EDO UNIVERSITY IYAMHO
Department of Physiology
PHS 201 Reproductive Physiology

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Lectures: Monday (1.00 ï 3.00 pm), Tuesday and Wednesday 8am ï 12.00 pm,
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Office hours: Monday ï Friday 12.00 to 1.00 PM (just before class), Office: College Building Ground Floor Room 39.

Teaching Assistants: *Mr. Adeniyi M. J.*

General overview of lecture: The fertility of the mature human female is cyclic. The release from the ovary of a mature female germcell or ovum occurs at a distinct phase of the menstrualcycle. Cyclic changes in luteinizing hormone (LH)and follicle-stimulating hormone (FSH)from the pituitarygland and estradiol and progesterone from the ovaries controlthe secretion of ovarian steroid hormones, estradiol andprogesterone, and the subsequent release of an ovum during the menstrual cycle. The cyclic changes in steroid hormone secretion cause significant changes in the structureand function of the uterus in preparing it for the reception of a fertilized ovum. At different stages of the menstrual cycle,progesterone and estradiol exert negative- and positivefeedback effects on the hypothalamus and pituitary gonadotrophs,generating the cyclic pattern of LH and FSH releasecharacteristic of the female reproductive system. The hormonalevents during the menstrual cycle are delicately synchronized;thus, stress and environmental, psychologic, and social factors can readily affect the menstrual cycle.

Prerequisites: Explaining the mechanism through which pulses of hypothalamicgonadotropin-releasing hormone regulatesecretion of luteinizing hormone and follicle-stimulatinghormone and the effect of these two gonadotropins onfollicular development, steroidogenesis, ovulation, andformation of the corpus luteum. Pregnancy and Menopause.

Learning outcomes:

1. Students should understand and know the endocrine control of male reproductive system.
2. Students should understand and know the testicular functions and regulations
3. Male reproductive disorders

4. Students should understand and know the endocrine control offemale reproductive system.
5. Folliculogenesis and Steroidogenesis
6. Menstrual cycle, ovulation, Contraceptives.
7. Fertilization, Pregnancy
8. Sexual Disorders and Infertility

Assignments: We expect to have 2 individual homework assignments throughout the course in addition to a Mid-Term Test and a Final Exam. Home works are due at the beginning of the class on the due date. Home works are organized and structured as preparation for the midterm and final exam, and are meant to be a studying material for both exams.

Grading: We will assign 10 % of this class grade to homework, 20% for the mid-term test and 70% for the final exam. The final exam is comprehensive.

Textbook:The recommended textbook for this class are as stated:

Ganong's Review of Medical Physiology
Authors: Kim E. Barrett, Scott Boitano, Susan M. Barman, Heddwen L. Brooks.
Publisher: (Twenty-Third Edition) a LANGE medical book. The McGraw-Hill Companies, Inc.
ISBN: 978-0-07-160568-7
MHID: 0-07-160568-1

Medical Physiology Principles for Clinical Medicine
Authors:Rodney A. Rhoades, Ph.D., David R. Bell, Ph.D.
Publisher:Lippincott Williams & Wilkins, a Wolters Kluwer business (Fourth Edition)
ISBN 978-1-60913-427-3

Essentials of Medical Physiology
Authors:K SembulingamPhD andPremaSembulingamPhD
Publisher:Jaypee Brothers Medical Publishers (P) Ltd (Sixth Edition)
ISBN 978-93-5025-936-8

Main Lecture:

Background: The female reproductive tract has two major components:the ovaries, which produce the mature ovum and secreteprogestins, androgens, and estrogens; and the ductal system,

which transports the ovum, is the place of the unionof the sperm and egg, and maintains the developing conceptus until delivery. The morphology and function of thesestructures change in a cyclic manner under the influence ofthe reproductive hormones.

