Chapter

The Concept of Male Reproductive Anatomy

Oyovwi Mega Obukohwo, Nwangwa Eze Kingsley, Rotu Arientare Rume and Emojevwe Victor

Abstract

The human reproductive system is made up of the primary and secondary organs, which helps to enhances reproduction. The male reproductive system is designed to produce male gametes and convey them to the female reproductive tract through the use of supportive fluids and testosterone synthesis. The paired testis (site of testosterone and sperm generation), scrotum (compartment for testis localisation), epididymis, vas deferens, seminal vesicles, prostate gland, bulbourethral gland, ejaculatory duct, urethra, and penis are the parts of the male reproductive system. The auxiliary organs aid in the maturation and transportation of sperm. Semen is made up of sperm and the secretions of the seminal vesicles, prostate, and bulbourethral glands (the ejaculate). Ejaculate is delivered to the female reproduc¬tive tract by the penis and urethra. The anatomy, embryology and functions of the male reproductive system are discussed in this chapter.

Keywords: AMH, TDF, SRY, SF1, DHT etc.

1. Introduction

Reproduction refers to the production of new offspring, also known as breeding in animals. It includes a set of physiological processes (usually) that take place in the female reproductive system with the association of behaviors and anatomical structures that are necessary in order to ensure the birth of the next generation of human, domestic, wild, and laboratory vertebrate organisms. Although these processes take place within the female's system, it is as a means of the fusion of haploid gametes each from male (sperm cell) and female (ovum) termed, fertilization in vertebrates. Testes, ductus deferens, epididymis, accessory glands, and penis make up the male reproductive system [1].

The males' reproductive system functions mainly in the production, nourishment and temporary storage of male gametes (spermatozoa), which is produced via spermatogenesis. It produces androgens and estrogen through steroidogenesis [1] and very importantly, connected to the organ of copulation (penis) which serves to introduce semen containing spermatozoa into the female genital system via mating.

2. Embryology of the reproductive system

The primordial germ cells have shifted from their previous extra embryonic position to the gonadal ridges by the six weeks of development in both sexes,

where they are surrounded by the sex cords to form a pair of primitive gonads. The forming gonad, whether chromosomally XX or XY, is potential until this point. The current theory is that the development of an ovary or testis is determined by the synchronized action of a series of genes that contribute to the development of the ovary when there is no Y chromosome or there is no Y testicular development. Unless a gene on the shooting arm of the Y named TDF (testis defined factor) acts as a switch, the ovarian pathway is followed, diverting development into the male pathway.

One of the leading current concerns in medical genetics is the search for the main testis-determined gene. The medullary tissue forms traditional testes with seminiferous tubules and Legdig cells in the presence of the Y chromosome that become capable of androgen secretion under the stimulation of human chorionic gonadotropin (HCG) from the placenta. Spermatogonia, produced by 200 or more successive mitoses from the primordial germ cells, forms the walls of the seminiferous tubules along with the supporting sertus cells. The gonad, by default, produces an ovary if no Y chromosome is present; the cortex develops, the medulla regresses, and oogonia starts to develop within follicles. Oogonia is obtained from primitive germ cells by a sequence of approximately 30 mitoses, less than the number necessary for spermatogenesis.

Oogonia joins meiosis 1 at about the end of the third month, but this process is interrupted at a point called dictyotene, in which the cell persists until ovulation happens several years later. Many of the oogonia degenerate before birth, and during the 30 years or so of sexual maturity of the female, only about 400 mature into ovas. Thickenings in the ridges suggest the developing genital ducts, the mesonephric (formerly called Wolffian) and paramesonephric (formerly called mellerian) ducts, while the primordial germ cells are migrating to the genital ridges. In the male, androgen is released by the Legdig cells of the fetal testes, which stimulates the mesonephric ducts to form the male genital ducts, and Sertoli cells produce a hormone that suppresses paramesonephric duct formation. The mesonephric ducts regress in the female (or in the non-gonadic embryo) and the paramesonephric ducts develop into the female duct system. The outer genitals consist of a genital tubercle, paired labio scrotal swellings and paired urethra folds in the early embryo. Under the influence of androgens, male external genitals develop from

