Physiology Team 439

MED439
KING SAUD UNIVERSITY

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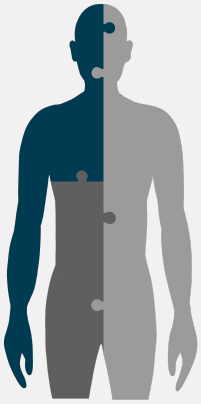


Androgens

Objectives:

- Understand the functions of the male reproductive organs and glands.
- Describe the synthesis, secretion, metabolism and effects of testosterone.
- Explain how the hypothalamus and anterior pituitary gland regulate male reproductive function.
- Describe the major testicular abnormalities.
- Discuss the normal mechanism of the male sexual act.

Color index:

- Important.
- Girls slide only.
- Boys slide only.
- Dr's note.
- Extra information.

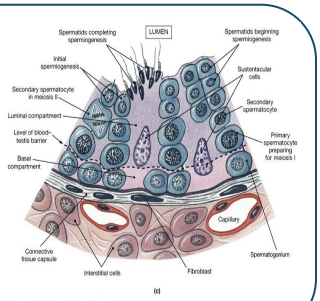
Editing File

Male Reproductive Anatomy

- **Testes**
- **Vas deferens**
- **Prostate**
- **Ejaculatory duct**
- **Epididymis**
- **Seminal vesicle**
- **Bulbourethral**
- **Urethra & Penis**

Testes

- The testes reside outside the abdominal cavity in the scrotum.
- This location maintains testicular temperature at about 2°C lower than body temperature.
- Each testis is composed of 300 lobules
- The seminiferous tubule is lined by a complex seminiferous epithelium contains two cell types:
  1. sperm cells in various stages of spermatogenesis and
  2. the Sertoli cell, which is a "nurse cell" in intimate contact with all sperm cells



Sertoli cells & Leydig cell

Sertoli cell

- Large with overflowing cytoplasmic envelopes.
- Surround the developing spermatogonia around the central lumen of the seminiferous tubules. Substance produced causes nourishment of the sperm
- **Form blood-testes barrier:**
  - Prevents autoimmune destruction of sperm.
  - Produce FAS ligand which binds to the FAS receptor on surface to T lymphocytes, triggering apoptosis of T lymphocytes.
  - Prevents immune attack.
- **Secrete inhibin**
- **Phagocytize residual bodies:**
  - May transmit information molecules from germ cells to Sertoli cells.
- **Secrete androgen-binding protein (ABP):**
  - Binds to testosterone and concentrates testosterone in the tubules.

Leydig cells*

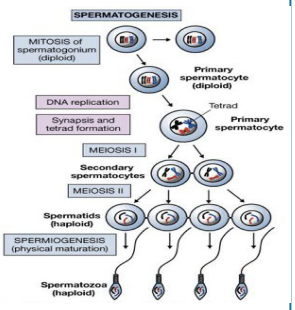
- Lie within the interstices between the seminiferous tubules.
- They are almost non-existent in the testis during childhood when the testes secrete almost no testosterone.
- Numerous in the newborn male infants for the first few months of life.
- Active at puberty & throughout adult life. It secrete testosterone.

Leydig cells disappear during childhood and then reappear at puberty under the effect of the anterior pituitary gonadotropic hormone and continues throughout life secreting testosterone.

Spermatogenesis

- Spermatogenesis is the formation of sperm.
- Occurs in the seminiferous tubules during active sexual life due to stimulation of AP-GnHs. (Anterior pituitary gonadotropic hormones)
- Begin at the age of 13 years. Depends on the family history and ethnicity.
- Seminiferous tubules contain:

- Spermatogonia: Stem cells involved in spermatogenesis.
- Sertoli (Sustentacular) cells: Sustain and promote development of sperm.



* At the bottom of the page u will find an explanation.

- Spermiogenesis: the final step of Spermatogenesis.

➢ Maturation of spermatozoa.