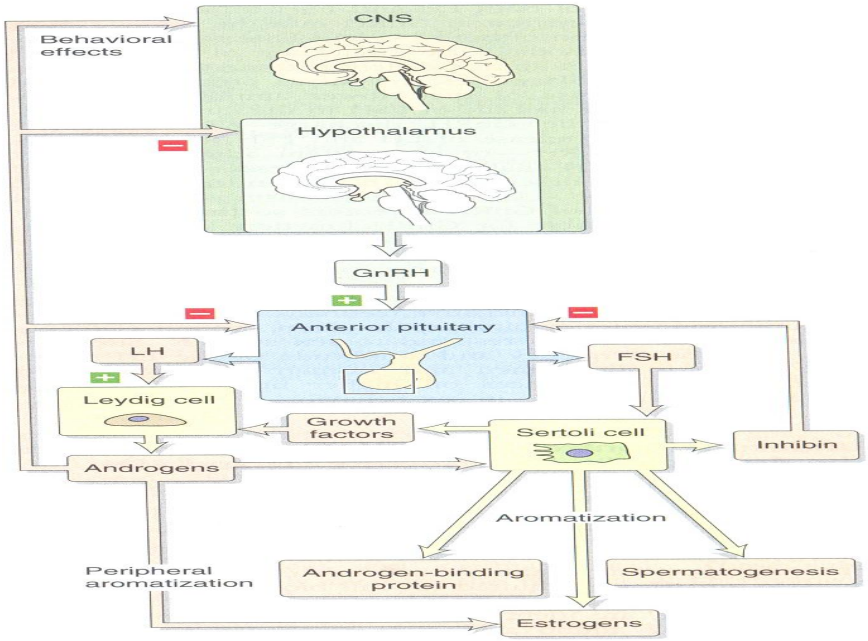

Figure 1: Hypothalamic-pituitary gonadal axis

The **uterus** is situated between the urinary bladder andrectum. On each upper side, an oviduct opens into the uterinelumen, and on the lower side, the uterus connects to the vagina. The uterus is composed of two types of tissue: The outer part is the **myometrium**, composed of multiple layers of smooth muscle. The inner part, lining the lumenof the uterus, is the **endometrium**, which contains a deep**stromal layer** next to the myometrium and a superficial epithelial layer. The stroma is permeated by spiral arteries andcontains much connective tissue. Uterine glands, which alsopenetrate the stromal layer and are lined by columnar secretorycells, interrupt the epithelial layer. The uterus providesan environment for the developing fetus, and eventually, themyometrium will generate rhythmic contractions that assistin expelling the fetus at delivery.

Male reproductive system consists of

The testes, the epididymes, the vas deferens, seminal vesicles, prostate, bulbo-urethral (Cowperôs) glands and the penis.