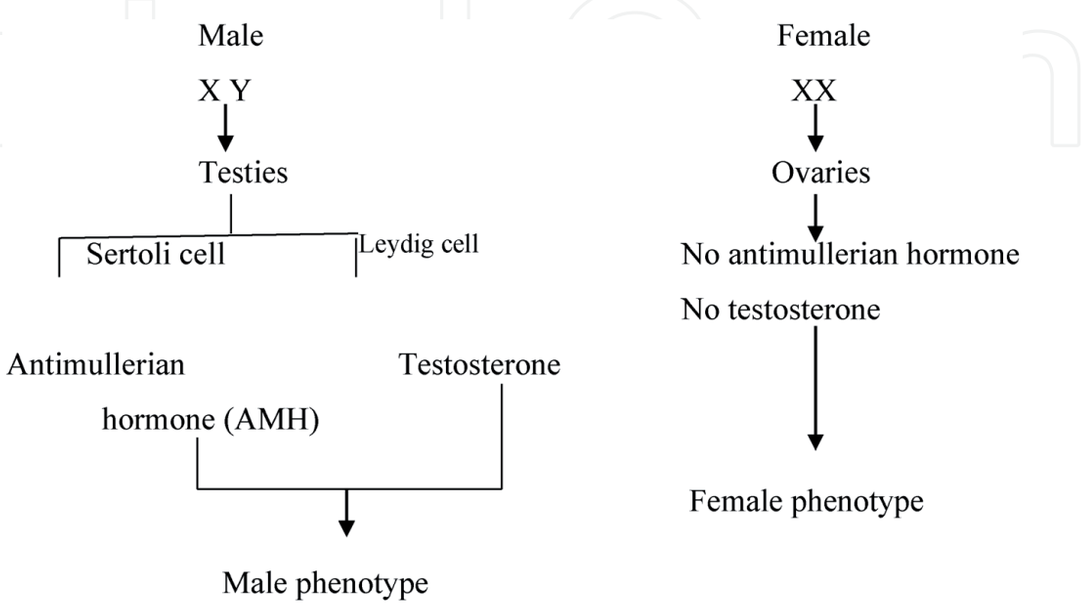

Figure 1.
Sexual differentiation in male and female.

this undifferentiated state or, in the absence of a testis, female external genitals are produced regardless of whether an ovary is present. The male and the female phenotype is as discuss below (**Figure 1**).

3. Male phenotype

- Fetal testicular cells secrete ample testosterone to increase blood concentrations to the same degree as those seen in adult males. Accumulation of testosterone is increased by an additional influence of the gene product TDF gene or SRY (sex determining region of the Y chromosome), which inhibits aromatase production and prevents the conversion of testosterone to estrogens. Testosterone promotes the growth and differentiation of the wolffian ducts that develop into the internal male genital tracts.

- Sertoli cells in the newly differentiated seminiferous tubule secrete a glycoprotein called antimullerian hormone (AMH) under the influence of the SRY gene product and various transcription factors, inducing apoptosis of tubular epithelial cells and atrophy or reabsorption of the mullerian ducts (which would have become the female internal genital tract).

- The primitive structures that give rise to the outside genitalia in both sexes are the urogenital sinus and genital tubarcle. Masculanization of these structures relies on the secretion of testosterone by the fetal testis to form the penis, scrotum and prostate gland. Those structures grow into the female external genitalia unless stimulated by androgen. Differentiation is incomplete when there is insufficient androgen in male embryos or too much androgen in female embryos and the external genitals are unclear. Male external genitalia distinction relies on dilydrotestosterone rather than testosterone.

4. Female phenotype

- Estrogen is secreted by the ovaries in gonadal females but not by testosterone antimullerian hormone.

- Wolffian ducts cannot distinguish without testosterone.

- Mullerian is not suppressed without antimullerian ducts and thus develops into the female internal genital tract.

5. Male reproductive system

The human male reproductive system is a collection of organs that contribute to the reproductive process situated outside the body and around a male's pelvic region. The key direct function of the male reproductive system is to supply the ovum for fertilization by the male gamete or spermatozoa. The male reproductive system is divided into four main compartments (as indicated in **Figure 2**):

