



PHYSIOLOGY

Sheet

Slide

Handout

Number

11

Subject

Physiology of male
reproductive system

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Date:

Price:

- ❖ This sheet was written according to section 3 record.
 - ❖ The order of some ideas may be different from the record.
 - ❖ Topics of the lecture: fetal development and cryptorchidism
 - Testosterone
 - Sperms
 - Infertility and impotency
 - Viagra; a drug to treat impotency
-

❖ Fetal development of the testes and Cryptorchidism:

➤ Scrotum is the place of spermatogenesis:

- Spermatogenesis requires a lower temperature than the body temperature to occur normally, that's why scrotum is the place in which spermatogenesis occurs.
- Scrotum's temperature is lower than that of the body by 2-3 degrees, and few factors aid in the process of controlling this temperature in its normal range; these factors are:
 1. Pampiniform plexus → it acts as a heat exchanger, cooling blood in adjacent arteries.
 2. Cremaster muscle → it responds to changes in temperature by moving the testes closer or away from the body.
- During the fetal development: the testes are in the abdominal cavity, in the last three months of pregnancy they descend gradually to the scrotum under the effect of testosterone. So testosterone is the normal stimulus for the testes to descend.
- *"Effect of Temperature on Spermatogenesis. Increasing the temperature of the testes can prevent spermatogenesis by causing degeneration of most cells of the seminiferous tubules besides the spermatogonia. It has often been stated that the reason the testes are located in the dangling scrotum is to maintain the temperature of these glands below the internal temperature of the body, although usually only about 2°C below the internal temperature. On cold days, scrotal reflexes cause the musculature of the scrotum to contract, pulling the testes close to the body to maintain this 2° differential. Thus, the scrotum acts as a cooling mechanism for the testes (but a controlled cooling), without which spermatogenesis might be deficient during hot weather." Guyton, 12th edition, page 997.*