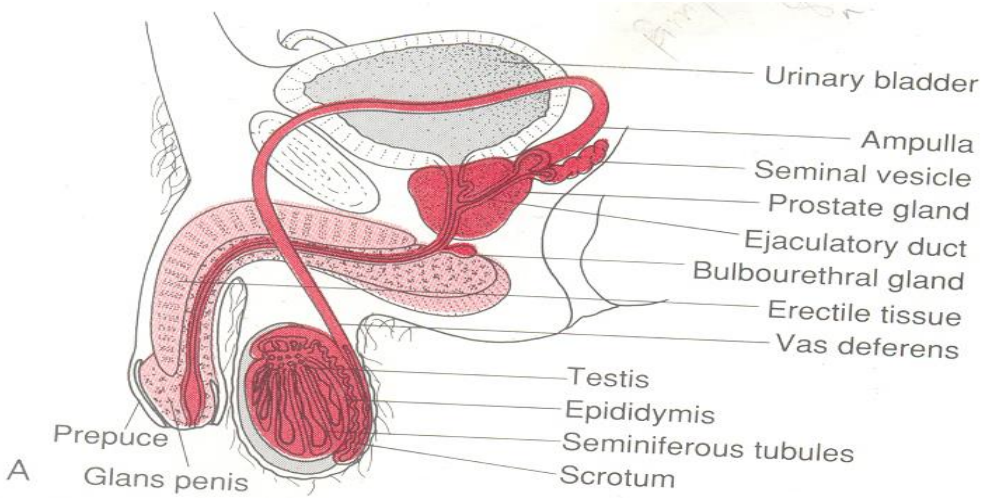

Figure 2: Male reproductive organ

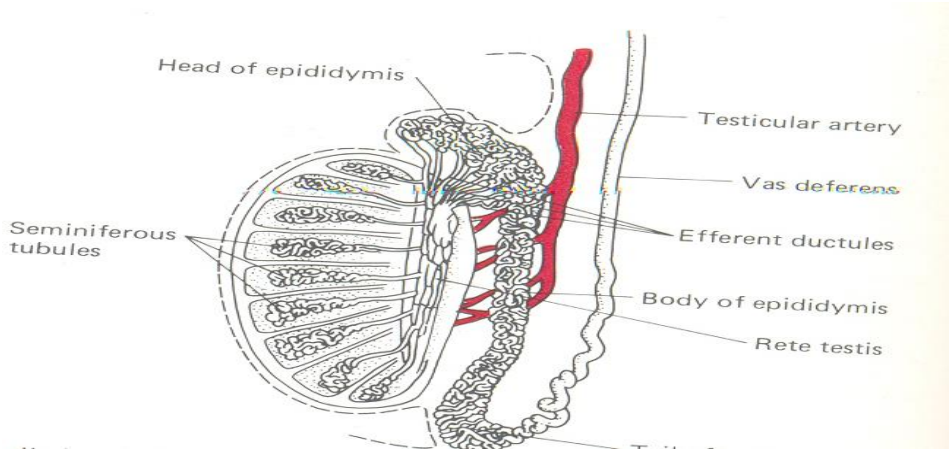

Figure 3: Structure of the Testis

Leydig Cell

Developed from mesoderm of the embryo.
Abundant in the 4th month of fetal life, fewer in the newborn
Continue to diminish to the end of childhood.
Number decreases at puberty.
Remain constant in number during sexual life in man
Finally diminish in old age.
Leydig cell secretes TESTOSTERONE
Secretion under the control of LH or ICSH
LH is secreted from the adenohypophysis

Testosterone

C_{19} steroid with an OH group in the 17 position.
Secretion rate in normal adult male is 4-9 mg/day.
99% of testosterone in plasma is bound to protein:
40% to ϐ-globulin called gonadal steroid binding globulin GBG, 40% to albumin, 17% to other proteins and 3% free.
Plasma testosterone level (free and bound) is about 525 ng/dl (18.2 nmol/L) in adult men and 30 ng/dl (1.0 nmol/L) in adul women.
The level declines with age in males.
Stimulates linear body growth, nitrogen retention and muscular development in the adolescent and mature male.
Stimulates adult maturation of the external genitalia and accessory sexual organs including the penis, scrotum, prostate and seminal vesicles.
Induces enlargement of the larynx and thickening of the vocal cords which results in the low-pitched voice
Stimulates beard and axillary and pubic hair growth as well as stimulate temporal hair recession and balding
Facilitates libido and sexual potential
Stimulates or suppresses organ- specific proteins in tissues such as the liver, kidney and salivary glands
Produces aggressive warlike behaviour
Produces differentiation of Wolffian ducts, external genitalia and brain in the male fetus

Sex Differentiation

Both male and female embryos develop identically until about seven weeks after fertilization.
At that point, one or more genes set into motion a cascade of events that leads to the development of a male.
In the absence of the gene(s), the female pattern of development occurs
Since 1959 it has been known that the Y chromosome is needed to initiate male development.
Experiments published in 1991 established that the prime male-determining gene is one called ***SRY*** (sex-determining region of the Y chromosome).
When a small DNA fragment containing this gene, called ***sry*** in mice, was inserted into 11 female mouse embryos, three of them developed as males.
The researchers suspected that the gene failed to be integrated into the genetic material in the other 8.
SRY apparently acts as a molecular switch to turn on the male pattern of development.
Whenever *SRY* gene is present in a fertilized ovum, the fetus will develop testes and differentiate into a male.

In the absence of *SRY*, the fetus will develop ovaries and differentiate into a female. An experiment of nature provides confirming evidence for humans.
In two cases investigated so far, phenotypic females with a XY genotype were found to have mutated *SRY* genes.
In other words, they failed to develop normally as males because their *SRY* gene was defective.

Synthesis of Testosterone

Cholesterol is the obligate precursor for androgens, as well as other steroids produced by the testis.
The Leydig cell can synthesize cholesterol *de novo* from acetyl coenzyme A or take it up as low-density lipoproteins from the extracellular fluid by receptor-mediated endocytosis.
The two sources appear to be equally important in humans.
The **Leydig cell** uses a series of five enzymes to convert cholesterol to testosterone.
Three of these enzymes are P-450 enzymes.
Because 3ß-hydroxysteroid dehydrogenase (3ß-HSD) can oxidize the A ring of four intermediates, testosterone synthesis from cholesterol can take four pathways.

1. The pathway for testosterone synthesis begins in the mitochondria, where the cytochrome P-450 side-chain-cleavage (SCC) enzyme (also called 20, 22-desmolase or P-450scc) removes the long side chain (carbons 22 to 27) from the carbon at position 20 of the **cholesterol** molecule (27 carbon atoms).
The rate ï limiting step in the biosynthesis of testosterone, as for other steroid hormones, is the conversion of cholesterol to pregnenolone.
LH stimulates this reaction and is the primary regulator of the overall rate of testosterone synthesis by the Leydig cell. LH appears to promote pregnenolone synthesis in two ways.

First, it increases the affinity of the enzyme for cholesterol.
Second, LH has long-term action in which it increases steroidogenesis in the testis by stimulating synthesis of the SCC enzyme.