1. The testis.

2. Accessory ducts: This includes Epidydimis, Vas deferens, Ejaculatory Duct.

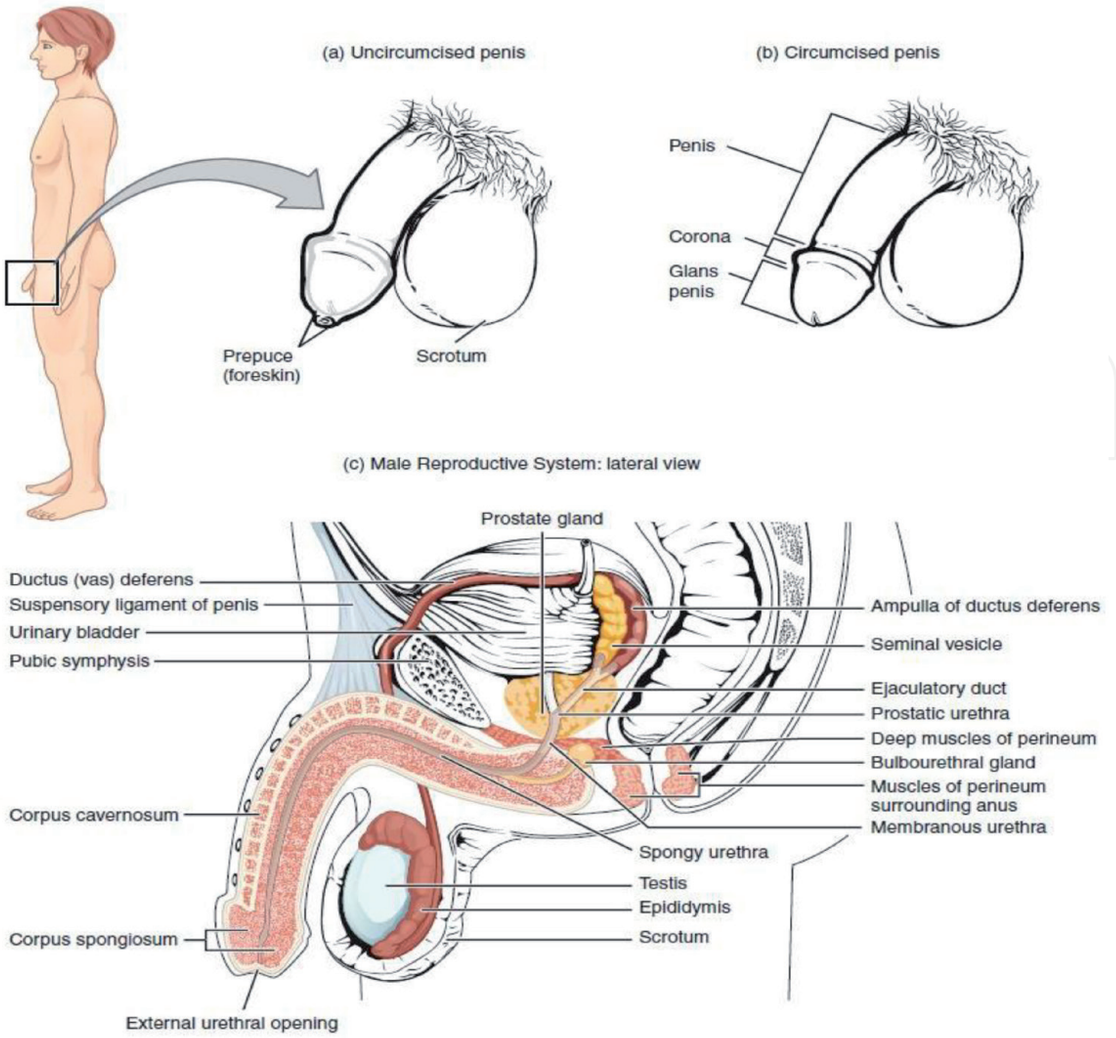

Figure 2.
Typical structure of the male reproductive system.

3. Accessory glands: Accessory glands are internal reproductive organs which supply fluids that nourish the sperm cells and lubricate the duct system. They are the seminal vesicles, the the bulbourethral glands, and the prostate glands (Cowper glands).

4. Supporting structures which include the scrotum and the penis.

In mammals, paired testes, epididymides, ductus deferens, accessory sex glands and penis are part of the male reproductive system. Tests perform two major roles that are very crucial for life perpetuation, spermatogenesis and steroidogenesis [2]. Within the seminiferous tubules of the testis, spermatogenesis or spermatozoa development takes place and steroidogenesis or testosterone synthesis occurs within the interstitial compartment. Spermatogenesis takes place within the stratified epithelium in the seminiferous tubules, while testosterone production takes place inside the Leydig cells that are spread between the seminiferous tubules in a vascular, loose connective tissue in the interstitial compartment [3]. In determining male secondary sexual characteristics, sperm development and fertility, testosterone, developed by the Leydig testis cells, plays an important role [4].