➢ Phagocytosis of cytoplasm by the Sertoli cells

Hormonal Factors that Stimulate Spermatogenesis

1. .**Testosterone**: Secreted by the leydig cells which are located in the interstitium of the testis. It is essential for the growth and division of the testicular germinal cells.

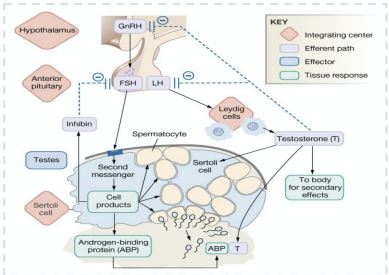
2. **Luteinizing hormone (LH):** Secreted by the anterior pituitary gland, stimulates the Leydig cells to secrete testosterone. It is also a trophic hormone (similar to TSH, it increases the size of the tissue)

3. **Follicle stimulating hormone: (FSH)**: Secreted by the anterior pituitary gland, stimulates the Sertoli cells, stimulate the conversion of spermatids to sperm (also important for spermatogenesis). It also helps the Growth hormone to work on Sertoli cells and increase its size (because it is a trophic hormone)

4. **Estrogen:** Formed from testosterone by the sertoli cells under FSH stimulation, also essential for spermatogenesis. (Sperm has receptors for estrogen, mutation in estrogen receptors reduces fertility) Testosterone is converted to estrogen by Aromatase enzyme

5. **Growth hormone (GH)**: Is necessary for controlling metabolic functions of the testis. GH promotes early division of Spermatogonia; in its absence (as in pituitary dwarfs), the spermatogenesis is severely deficient or absent, thus causing infertility.

6. **Inhibin feedback** – FSH, testosterone – short & long loops



* Synthesis of the sperm takes place in the seminiferous tubules. During intrauterine life, the primordial germ cells will migrate into the testis and develop into spermatogonia. Then spermatogonia will undergo mitotic division forming the primary spermatocytes. Spermatogonia and primary spermatocytes both have a diploid number of chromosomes. However, once primary spermatocytes undergo meiotic division, they form secondary spermatocytes which have a haploid number of chromosomes and 2 strands of DNA. Secondary spermatocytes then undergo second meiotic division forming spermatids which are haploid and have a single strand of DNA. Spermatids will then mature forming spermatozoa with a head, body and tail. (Mature sperm)

Maturation of Sperm in the Epididymis

- After formation in the seminiferous tubules, the sperm require several days to pass through the epididymis (still non-motile). Sperm in the early portion of epididymis are non-motile.

- After the sperm have been in the epididymis for 18 to 24 hours, they develop the capability of motility, even though several inhibitory proteins and cholesterol in the epididymal fluid still prevent final motility until after ejaculation. (When they are in the epididymis they are capable of motility, but their motility is being inhibited
- After ejaculation they become motile.

❖ **Physiology of mature sperm:**

Mature sperm are motile & capable of fertilizing the ovum.

■ Their activity is greatly enhanced in a neutral and slightly alkaline medium, but it is greatly depressed in a mildly acidic medium.

■ The life expectancy of ejaculated sperm in the female genital tract is only 1 to 2 days. هذه الحقيقة تستخدم في تنظيم الحمل، حيث أن البويضة تحتاج الى الى ما يقارب ال9 أيام حتى تنضج بعد نزول دم الحيض. فإن حصل القذف بعد الحيض مباشرة ومات المني قبل نضوج البويضة لن يحصل الإخصاب باذن الله

Storage of Sperm*

- The two testes of the human adult form up to 120 million sperm each day.
- Most of these sperm are stored in the epididymis, although a small quantity is stored in the vas deferens.
- They can remain stored for months while maintaining their fertility, for at least a month.
- The sperm are kept inactive by multiple inhibitory substances in the secretion of the ducts.

After Ejaculation*

- The sperm become motile and capable of fertilizing the ovum, a process called "maturation".
-
- The sertoli cells and the epithelium of the epididymis secrete a nutrient fluid (that is ejaculated along with the sperm) which contains hormones (testosterone & estrogens), enzymes, and special nutrients that are essential for sperm maturation.