2. The product of the SCC-catalyzed reaction is pregnenolone (21carbon atoms).
In the smooth endoplasmic reticulum (SER), 17Ŭ-hydroxylase (P-450c17) then adds a hydroxyl group at position 17 to form 17Ŭ-hydroxy-pregnenolone.
3. In the SER, the 17, 20-desmolase (a different activity of the *same* P-450c17 whose 17Ŭ-hydroxylase activity catalyzes the previous step) removes the side chain from carbon 17 of 17Ŭ-hydroxypregnenolone. That side chain begins with carbon 20. The result is a 19-carbon steroid called **dehydroepiandrosterone (DHEA).**
4. In the SER of the Leydig cell, a 17ß-hydroxysteroid dehydrogenase (17ß-HSD, which is not a P-450 enzyme) converts the ketone at position 17 to a hydroxyl group to form **androstenediol.**

Finally, 3ß-HSD (not a P-450 enzyme) oxidizes the hydroxyl group at position 3 of the A ring to a ketone to form **testosterone.**

In addition, the testis can also use 5Ŭ-reductase, which is located in the SER, to convert testosterone to:

- Å dihydrotestosterone (DHT).
- Å However, it is extratesticular tissue that is responsible for most of the production of DHT.

Mechanism of action

Testosterone combines with
- Å intracellular protein receptors and
- Å the complex binds to DNA promoting formation of mRNAs that in turn
- Å direct the formation of new proteins which modify cell function.
- Å Testosterone is converted in peripheral tissues to:
- Å dihydrotestosterone by 5Ŭ-reductase.
- Å DHT binds to the same intracellular receptor as T.
- Å T-R complexes is less stable than DHT-R complexes in target cells and they:
- Å transform less well to the DNA-binding state.
- Å Thus DHT formation is a way of amplifying the action of T in target tissue.

Blood testis barrier

The barrier is important because spermatozoa and developing cells produce surface antigens that are recognized as foreign by the immune system.
The barrier prevents an immune response against the antigens by isolating the cells from the blood.

Sertolic Cell Function

Supports and protects developing spermatogenic cells
Nourishes spermatocytes, spermatids and spermatozoa
Mediates the effects of testosterone and FSH on spermatogenesis
Phagocytizes excess spermatid cytoplasm as development proceeds
Controls movements of spermatogenic cells and the release of spermatozoa into the lumen of the seminiferous tubule
Secretes fluid for sperm transport
Secrete hormone, inhibin which helps regulate sperm production by inhibiting secretion of FSH

Seminal Vesicle

Expel a viscous secretion to keep spermatozoa alive and motile.
Secretion is rich in K+, fructose, fibrinogen, phosphorylcholine, citric acid and ascorbic acid.
Seminal vesicles also synthesize and secrete prostaglandins.

Prostate Gland

A single gland that secretes prostatic fluid which is slightly acid in reaction (pH= 6.4).
The secretion is rich in Ca+ and contains
Zinc, citric acid, Na^+
The enzyme fibrinolysin, and acid phosphatase

Epididymis

Is attached to the back of the testis
Consists of a coiled tube about 7 meters long which continues into the vas deferens
After spermiogenesis, spermatozoa are moved through the ductuliefferentis to the tail of the epididymis where
They are stored and can remain there for 1month and still be able to fertilize an ovum.
The wall of the epididymis contains smooth muscle and a secretory columnar epithelium,
The secretion of which nourishes spermatozoa and helps them to mature.
The spermatozoa are non-motile in the epididymis and they become motile only when they are
Exposed to oxygen or to a substance which can be metabolized to lactic acid.
Epididymal secretion is rich in K and has a high K/Na ratio
It has a high concentration of glycerylphosphorycholin, a potential source of energy.
An enzyme which splits off choline and releases glycerophosphate is found in the endometrium of many animal species;
This could enhance motility *in utero.*Epididymal fluid also contains testosterone which may help in the maturation of spermatozoa.

Semen analysis

Valuable tests for evaluating male fertility.

Factors analyzed include:

- Volume of semen
- Sperm motility
- Sperm counts
- Liquefaction
- Morphology
- pH
- Fructose

Average semen volume/ejaculate is 2.5-5ml; sperm count 50-150 million/ml.

Male infertility is likely when the count is below 20 million/ml.
Semen pH, slightly alkaline, 7.2- 7.6.
Semen contains an antibiotic, seminalplasmin which
Has the ability to destroy certain bacteria.
Colour is white and the specific gravity 1.028

Capacitation

Capacitation refers to the functional changes that sperm undergo in the female reproductive
These allow them to fertilize a secondary oocyte.
During this process,
The membrane around the acrosome becomes fragile
So that several destructive enzymes- hyaluronidase, trypsin-like protease, acrosin and neuraminidase-
Are secreted by the acrososme.
The enzymes help penetrate the *corona radiata*-
Several layers of follicular cells around the oocyte and
A gelatinous glycoprotein layer internal to the *corona radiata* called *zonapellucida.*


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