Epididymis is a single, long and extremely convoluted duct that connects the vas deferens (a coiled duct that connects epididymis to the ejaculatory duct) to the testicular efferent ducts. In the transport and storage of testicular spermatozoa,

epididymis plays an significant role. Epididymis is categorized in most mammals into three distinct regions on the basis of its gross morphology; caput or head, corpus or body and region of cauda or tail. The area of the corpus is thinner and it joins the larger segments, caput and cauda. There is an additional canal in reptiles between the testes and the epididymis head, which receives the numerous efferent ducts. However, in both birds and mammals, this is missing [5]. A pseudostratified epithelium surrounds the epididymis. The epithelium is divided from the connective tissue wall, which has smooth muscle cells, by a basement membrane. In the epithelium, the main cell types are:

Principal cells: Columnar cells, with much of the epithelium in the basal cells. They also have non-motile stereo cilia, which are long and branching in the head region and shorter in the tail region, extending from the lumen to the basal lamina. [5]. Carnitine, sialic acid, glycoproteins, and ghycerylphosphorylchlorine are also secreted into the lumen as well.

Basal cells: shorter, pyrmid-shaped cells that, before their apical surfaces enter the lumen, touch the basal laminal but taper off [5]. These are known to be undifferentiated primary cell precursors.

Apical cells: These are predominantly located in the head region [5]

Intraepithilial lymphocytes: distributed throughout the tissues.

Clear cell: Predominant in the tail region. The clear cells in the rat epididymis are subdivided into two types and are concerned with the secretion of either glycoproteins or glylipoproteins. The blood epididymal barrier, constituted by the zona occludens of the functional complexes at the apical ends of principal cells [5] also appears to play a vital role in maintaining a physiological millieu in the epididymal canal suitable for sperm maturation.

Spermatozoa formed in the testis are functionally immature and as they migrate through the epididymis they attain functional maturity. Epididymal epithelium absorptive and secretory behavior helps to maintain a particular intraluminal environment that is necessary for sperm maturation [6]. They transfer into the vas deferens, where it is processed before ejaculation, as spermatozoa mature. Sperm flows from the lower portion of the epididymis (which acts as a storage reservoir) during ejaculation. They have not been activated by prostate gland products and are unable to swim, but are transported inside the vas deferens by the peristaltic action of muscle layers and are combined before ejaculation with the diluting fluids of the seminal vessels and other accessory glands. There are some apical variations in the epithelial cells of the epididymis that are sometimes referred to as stereo cillia, as they appear like cilia under the light microscope. However, as electron microscopy has shown that they are more similar to microvilli structurally and functionally, some now refer to them as stereovilli. Stored sperm remain fertile for 40 to 60 days, but they disintegrate and the epididymis resorbs them if they become too mature without being ejaculated. A thin tube approximately 43.2 centimeters long that begins from the epididymis to the pelvic cavity is the vas deferens, also known as the sperm duct. In order to transfer sperm, there are two ducts which connect the left and right epididymis to the ejaculatory ducts. Each tube (in humans is about 30 centimeters long and surrounded by smooth muscle.

The smooth muscle in the walls of the vas deferens contract reflexively during ejaculation, thereby propelling the sperm forward. This is often referred to as peristalsis. The sperm is passed into the urethra from the vas deferens, gathering secretions from the male accessory sex glands, such as the seminal vesicles, the prostate gland, and the bulbourethral glands that make up the majority of the semen. The rate of fluid transfer by the vas deferens is not known in humans. The testes are brought up close to the abdomen just before ejaculation, and fluid is rapidly transferred through the vas deferens into the area of the ejaculatory ducts and then into

the prostatic urethra. Intravasal fluid is transported back into the epididymis after ejaculation and even sometimes into the seminal vesicles [7]. Videoradiography during ejaculation after vasography has recorded the retrograde transport of sperm to the seminal vesicles. For some men after vasectomy, the return of sperm to the seminal vesicles after ejaculation can help to explain the prolonged presence of sperm in the ejaculate. The vas deferens can be obstructed or entirely missing, causing male infertility (the latter a possible characteristic of cystic fibrosis). Testicular sperm extraction (TESE), extracting sperm cells straight from the testicles, will resolve it. Seminal vesicles (glandulae vesiculosae) or vesicular glands are paired sac-like or simple tubular glands attached near the base of the bladder to the vas deferens [8]. They are glands of approximately 10 to 15 cm in length that are extremely convoluted [8, 9]. Tubular alveoli with active secretary epithelium are composed of seminal vesicles. The inner surface of the seminal vesicles consists of tubules that form irregular diverticula and are thrown into an intricate system of folds. The main portion of seminal fluid, the fluid that carries spermatozoa, is around 50–80% of the seminal vesicle secretions [10]. A large proportion of the substance that eventually becomes semen is secreted by the seminal vesicles. Dead epithelial cell lipofuscin granules give the scretion its yellowish hue.