Function of:

Seminal Vesicle

Seminal vesicles: are small glands present at the end of the ejaculatory duct, where the prostate gland opens.

Secretes a mucoid material containing fructose, citric acid, and other nutrient substances, as well as large quantities of prostaglandins & fibrinogen.

The prostaglandins-previously thought to be secreted from the prostate- **are important help in fertilization by:**

1. Reacting with the female cervical mucus making it more receptive to sperm movement.
2. Causing backward reverse peristaltic contractions of the uterus & fallopian tubes to move the ejaculated sperm toward the ovaries.
3. Helps to dissolve the mucus in the female tract

Prostate Gland

The prostate gland secretes a thin milky fluid that contains Ca2+ ion, citrate ion, phosphate ion, a clotting protein, and a profibrinolysin.
The alkaline prostatic fluid is important for successful fertilization of the ovum.

Alkaline Prostatic fluid*

Successful fertilization of the ovum.
Help to neutralize the slightly acidic fluid of the vas deferens (due to the presence of citric acid and metabolic end products of the sperm that inhibit sperm fertility).
Helps to neutralize the acidity of other seminal fluid during ejaculation and thus enhances the motility & fertility of the sperm.

All of these fluids are mixed during emission

Semen

- Milky white, sticky mixture of sperm and accessory gland secretions.
- Ejaculated semen during sexual act is composed of the fluid & sperm.
- Provides a transport medium and nutrients (fructose), protects and activates sperm, and facilitates their movement.
- The average pH is about 7.5, the alkaline prostatic fluid help to neutralize the mild acidity of other portions of the semen.
- The prostatic fluid gives the semen a milky appearance.
- Fluid from the seminal vesicles and mucous glands gives the semen a mucoid consistency.
- Prostaglandins in semen:
  - Decrease the viscosity of mucus in the cervix
  - Stimulate reverse peristalsis in the uterus
  - Facilitate the movement of sperm through the female reproductive tract
- Clotting factors coagulate semen immediately after ejaculation, then fibrinolysin liquefies the sticky mass during the next 15-30 minutes[1].
- After ejaculation, sperms can live 24-48 h.

Fluid from the seminal vesicles (≃60%, 65%).

Fluid from the vas deferens (≃10%).

Fluid from the prostate gland (≃30%, 25%).

Small amounts from the mucous glands, especially the bulbourethral glands.

Factors Affecting Fertility

Sperm Count

- The quantity of ejaculated semen during each coitus is about 3.5 ml (2-5 ml).
- Normal male count vary between 35 million to 200 million sperm/ml (Each milliliter contains about 120 million sperm).
- Sperm count below 20 million leads to infertility.
- Sperm count less than 10 million = almost completely sterile

Sperm Morphology & Motility

When the majority of the sperm are morphologically abnormal or nonmotile then person is likely to be infertile.

Abnormal Shape	Abnormal Motility
Sometimes sperm count is normal but still infertile when about one half of the sperm have abnormal shape.	Sometimes the shape of the sperm is normal but they're either relatively non-motile or entirely non-motile which causes infertility.

Capacitation of the Spermatozoa

Capacitation "التمكين" = Making it possible for spermatozoa to penetrate the ovum:

Sperm in the epididymis is kept inactive by multiple inhibitory factors secreted by the genital duct epithelia.

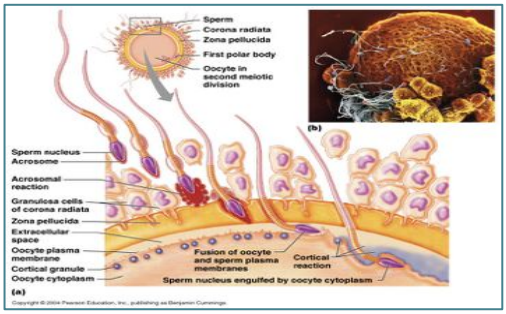
They will be activated in the female genital tract, for the processes of fertilization. These activation changes are called capacitation of the spermatozoa (it requires from 1 to 10 hrs).

