Sheets Physiology

Number 12

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SPERMATOGENESIS

Spermatogenesis begins by the division of spermatogonia which are immature cells that'll differentiate to form the spermatids , each spermatid has half number of chromosomes (23) but still it's not fully mature and it has to undergo further changes.
As we said previously . The spermatids has two stages of development ; the rounded stage which will eventually lead to the elongated stage and by that reaching the final shape of spermatids.
These stages include series of processes in which the spermatid is devoid of everything except the nuclear material, their contractile elements and the ciliary pattern ; which in general is composed of two single microtubules in the center surrounded by peripheral ones , this ciliary pattern is responsible for the ciliary movement ,in addition to all of these the final stage of the spermatid will have the energy producing system which is a collection of mitochondria.

- The final shape of the spermatids will give us the immobile sperm that will be released from the seminiferous tubules in the testis to reach the second station which is the epididymis – the doctor will talk later about the details of this process and how it is regulated- .

❖ These nonmotile spermatids (have no movement ability) that are traveling to the epididymis will continue to mature during this process and once they reach the epididymis these spermatids will gradually attain the capability of movement (probability) during their time spent in epididymis . Moreover the epididymis is the site of storage for these viable spermatids that will remain stored for a period of more/less than one month and during this period addition of certain materials will happen - and it will be further explained- . By now what we have in the epididymis is the stored spermatids which are attaining their capability of movement but not the ability to fertilize.

- Now to get the sperm out a process called ejaculatory process must ensue which will give the resultant semen that contains secretions along with the sperms . Again the overall process has started by the spermatogenesis in seminiferous tubules which formed the spermatozoa that was transported to epididymis and the last step is ejaculation , and in order for ejaculation

to happen there are specific materials secreted from epididymis, and seminal vesicles which are added to spermatozoa to form semen.

❖ Discussing briefly types of these secretion:

- Secretions from seminal vesicles, it secretes certain nutrients which are :
  - Fructose
  - Fibrinogen, it has a role in forming a clot around the semen after its release into the vagina , this clot will be dissolved eventually (further details will be taken later).
  - Prostaglandins , they are molecules that exert their effect after ejaculation happens in the female reproductive system, their effects include:
    a. Make cervical mucus more receptive to sperm movement.
    b. Reverse peristaltic contractions in the uterus and Fallopian tubes ; normally the semen is ejaculated in the posterior vaginal fornix from there the semen which include the sperm has to move through cervix towards the site of fertilization. This movement won't be achieved without the effect of prostaglandins on the contractility of the uterus . Because theoretically if we didn't have prostaglandins the ejaculated semen won't be able to reach the fertilization site and this is due to two reasons. First the cervix is hostile in nature except for a certain period of time, therefore if there is no prostaglandins the cervix won't become receptive and the spermatozoa won't be able to move through the cervix. The second reason is ; uterine contraction, without the effect of prostaglandins is from fundus to cervix which is opposite to the movement of the spermatozoa that is trying to traverse the cervix . In short, the prostaglandins are the ones responsible for the non-hostile environment in cervix as well as the reversal pattern of uterine contraction needed to aid the movement of the spermatozoa.

       * hostile means severe or offensive environment , so it's not possible for the sperm to stay in a hostile environment .

- Secretions of the prostate gland , it mostly contains electrolyte (Cl, Ca, HPO_3) also clotting enzymes , LMW polypeptides, proteins .

- In addition to all the secretions mentioned above we also have a small amount of secreted material from Sertoli cells that are added to the sperm in order to form the final composition of the ejaculated semen , which is entirely composed of spermatozoa and the secreted elements mentioned .

- There are different criteria for the classification of semen . The table shows certain characteristics of semen (The doctor is not concerned with numbers mentioned in the table) :

WHO semen reference values

Volume	2-6 ml or more
pH	7.2 or more
Conc.	$20x10^6$/ml or more
Motility	50% (T1&T2)
Morphology	15%

1. Numbers of spermatozoa ejaculated : from the table you can notice the huge amount of spermatozoa secreted in certain volume of ejaculated semen which is almost 100 million . This huge number has actually small significance because even if the number of spermatozoa secreted was less it has no effect on the ability of the ejaculated spermatozoa to fertilize the oocyte . Therefor the number of spermatozoa whether 100 million or even more or less than 100 million is not that significant because in the end it is only a statistical number and it has no importance on fertilization ability of the sperms .

- Fertility is thus defined as the ability of spermatozoa to fertilize the oocyte in order for pregnancy to happen despite the number of ejaculated spermatozoa.