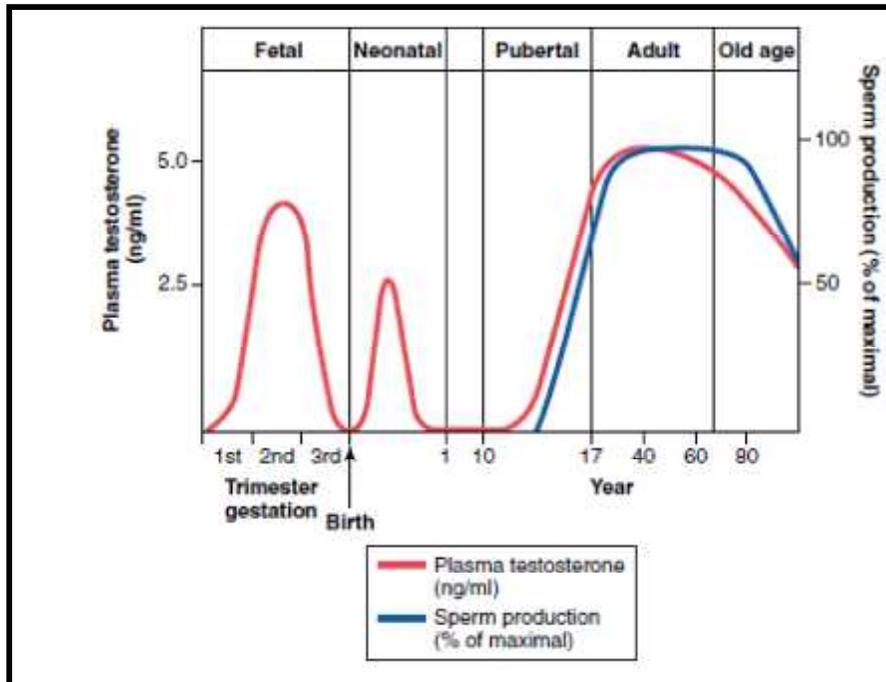
➤ **Cryptorchidism:**

- It is a congenital anomaly in which the testis fails to descend from the abdomen into the scrotum, and most probably it results from inadequate levels of testosterone during the fetal life.
 - In such case, the doctors wait for a round one year for the testes to descend; if the testes did not descend then surgery is needed.
 - In case that Cryptorchidism was not treated, spermatogenesis will not take place due to the high temperature in the abdomen, therefore fertility will be affected.
 - The percentage of Cryptorchidism:
 - ▶ In full term infants is 1-3%.
 - ▶ In premature infants, the percentage rises up to 30%.
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❖ **Testosterone; levels and functions:**

➤ **Levels of testosterone:**

- I. **During fetal life:** Testosterone levels are high especially during the second trimester of the pregnancy, and during this period testosterone is secreted by the effect of human chorionic gonadotropin hormone (hCG) which is released from the placenta *-not because of LH from the pituitary gland as it is not mature yet-*.
- II. **During childhood:** very low levels of testosterone and almost no difference in this level between males and females. Thus there are no differences between girls and boys in body mass, skeletal mass and the body fat due to the similarity in testosterone levels.
- III. **After puberty:** testosterone starts to rise → so differences between males and females start to appear, for example: males will have twice the number of muscle cells in females and 1.5 times the muscle mass of the females.
- IV. **At the age of 70 years:** there is a **slight decrease** in the testosterone level. This decrease differs from one individual to another but usually it does not occur before 60 or 55 years. This reduction in testosterone is called climacteric.



- **Notes:**

- The age does not affect fertility that much -i.e. reproduction, and not sex capability-. However; there are some changes that occur with aging that will affect fertility such as the viscosity of the semen and the number of chromosomes in the formed sperms - I think the doctor means that with aging genetic abnormalities in the formed sperms will be more-. In conclusion the doctor said that fertility will be affected but not that much.
- Testes may also produce little amounts of HCG as well as pituitary gland.
- Note that there is no zero level of testosterone from the fetal life till death.

“After puberty, gonadotropic hormones are produced by the male pituitary gland for the remainder of life, and at least some spermatogenesis usually continues until death. Most men, however, begin to exhibit slowly decreasing sexual functions in their late 50s or 60s, and one study showed that the average age for terminating intersexual relations was 68, although the variation was great. This decline in sexual function is related to decrease in testosterone secretion, as shown in Figure 80-9. The decrease in male sexual function is called the male climacteric.” Guyton, 12th edition, page 984.

➤ Testosterone is pro-hormone:

- Several tissues produce testosterone (*as well as other androgens*) other than testes (1), these are:
 - 2) Adipose tissue.
 - 3) Muscles.
 - 4) Brain.
 - 5) Skin.
 - 6) Adrenal cortex.
- Testosterone is a pro-hormone found in the testes, pituitary and muscles.
- In the liver, kidney, adipose tissue, CNS, skin and hair; testosterone is converted into estradiol as there is aromatase enzyme in such tissue.
- In prostate, scrotum, penis and bone testosterone is converted into dihydrotestosterone by the action of 5-alpha-reductase enzyme.
- It is found in the liver and kidney as 17-ketosteroids.
- These substances are produced de-novo or by peripheral conversion of the precursors.

So testosterone is a pro-hormone.

➤ Testosterone derivatives:

1- Dihydrotestosterone:

- The most important derivative of testosterone is dihydrotestosterone; it is 30-50 times more biologically active than testosterone; which means that dihydrotestosterone is stronger than testosterone.
- As mentioned before, it is produced from testosterone by the enzyme 5-alpha-reductase.
- As we know from Dr. Faraj lectures; this derivative of testosterone is responsible for the differentiation of penis, scrotum and prostate. It is also the one that is responsible for prostate GROWTH.

→ Drugs that inhibit 5-alpha-reductase enzyme are currently used to manage prostatic hyperplasia as dihydrotestosterone induces prostate growth.