1. Uterine and fallopian tube fluids wash away the inhibitory factors which suppress the sperm activity in the male genital ducts. *
2. Cellular membrane covering the acrosome is covered with cholesterol which prevent the release of its enzymes. After ejaculation, the sperm is removed -swims away- from the cholesterol vesicles & this makes the membrane of the sperm head (the acrosome) becomes much weaker.*
3. **The sperm membrane becomes more permeable to Ca2+ ion** which increase their movements & help to release the proteolytic enzymes from the acrosome which aid in penetrating the ovum.*

Acrosome enzymes, the "Acrosome Reaction" & Penetration of the ovum: Female slides

Acrosome covers the anterior ⅔ of the sperm head

- The acrosome of the sperm store large quantities of hyaluronidase and proteolytic enzymes.
- Hyaluronidase depolymerizes hyaluronic acid polymers in the intercellular cement that hold the ovarian granulosa cells together.
- Also the proteolytic enzymes digest the proteins.

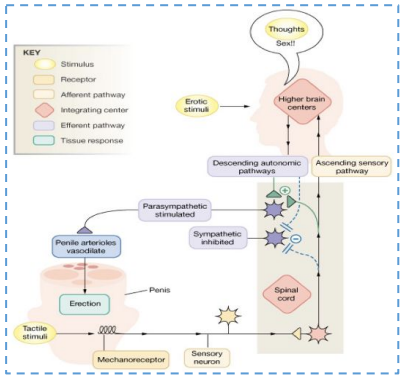


Stages of Male Sexual Act

1. Penile erection:

- Enlargement and stiffening of the penis from engorgement of erectile tissue with blood.
- Erection is caused by parasympathetic impulses that pass from the sacral portion of the spinal cord through the pelvic nerves to the penis.
- Erection is initiated by sexual stimuli including:
  - Touch and mechanical stimulation of the glans penis and other parts.
  - Erotic sights, sounds, and smells.
  - Erection can be induced or inhibited solely by emotional or higher mental activity

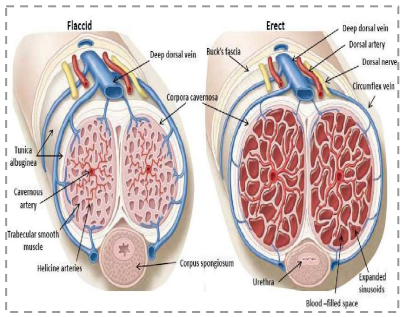
Ejaculation is sympathetic
Erection is parasympathetic



Mechanism:

1. During sexual arousal, a parasympathetic reflex promotes the release of nitric oxide, VIP, and Acetylcholine.
2. Nitric oxide relaxes the penis arteries and causes erectile tissue to fill with blood
3. Expansion of the corpora cavernosa:

- Compresses their drainage vein
- Retards blood outflow and maintains engorgement



2-Lubrication*

Parasympathetic impulses cause the urethral glands & the bulbourethral glands to secrete mucous.

3-Emission and ejaculation:

Emission

- When the sexual stimulus becomes extremely intense, spinal cord begins to send sympathetic impulses to initiate **emission**.
- Emission begins with contraction of the vas deferens and the ampulla to cause expulsion of the sperm into the internal urethra
- Contraction of the prostate & seminal vesicles to expel their fluid into the urethra .
- All these fluids mix in the internal urethra with the mucus already secreted by the bulbourethral glands to form the semen.
- This process at this point is called **emission**.

ejaculation

- Filling of the internal urethra with semen elicits sensory signals, that are transmitted through pudendal nerves to the sacral region of the cord, which promotes ejaculation.
- Fullness of the internal urethra causes rhythmical contractions of the internal genital organs which increases their pressure to ejaculate the semen to the outside. This process is called **ejaculation**.