2. Motility of the ejaculated spermatozoa: 50% of the spermatozoa are immotile . Motility of spermatozoa is divided to four types:
    - straight forward movement (fast)
    - straight forward movement (slow)
    - movement that lacks direction
    - circular motion , the sperm is moving around it self .

- The doctor explained this point similar to the university square in which students pass by it in a forward direction towards the lecture, in comparison with other students that hang out there or move around it .
- It is important to know that the only spermatozoa which we care about are the ones with straight forward type of movement. the other two types are of no importance and they can't reach the fertilization site thus considered useless.

3. Morphology: in addition to the 50% immotile spermatozoa , almost about 85% of ejaculated spermatozoa have abnormal morphology whether the shape of the head , tail , or the body .

- From all the mentioned points above it is clear that the number of normal spermatozoa approximately accounts for only 7% of ejaculated spermatozoa. And this number is further reduced in other semen classifications to reach 1-2%.
- Even with this small amount left only certain number of spermatozoa (100 to 1000 sperm)can cross the cervix , the other spermatozoa will stay in the vagina and eventually go outside.
- From the photo you can also notice that only few spermatozoa surrounds the oocyte despite the huge amount of spermatozoa ejaculated thus it is concluded that the majority of ejaculated spermatozoa are useless .
- High concentrations of ejaculated spermatozoa, give higher probability to fertilize but it is not the reason why fertilization happen .

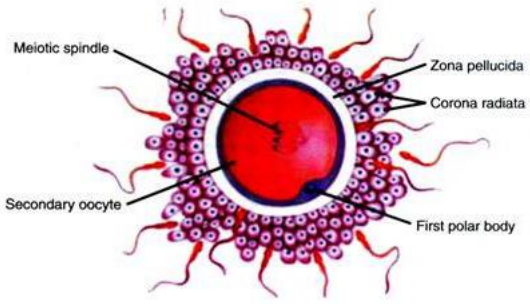


Image 9.9. Ovum surrounded by few sperms

- **Production of hormones by the testis** , it is the second function after production of germ cells . In the testis there are two types of cells : Leydig cells , and Sertoli cells which are found inside the seminiferous tubules.

- Interstitial cells of Leydig produce testosterone which is a steroid . Steriodogenesis involves cholesterol as the precursor molecule for the synthesis of steroids , and as we already know this process happens normally inside the adrenal glands in both male or female , which is under the control of ACTH released from the anterior pituitary gland. But in the male we also have steroid synthesis in the Leydig cells which is under the control of Luteinizing Hormone (LH).

    - A review of steroid synthesis: it starts by the conversion of cholesterol to progesterone then slight modifications at the position of hydroxyl groups and the number of carbon atoms will yield different compounds , for example aldosterone has an aldehyde group and two hydroxyl groups , whereas hydroxylation of progesterone at positions -carbon 11 , 17 , 21 – will produce cortisol which is a glucocorticoid. Also progesterone is a delta 4 molecule and the other produced steroid hormones are mainly delta 5 including testosterone. In order for testosterone to be synthesized, progesterone is converted to dihydroandroepisterone DHEA and then to androstenedione which forms testosterone. In general all steroids differ in the position of hydroxyl groups between C – 11 ,17 ,21 – except for mineral corticosteroids which have their hydroxyl group at C-18.
        - You don't have to memorize the details just know the general picture .

    - As we said LH stimulates steroidgenesis in Leydig cells to produce only androgens which are male sex hormones that are also derivatives of cholesterol. These hormones have only 19 carbon atoms compared to cholesterol which has 27 carbon atoms . we do so by removal of 6 carbon atoms from cholesterol to form progesterone and then removal of another two carbon atoms to form androgens. Most of the androgens produced by Leydig cells are released out to the circulation and only few will be given to the seminiferous tubules which will exert their effect in spermatogenesis.

- Functions of testosterone: in order for testosterone to perform its function it has to have a receptor that must be located on target tissue , these receptors are androgen receptors (work with cGMP) located in (porstate , testes , sertoli cells , Laydig and myoid cells , epididymis, seminal vesicles, neurons in CNS anterior pituitary, thyroid , skin , adrenal cortex , liver , kidney tubules , cardiac muscles and strained , bladder , bone , vasculature).

