uterine contractions. This is one of the factors stimulating the process of giving birth.

3.6 – Breast Development

- Breast development depends on estrogen
- During puberty, estrogen stimulates lobular duct growth. The areola (area around the nipple) enlarges, and the amount of adipose tissue increases.

RECALL

Endocrine physiology – Prolactin
The major functions of prolactin are growth, development, and lactation of breasts during pregnancy

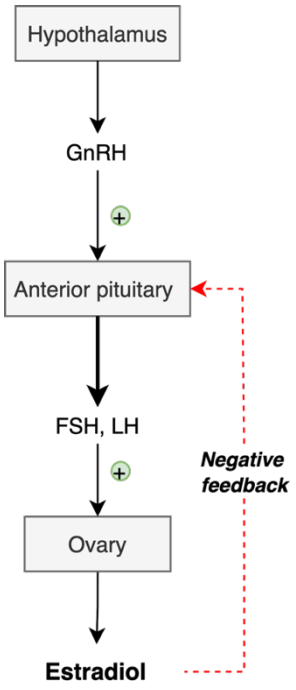
CLINICAL CORRELATION

Estrogen metabolism – men with boobs
Estrogen is metabolized by the liver. In cirrhosis (end-stage liver failure), this process is impaired and the amount of estrogen in the body will increase. Resulting in the development of fatty breast tissue in men, called gynecomastia.

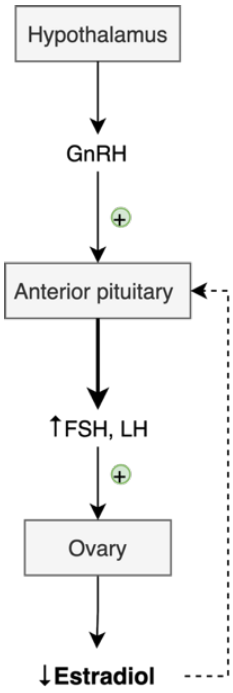
3.7 – Menopause

- Cessation of the menstrual cycle and typically occurs around 50 years of age
- Estrogen secretion gradually decreases stopping the negative feedback to the anterior pituitary, increasing FSH and LH production
- Symptoms of menopause are due to low levels of estrogen, including thinning of the vaginal epithelium, decreased breast mass, bone density loss and hot flashes
- Menopause can be managed with estrogen replacement therapy

Normal hypothalamic-ovarian axis



Axis after menopause



3.8 – Test Yourself

1) What cell type is responsible for the production of progesterone in the ovaries?

a) Theca cells
b) β-cells
c) Granulosa cells
d) Leydig cells

2) Find in the table below with the correct statements

- Peak of estradiol
- Follicular phase
- Corpus luteum
- High levels of progesterone
- Preparation for possible fertilization
- Menstrual bleeding
- Luteal phase
- This stage may vary in length

	Ovulation	
Day 0-14	Day 14	Day 14-28
Steady levels of estrogen		
	Release of the ovum	

3) Which of the following is <u>not</u> an effect of estrogen?

a) Decrease blood concentration of LDL cholesterol
b) Important for breast development
c) Cause of secondary female characteristics in women
d) Osteoporotic effect on bone

4) When is the second meiotic division complete?

a) In the primary follicle
b) In the dominant follicle
c) When oocyte is fertilized by the sperm cell
d) When the oocyte is implanted in the uterus

5) What statement is correct about menopause?

a) Estrogen levels suddenly drops
b) FSH and LH levels will increase
c) When a woman reaches menopause, she will have around 100.000 oocytes left in the ovaries
d) Menopause is a reversible disorder and can be treated with estrogen supplementation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