4. Resolution*

After orgasm, the excitement disappears within 1-2 minutes (resolution)

Testosterone and Other Male Sex Hormones: Secretion, Metabolism & Chemistry

- Secretion of testosterone by the interstitial cells of leydig in the testis.
- The testes secrete several male sex hormone called androgens, including testosterone, dihydrotestosterone & androstenedione.
- Testosterone is the most abundant form while dihydrotestosterone is the more active form.
- Testosterone is converted into dihydrotestosterone in the target cells.

Secretion & Chemistry of androgens in the body:

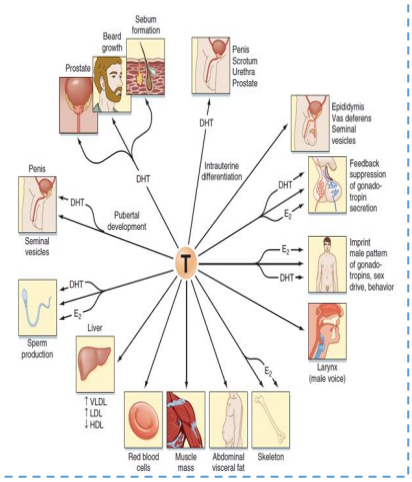
- From the testes and adrenal glands.
- It is synthesized either from cholesterol or directly from acetylcoenzyme A.

Metabolism of testosterone*:

- Testosterone binds to a beta globulin and circulates in the blood for 30 minutes to several hours.
- Converted to estrogen in the liver.
- Excreted either into the gut through liver bile or into the urine through the kidneys.

Testosterone Functions (males slides)*

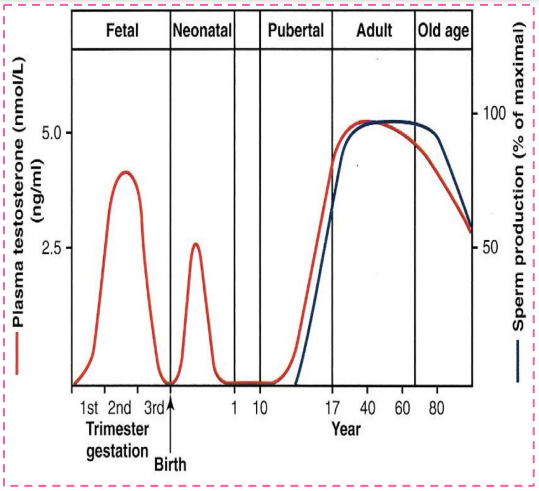
1. Testosterone targets all male reproductive organs and accessory glands, its deficiency causes these organs to atrophy
2. It causes testes descent during the last 2-3 months of gestation
3. Causes the appearance of pubic, axillary, and facial hair
4. Enhances growth of the chest and deepening of the voice
5. Skin thickens and becomes oily
6. Bones grow and increase in density and calcium retention. It is also responsible for the male pelvis shape (narrow, long, funnel-like shape).
7. It increases basal metabolic rate
8. Increases red blood cells
9. It also causes hair growth (pubic, axillary) and libido in females and males.
10. Spermatogenesis and erection.



Testosterone Functions (female slides)*

- It is responsible for the characteristic masculine body.
  The testosterone is secreted form different organ each age

1. **<u>During fetal life</u>** the testis are stimulated by placenta chorionic gonodotropin to produce testosterone throughout fetal life & the 10 weeks after birth
2. **<u>During childhood</u>** there is no more testosterone production
3. **<u>At puberty</u>** under the anterior pituitary gonadotropic hormones stimulation and throughout life
4. **<u>Beyond 80</u>** years it decline to 50%.



Testosterone Functions *

This whole page was only in female slides

1- Function of testosterone during fetal development - fetal life-

- Testosterone secreted by the genital ridges.
- Later by the fetal testis
- It is responsible for development of the male body
- Penis & scrotum.
- Prostate gland, seminal vesicles
- Male genital ducts .
- Suppressing the formation of female genital organs.