1. Before birth (chorionollgically -intrauterine-): Testosterone production also happens before birth at weeks 5, 6, 7 but it is a result of direct expression of the Y chromosome. This testosterone is essential for the wolffian duct development and the formation and development of sex organs followed then by enlargement of male sex organs during intrauterine life which is the first enlargement that will be followed later with the 2nd enlargement at puberty and between these two enlargements there will be minimal changes . In addition to these functions , testosterone at this period along with hCG is essential for the descend of testis from the abdomen towards their place in scrotum at the last part of pregnancy as well as the testes enlargement.

2. Functions of testosterone at puberty: after the intrauterine period, levels of testosterone will seize down and it raises up again by the time puberty starts and this increase will be responsible for:
    - The second enlargement of testes and all sex organs from epididymis to penis.
    - Appearance of secondary sexual characteristics which are divided in two groups
        a) Behavioral aspect , in which masculine pattern of behavior starts to appear.
        b) Physical aspect :
            1) abrupt rapid rise of growth rate in combination with insulin, growth hormones , thyroid hormones and glucocorticoid.

            2) male pattern of hair growth including facial, axillary and pubic areas.

3) effect in the voice by certain changes in the larynx and the characteristics of laryngeal mucosa.

4) development of Acne due to changes in sebaceous cysts.

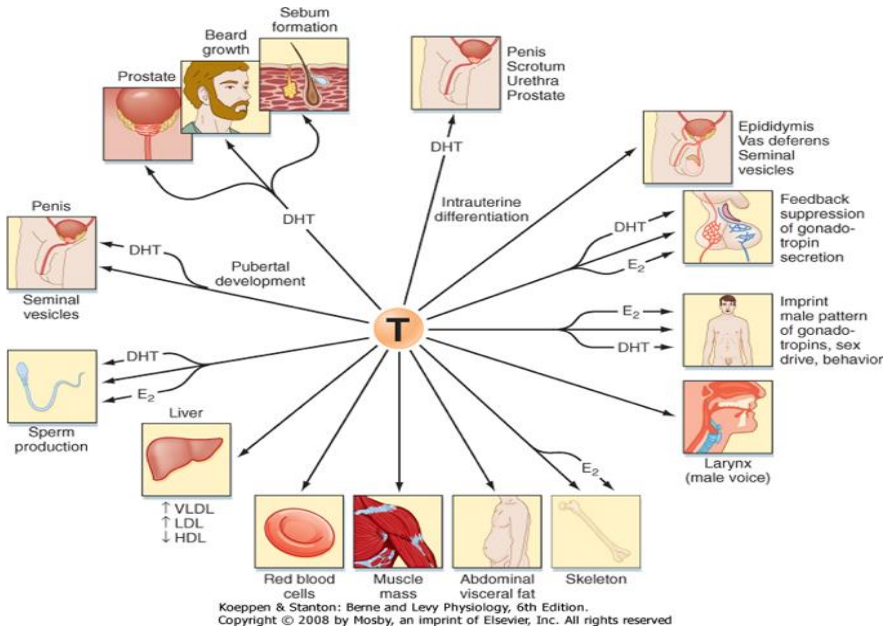
5) increase protein formation and muscle development, testosterone increases the tension- length relationship of the muscle. For example if we put a female muscle and a male muscle which have the same structure in a culture media and stimulated them , both muscles will contract with equal forces, but in vivo we have testosterone that acts as positive ionotropic factor that causes the male muscle to have stronger contraction , this stronger contraction can also be established if we added testosterone to the female muscle .

6) production of more red blood cells. Testosterone has a positive effect in erythropoiesis thus causing more red blood cells in male in contrast with females . If both male and female have no testosterone , the amount of red blood cells will be the same .

- Both testosterone and spermatogenesis make the male individual has the ability to reproduce and thus reaching the puberty stage which is a systemic period that last for a 1 year or maybe 2 , 3 , or 4 it depends on the individual. This stage is characterized by the previously mentioned points of enlargement of the testes and spermatogenesis..etc. but it is important to note **that it is not a must** to attain the ability of reproduction because there are some pathological cases that makes the individual unable to reproduce despite reaching the puberty stage.
- Testosterone exert its effect through nuclear receptors that causes the transcription of mRNA which is translated to produce other proteins important for development.
- Most of testosterone function comes indirectly by Dihydrotestosterone which is a derivative of testosterone -This is similar to thyroid hormones in which T3 a derivative of T4 does most of the function- All steroid

hormones are transported through the plasma by specific carrier mainly albumin and pre-albumin and that's why steroids have relatively longer half life than non steroidal as well as thyroxin hormones.

- Masculine type of behavior is seen in all male species in both animals and human .
- Male menopause which means cessation will be discussed later when talk about female menopause.