→ **Clinical correlation “GnRH and prostate hyperplasia”:**

- Normally, GnRH is released in **pulsatile manner** from the hypothalamus → it stimulates the release of FSH and LH from anterior pituitary → then these two hormones will stimulate the synthesis and release of testosterone → and once testosterone level is increased → the production of its derivative “dihydrotestosterone” will also increase.

But

- If the GnRH was released **continuously** → it will result in **suppression** of FSH and LH release → thus testosterone and dihydrotestosterone levels will decrease.
- Based on that, continuous GnRH administration is used to treat prostate hyperplasia;

EXTRA NOTE:

Castration (also known as gonadectomy) is any action, surgical, chemical, or otherwise, by which an individual loses use of the testicles. Surgical castration is bilateral orchiectomy (excision of both testes), and chemical castration uses pharmaceutical drugs to inactivate the testes. Castration causes sterilization (preventing them from reproducing); it also greatly reduces the production of certain hormones, such as testosterone. Wikipedia

****Continuous GnRH administration → inhibits dihydrotestosterone synthesis
→ reduction in prostate growth.****

- This mechanism of therapy is called **chemical castration**. Further explanation in the text box to the right.
- *“Although pulsatile GnRH discharge elicits a corresponding pulsatile release of LH and FSH, continuous administration of GnRH or intermittent administration of high doses of GnRH suppresses the release of gonadotropins. Clinical application of this principle is in prostatic cancer. Where the administration of GnRH analogues lowers LH and FSH thus lowering testosterone production (i.e. chemical castration).” From slides*
- **NOTE:** sometimes surgical castration is done to treat prostate enlargement when chemical castration fails.
- Castration of adult males leads to decline but not complete loss of sexual interests. On the other hand sexual activity will be totally lost within one month.
- Castration of adult men results in regression of reproductive tract and involution the accessory gland as well.

→ **Dihydrotestosterone and acne:**

- Growth and secretion activity of sebaceous glands are stimulated by androgens - mainly dihydrotestosterone- and inhibited by estrogen. Increased sensitivity of target cells to androgens especially during puberty is the cause of acne in both males and females.
- The best treatment to remove acne is **ROACCUTANE**-concentrated vitamin A-, but only used in severe cases due to its many side effects.

2- Estradiol:

- By Aromatization, testosterone is converted into estradiol.
- Aromatization of testosterone is under the control of FSH.
- Although some tissues -such as adipose tissue- lack FSH receptors but still aromatization can occur.

Thus testosterone is converted to dihydrotestosterone and estradiol for normal health and well-being especially to protect against osteoporosis.

➤ **Functions of testosterone:**

A- Functions of Testosterone During Fetal Development:

- ◆ Intra-urine differentiation of male reproductive organs;
 - Seminal vesicles, epididymis and vas deference (require testosterone as it is)
 - Scrotum, penis and prostate (require dihydrotestosterone).
- ◆ Descending of the testes from the abdomen to the scrotum.

B- Effect of Testosterone on Development of Adult Primary and Secondary Sexual Characteristics:

- ◆ Testosterone is important for sex drive and behavior.
- ◆ It also affects adipose tissue and cholesterol derivatives (LDL, VLDL and HDL).
(Doctor Saleem did not mention how does testosterone do this. However; in the book it is mentioned that testosterone increases basal metabolic rate).
- ◆ It increases muscle cells, RBCs.
- ◆ It is needed for spermatogenesis.
- ◆ It is also responsible for baldness.