Effect of testosterone to cause descent of the testis:

The testis descend into the scrotum during the last 2 to 3 months of gestation when the testis begin secreting reasonable quantities of testosterone

2-After

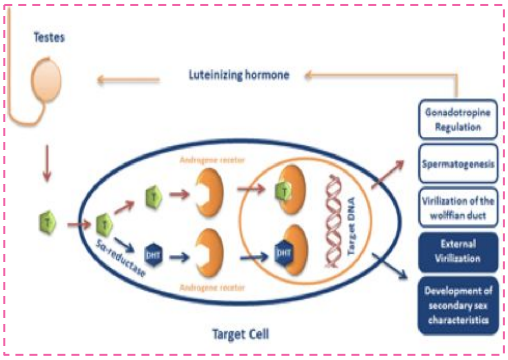
The increasing amounts of testosterone cause enlargement of the penis, scrotum, testis & secondary sexual characteristic

3-Effect of testosterone on development of adult primary and secondary sexual characteristics

distribution of body hair	-Testosterone causes growth of hair:Over the pubis (upward along the linea alba of the abdomen to the umbilicus) On the face, chest -Less often on other regions such as the back.
Baldness	Testosterone decreases the growth of hair on the top of the head. Due to two factors : 1) Genetic background 2) Large quantities of androgenic hormones.
voice	hypertrophy of the laryngeal mucosa, enlargement of the larynx (typical adult masculine voice)
skin and acne	Testosterone increases the thickness of skin over the body & subcutaneous tissues. It also increases the secretion of the sebaceous glands & sebaceous glands of the face causing acne
Protein & muscle	Testosterone have anabolic effect by: Increasing muscular development after puberty by 50% in muscle mass over that in female Increasing protein content in non-muscle parts of the body
bone & Ca2+ retention	Bones grow thicker&deposit additional Ca2+thus it the total quantity of bone matrix causes Ca2+ retention (anabolic effect). specific effect on the pelvis: 1-Narrow the pelvic outlet 2-Lengthen it 3-Cause the funnel-like shape instead of the broad ovoid shape of the female pelvis. it causes the epiphyses of the long bones to unite with the shafts of the bones & early closure of the epiphyses.
metabolism	It increases the basal metabolic rate by about 15% (indirectly as a result of the anabolic effect).
RBC	It increases red blood cells/ml (due to increase metabolic rate).
electrolyte and water balance	It increase the reabsorption of Na+ in the distal tubules of the kidneys.

The Basic Intracellular Mechanism of Action of Testosterone

- Once it diffuses to cells it either binds to androgen receptor or converted to DHT (by 5-alpha reductase) which then binds to the androgen receptor.
- It increases the rate of protein synthesis in target cells
  This combination moves to the cell nucleus, where it binds a nuclear protein and induces protein formation.
- It binds to testosterone–binding globulin (TeBG), ABP, serum albumin, or to corticosterone-binding globulin (CBG)

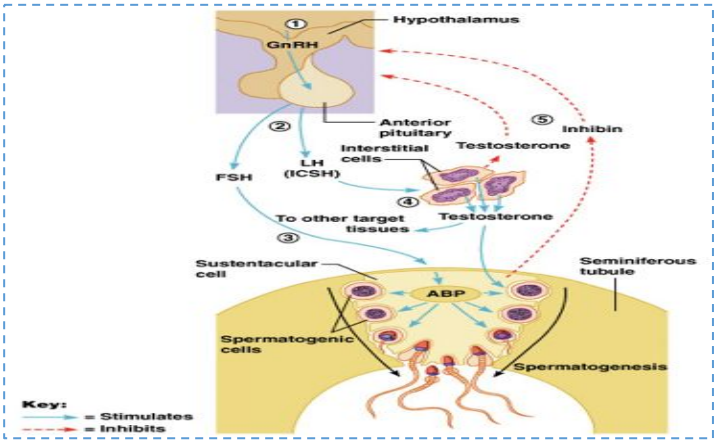


Hormonal Regulation of Testicular Function

The hypothalamus releases gonadotropin-releasing hormone (GnRH).
- GnRH stimulates the anterior pituitary to secrete FSH and LH.
-FSH causes Sertoli cells to release androgen-binding protein (ABP).
-LH stimulates interstitial (Leydig) cells to release testosterone.
-ABP binding of testosterone enhances spermatogenesis.