❖ Regulation of spermatogenesis and testosterone production:

Regulation begins when GnRH which is a 10 amino acid peptide released from the hypothalamus in the median eminence to reach the anterior pituitary. Recall that GnRH cells during development migrates to the hypothalamus and what regulates their migration also regulates migration of olfactory nerve , therefore if there is failure in migration of these cells , a failure of olfactory nerve migration will also happen and it won't reach the nose . Failure of GnRH cells migration to the hypothalamus means failure of their fibers to reach the median eminence and thus GnRH won't be able to reach the anterior pituitary. This is important because the anterior pituitary cells are highly dependent on GnRH stimulation in order to release LH and FSH ; these two are glycoprotein hormones with two subunits (same alpha subunit but different beta subunit for both of them).

- <u>Now , what are the functions of FSH and LH ?</u>

- LH exerts its effect on Laydig cells and stimulates it to produce testosterone which also acts as a regulator for LH release in a negative feedback way .
- FSH exerts its effect on Sertoli cells and stimulates it to produce different molecules one of these is a protein called inhibin which is important in regulation of FSH release also in a negative feedback way.
- Individuals who lack FSH and LH are incapable of starting spermatogenesis unless given exogenous supplements of FSH and LH.

  - Negative feedback control of testosterone.
    In the testis we have mainly testosterone and small amount of inhibin, this testosterone serve as a negative regulator for LH release more than FSH by decreasing LH release from anterior pituitary.
  - Negative feedback control of inhibin.
    By observing LH and FSH levels in blood they found that their concentrations are not equal despite the fact they are both released in response to GnRH from anterior pituitary this difference is mainly due to the preferential negative feedback control on FSH levels by inhibin .

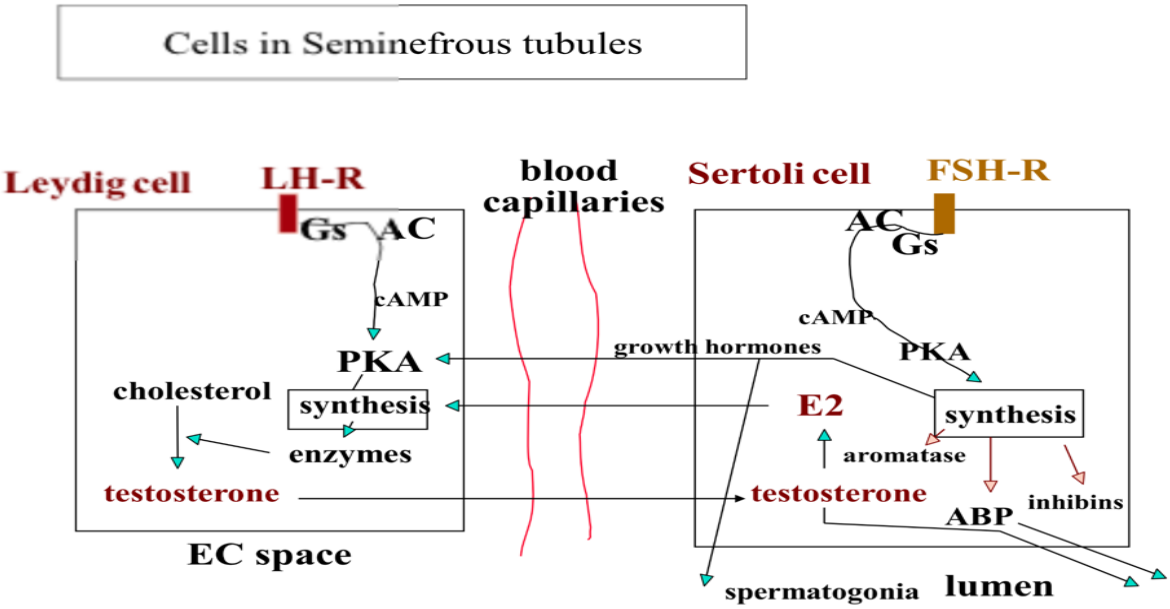
    Notes:

- If inhibin also strictly regulated LH release for the same degree as FSH , in this situation FSH and LH must have equal concentrations.
- There are also great difference in LH and FSH levels in females.