****So testosterone functions starts from fetal life till death. ****

- Unlike most species which only want to produce off-spring. In humans sexual activity and procreation are not highly linked, superimposed on the effect of reproductive mechanism dictated by hormones are numerous physiological and sociological factors.
 - **NOTES:**
 - *You may notice that some of these notes are not understandable and they may even oppose each other, I really do not know the purpose of mentioning such unrelated notes; however I wrote them as the doctor said them.*
 - In normal men; No correlation has been found between circulating testosterone levels and sexual drive, frequency of intercourse or sexual practices. So normally standard level of testosterone is needed -not more or less-.
 - Higher levels may not produce any difference but lower levels may do so.
 - No correlation between testosterone levels, impotency and homosexuality.
 - So homosexuals may have normal or even higher levels of testosterone. Thus homosexuality is not related to testosterone.
 - Some males may use testosterone injection in order to increase sex drive, but actually it does not increase it. And if there is any effect, then it is psychological effect rather than true pharmacological effect. Some of those who use testosterone injection may turn into homosexuals.
 - Also those who use steroids -like athletes- may end up being homosexuals, as estrogen is produced from testosterone and steroids ;thus elevated levels of those precursors may result in increased estrogen levels.
 - Administration of testosterone to homosexuals intensifies their homosexual drive but not convert it to a heterosexual drive.
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❖ **Sperms:**

- Sperms consist of head, neck and tail.
 - In the head, the nucleus ($22+X/22+Y$) is located and covered by acrosomal cap; which contains lytic enzymes to lyse the membranes around the ovum.
 - The mitochondrial sheath around the middle piece is for energy production.

- The tail is for movement.

We know more details about the structure of the sperm from doctor Faraj lectures but those mentioned here are what dr. Saleem mentioned.

EXTRA NOTE: one of the most important uses of Hyaluronidase is increasing the absorption of other injected medicines or fluids.

- **The acrosomal enzymes:**

→ These enzymes are:

- Hyaluronidase -the most important-
- Phospholipase A
- Acrosin
- Neuroamidases
- Esterases

→ They are not released unless the sperm is in contact with the ovum. They are released by more than one sperm but only one sperm will make it and penetrate the membranes around the ovum.

→ NOTE: Hyaluronidase is used in dentistry to treat gum infections and used as a component of creams for ladies. *Hyaluronidase has many other more important clinical uses but the doctors mentioned only these two.*

❖ **Puberty:**

- Puberty in females occurs at ages from 8-13 years old whereas in males it occurs at ages 9-14 years.

- **Causes of delayed puberty:**

- Normal variants:
 - Familial.
 - Racial.
- Coincidental serious illness such as those which increase the body temperature and severe chronic diseases -like tuberculosis-.
- Psychological stress.
- Hypogonadism from any cause.
- Hyperprolactinaemia.

❖ Infertility and impotency:

Firstly, we will discuss the physiology of erection to understand impotency, its causes and the drugs used for such condition:

➤ **Physiology of erection:**

- Stimulation of parasympathetic nerves → causes nitric oxide release from vascular endothelial cells → it activates guanylyl cyclase enzyme → which produces cGMP from GTP → resulting in calcium channels closure → decrease in intracellular calcium → vascular smooth muscle relaxation → As the vascular smooth muscles relax, blood flow into the penis increases, causing release of nitric oxide from the vascular endothelial cells and further vasodilation.
- Then cGMP is converted into GMP by phosphodiesterase enzyme in order to terminate the relaxation.

➤ **infertility and impotency:**

- Impotency: sexual dysfunction characterized by the inability to develop or maintain an erection of the penis during sexual activity in humans. Thus impotency is erectile dysfunction. It is one of the causes of sterility -infertility-
- On the other hand; sterility or infertility means: inability to reproduce. it has many causes; one of those is impotency. *The doctor said that infertility means that there are no sperms to penetrate the ovum for any reason.*

So impotency leads to sterility but sterility does not always mean impotency.