■ **Feedback inhibition on the hypothalamus and pituitary results from:**

-Rising levels of testosterone.
-Increased inhibin.



Abnormalities of Male Sexual Function*

Prostate gland and its abnormalities	• Benign prostatic fibroadenoma, develops in older men, due to overgrowth of prostate tissue (not caused by testosterone). • Cancer of the prostate gland caused by stimulation of cancerous cells by testosterone.
Hypogonadism in male	• **During fetal life when the testis are non-functional**, none of the male sexual characteristics develop in the fetus Instead female organs are formed. • **If the boy loses his testis before puberty**, a state eunuchism (he have infantile sex organs & infantile sexual characteristics) & the height of an adult eunuch is slightly greater than normal because of slow union of the epiphyses. • **If a man is castrated after puberty**, sexual organ regress in size and voice regress - loss of the thick musculine bones -loss of masculine hair production -loss of musculature of the virile male. • **Adiposogenitial syndrome, Frohlich's syndrome orhypothalamic eunuchism:** -hypogonadism due to genetic inability of the hypothalamus to secrete normal amount of GnRH & abnormality of the feeding center of the hypothalamus result in obesity with eunuchism.
Cryptorchidism	Failure of the testes to descend in the scrotum which normally occur During fetal life • 10% of newborn males and it falls to 2% at age 1 year • 0.3% after puberty • They should be treated before puberty because of higher incidence of malignant tumors.
Testicular tumors and hypergonadism in male	• Interstitial leydig cell tumors (rare), overproduction of testosterone. • **In children**, causes rapid growth of the musculature and bones and early union of the epiphyses and causes excessive development of male sexual organs. • Tumor of the germinal epithelium (more common).

MCQ & SAQ:

Q1: 1. What is the correct trajectory of sperm during ejaculation?

A) Ejaculatory duct, epididymis, vas deferens, ampulla of vas deferens, urethra.

B) Epididymis, ejaculatory duct, ampulla of vas deferens, vas deferens, urethra.

C) Epididymis, vas deferens, ampulla of vas deferens, ejaculatory duct, urethra.

D) Vas deferens, ejaculatory duct, ampulla of vas deferens, urethra.

Q2: What is the function of the epididymis?

A. Sperm maturation and storage.
B. Produces the bulk of seminal fluid.
C. Provides nitric oxide needed for erections
D. Spermatogenesis

Q3: which of the following not stage of male sexual act :

A.erection
B. Emission
C. Lubrication
D.Spermatogenesis

Q4: A1-year old boy comes to the office for a routine check-up. Physical examination shows that his right testis is not palpable in the scrotum. This same finding was noted on his discharge from the newborn nursery. What is your provisional diagnosis?

A.Cryptorchidism
B.Prostatic Fibroadenoma
C.Hypergonadism
D.Adiposogenital syndrome.

Q5: Which one of the following are the earliest cells of spermatogenesis?

A. Primary spermatocytes.
B. Spermatids
C. Secondary spermatocytes.
D. Spermatogonia

answer key:
1: C
2: A
3:D
4:A
5: D

1- explain the testosterone level throughout male life .

A1: **During fetal life** the testis are stimulated by placenta chorionic gonodotropin to produce testosterone throughout fetal life & the 10 weeks after birth
During childhood there is no more testosterone production
At puberty under the anterior pituitary gonadotropic hormones stimulation and throughout life
Beyond 80 years it decline to 50%.

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