➢ <u>Reviewing regulation again:</u>

- Leydig cells have LH-Receptors , they respond to LH which will induce the synthetic machinery of the cells in order to produce testosterone , most of the produced testosterone will be released to the circulation except for a few amount which is transported to Sertoli cells .
- Sertoli cells have FSH receptors that bind FSH . FSH will also induce the synthetic machinery for the production of inhibin , other needed proteins , and Aromatase enzyme which causes the conversion of testosterone to estrogen by loss of one carbon . This estrogen which is produced in Sertoli cells will exert its effect locally and it won't be secreted out of the cell . Estrogen with testosterone are both essential for the process of spermatogenesis.

- Note that both LH and FSH receptor works by second messenger pathway.



❖ REGULATORS OF SPERMATOGENESIS:

Estrogen and testosterone are the two hormones that are directly essential for spermatogenesis, whereas FSH and LH are considered essential because they indirectly induce spermatogenesis by stimulating the production of estrogen and testosterone , therefor deficiency of these essential hormones will impair spermatogenesis entirely . On the other hand growth hormones , thyroid hormones, prolactin, all these have indirect connection with spermatogenesis but they are also important because deficiency in one of them affect spermatogenesis but it doesn't stop it .

For example:

- growth hormones deficiency will cause less effective spermatogenesis and its replacement will restore spermatogenesis back to normal .
- Prolactin in small amount is needed for spermatogenesis , but excess amount of prolactin will cause suppression of spermatogenesis and the absence of prolactin will cause slight reduction in it .

- Thyroid hormones , if there is TSH deficiency the patient will have suppressed spermatogenesis. If the patient has hypothyroidism he will have suppressed spermatogenesis but the correction of thyroid deficiency will reset that process back to normal .

Note:

- How these hormones affect spermatogenesis is not known , the effect of growth hormone on spermatogenesis is not understood but it is needed because its absence affects it.
- The core regulators are estrogen, testosterone, FSH , LH.

❖ Puberty stage : we said it is a phase that happens over a period of time averages between 2 to 6 years . It starts at age between 9 to 12 years old in which the male undergoes changes one of these is the completion of linear growth that happens by continuous stimulation of androgen to the epiphyseal plate thereby causing its closure at the end of the puberty stage in which the maximum height of linear growth has been reached.

- Again the most important thing about this stage is the transition from quiescent stage (inability to reproduce) to a state of reproductive function (ability to reproduce) which is accompanied by all the physical changes mentioned not just the testicular function , there must be a simultaneous well development to all structures in order for reproduction to happen. If any of the structures are not well developed the individual will not be able to fulfill the criteria of puberty.

❖ Female Reproductive System:

- During intrauterine life , migration of cells from yolk sac to the genital ring will happen , after that proliferation of these cells occurs forming the primordial germ cells which reach around 7 million cells , these cells will cross talk with surrounding cells and each primordial germ cell will be surrounded by a single layer of cells. This single layer of cells along with the primordial germ cell will form the primordial follicle and thus forming 7 million follicles .
- Most of the primordial follicles will go through sleeping stage were they become dormant , by the time of delivery most of them will die in a process

called atresia reaching 2 million in number . so we have a negative activity (a decrease in number).

- After delivery the cells will stay dormant and further reduction of primordial follicles (destructive activity)will occur until reaching the puberty stage and by that time the female ovaries will only contain 400 thousands of primordial follicles .
- At puberty stage recruitment of primordial follicles will start during the female reproductive years in which 10 to 20 follicles are recruited periodically and only one of them will continue the development and the rest will die , this is in addition to the point that not all the 400 thousands follicles will be recruited , some of them will remain dormant and will undergo degeneration eventually. The recruitment duration takes a period of 2 to 4 weeks , and the only recruited follicle will undergo certain changes to form a single oocyte which needs another two weeks to happen. Thus most of 7 million primordial follicles will degenerate , and only one cell of the 10 – 20 recruited cells will continue its development, therefore if we calculated the number of recruitments by the time of the puberty onset in a female at age of 50, it is expected to found zero follicles at this age , this means if the female at each month produced one oocyte she will need to produce 12 oocyte each year which means she needs 500 oocyte (~ 12*40 yrs) during 40 years of life .
- Lastly the primordial follicles contain cells that are arrested at certain meiotic stage , these cells will resume their meiosis after recruitment , these cells are arrested in meiosis one and they haven't undergone second meiotic division yet.

➢ <u>Differences between spermatogenesis and oogenesis:</u>

1. In spermatogenesis we stimulate all the cells but at different phases . Whereas in oogenesis we recruit only 10 to 20 cells periodically.
2. In spermatogenesis the cells will remain dormant but they won't die in comparison to the dormant phase of oogenesis were most of the cells die.

~ please check the slides , and best of luck .