➤ **Causes of impotency:**

- ◆ Psychological disturbances -the most common cause-.
 - ◆ Drugs like cocaine.
 - ◆ Autonomic neuropathy like those caused by diabetes.
 - ◆ Hyperprolactinaemia.
 - ◆ Hypogonadism.
 - ◆ Heart disease and surgeries.
- Read the following paragraph and note that impotency can result from any abnormality in one of the steps of the erection mechanism:

“Neurological problems, such as trauma to the parasympathetic nerves from prostate surgery, deficient levels of testosterone, and some drugs (nicotine, alcohol, antidepressants) can also contribute to erectile dysfunction. In men older than age 40, erectile dysfunction is most often caused by underlying vascular disease. As

discussed previously, adequate blood flow and nitric oxide formation are essential for penile erection. Vascular disease, which can occur as a result of uncontrolled hypertension, diabetes, and atherosclerosis, reduces the ability of the body's blood vessels, including those in the penis, to dilate. Part of this impaired vasodilation is due to decreased release of nitric oxide." Guyton, 12th edition, page 986.

Remember that nitrates are vasodilators used for angina pectoris. They lead to vasodilation thus if used with Viagra, they will cause severe vasodilation resulting in drop of blood pressure

❖ Viagra (sildenafil):

- NOTE: Viagra is the brand name of sildenafil.
- It is the most common drug used in case of impotency.
- Viagra is a phosphodiesterase inhibitor used to treat impotency.
- It inhibits phosphodiesterase enzyme → thus it prevents the degradation of cGMP to GMP → prolonging the effect of cGMP → prolonging the duration of smooth muscle relaxation and maintains erection.
- NOTE: in severe diabetes and heart diseases; Viagra does not function.

- Viagra is used mainly by young people; around 40% of its users are younger than 40 years old (*according to Google; however the doctor was not convinced by Google and said that 70% of its users are younger than 40*).
- This drug was firstly used as anti-hypertensive drug. It did not control the blood pressure adequately **BUT** it was noticed that impotent patients, who used the drug, reported improved erection. Then after many studies, **Viagra was proved to be effective against impotency.**
- Viagra is not an aphrodisiac drug like most drugs used before it; these drugs- unlike Viagra- work immediately; which means that they should be taken just before the intercourse.
- Sexual stimulation is essential for its activity.

- **Precautions:**
 - Like most drugs, it should be given in cautious to those with liver, kidney, heart and lung diseases. And it is important to be aware of its drug-drug interactions.

- **Contraindications:**

- It is contraindicated to use Viagra in patients taking organic nitrates or nitric oxide donors as combining Viagra with such drugs will result in severe drop of blood pressure that could prove fatal.
- Should not be taken with any antihypertensive drug especially ACE inhibitors. If it was taken with such drugs neither Viagra nor ACE inhibitors will work.

➤ **Other effects of Viagra :**

- Many infected patients with malaria were cured when used Viagra.
- Viagra also has some good effects in case of jet lag. A study was made in Argentine showed that Viagra is effective in all sleep disorders affecting the travelers.
- In diabetes mellitus: it normalizes the blood glucose level. *The doctor said that all diabetic patients take Viagra.*
- In heart failure and strokes. *Almost all those with heart diseases use Viagra.*
- In fatty acid metabolism.
- In prostate cancer.
 - ❖ So you can notice that Viagra has many effects thus it is widely used.
 - ❖ These effects were known by observation.
 - ❖ To be more precise;

"PDE-5 inhibitors have also been studied for possible use in other conditions. Clinical studies show distinct benefit in some patients with pulmonary arterial hypertension but not in patients with advanced idiopathic pulmonary fibrosis. The drugs have possible benefit in systemic hypertension, cystic fibrosis, and benign prostatic hyperplasia. Both sildenafil and tadalafil are currently approved for pulmonary hypertension. Preclinical studies suggest that sildenafil may be useful in preventing apoptosis and cardiac remodeling after ischemia and reperfusion."

Katzung pharmacology, 12th edion, page199 .

Sorry for any mistakes,

Wish you all great clinical journey~

Special thanks to Tala Rawashdeh



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