Seminal vesicles are highly androgen dependent and contain prostaglandins, proteins, amino acids, citrate, fructose, flavins, enzymes, vitamin C and phosphoryl choline and their secretions are alkaline.

When processed in semen in the laboratory, the high fructose content provides nutrient energy for the spermatozoa. Seminal vesicle secretions enhance sperm capacity, increase sperm stability and help prevent sperm immune response in the female reproductive tract [11]. Alkaline secretion helps to neutralize the vaginal tract ‘s acidity, thus increasing sperm lifespan [8]. Secretion of the seminal vesicle in semen also tends to improve sperm chromatin stability. In addition, from the fructose found in the seminal secretion, spermatozoa acquire their key energy source.

Prostate is a fibromuscular elastic, donut shaped gland covering the urethra inferior to or at the urinary bladder neck [6]. A thin vascularized fibroelastic tissue layer [6] encapsulates the prostate. It is roughly 2 × 3 × 4 cm in diameter and weighs approximately 20 g. From these endodermal cells, the glandular epithelium of the prostate differentiates and the related mesenchyme differentiates into the prostate ‘s thick, solid and smooth muscle [12]. The primary function of the prostate is to secrete milky fluid containing proteins and hormones that are part of the seminal fluid produced by seminal vesicles. The prostate fluid is rich in phosphate acids, citric acid, fibrinolysin, antigen specific to the prostate, amylase, callikrein, zinc and calcium, which are essential for spermatozoa to function normally. The secretions of the prostate make up 30 percent of the amount of seminal fluid. The prostate is an androgensensitive organ and relies on the presence or absence of circulating androgens for growth and regression.

Two small glands situated on the sides of the urethra just below the prostate gland are the bulbourethral glands, often referred to as Cowper glands. These glands create a transparent, slippery fluid that directly empties the urethra. They are homologous in female to the Bartholin glands [13]. Compound tubulo-alveolar glands, each about the size of a pea in humans, are the bulbourethral glands [13]. They are made of several lobules with a fibrous covering kept together. Each lobule consists of a number of acini, lined by columnar epithelial cells, opening into a duct that forms a single excretory duct joining the ducts of other lobules. This duct is about 2.5 cm long and opens up at the base of the penis into the urethra. With advancing age, the glands decline steadily in size. Each gland causes a clear, salty, viscous secretion known as pre-ejaculate during sexual arousal. This fluid helps to lubricate the urethra to move through spermatozoa, neutralizing traces of urethra

acidicurine [7], and helps to flush out any residual urine or foreign matter. Since there is no sperm in the preejaculate, it is possible for this fluid to absorb sperm, stay in the urethral bulb from previous ejaculations, and conduct it until the next ejaculation. Some amount of prostate specific antigen (PSA) is also produced by the Cowper's gland, and Cowper's tumors can increase PSA to a level that makes prostate cancer suspected [7].

6. Fundamental component of male reproductive anatomy

The male reproductive anatomy is divided into five components which are very fundamental to human reproductive health. These include;

1. **Gonadal development:** At eight weeks of gestation (perios of preganacy), Y chromosomes synthesis of H-Y antigen occurs. In the male, this H-Y antigen causes undifferentiated sex glands to devlop into testes while in female, lack of H-Y antigen causes undifferentiated sex glands to develop into ovaries.

2. **Duct development:** In this case, both sexes start out with two system such as mullerian ducts which develops into fallopian tubes, uterus, inner vagina; Wolffian duct which develops into epididymis, vas differens and seminal vesicles. In the developmental processes, the male fetal leydig cells of the testes secretes sufficient testosterone as those seen in aduct men while the sertoli cells of the testes secretes the antimullerian hormone (AMH). The testosterone (androgen) so secreted is responsible for male sex differentiation during embryogenesis (9th and 13th weeks of pregnancy) and its accumulation is enhanced by an additional effect of the testes determining factor (TDF) gene or *sex determining region of the Y chromosome* (*SRY*) gene product which blocks the expression of aromatase, thus preventing the conversion of testosterone to estrogen. The testosterone thereby stimulate the growth and differentiation of the wolffian ducts, which develop into the male internal genital tracts. However, under the influence of the SRY gene product and specific transcription factors, sertoli cells in newly differentiated seminiferious tubule secretes a glycoprotein called antimullerian hormone (AMH), which causes apoptosis of tubular epithelia cells and atrophy or reabsorption of the mullerian ducts 9 (Which would have become the female internal genital tract). Notwithstanding, the downstream of genes that makes up the *SRY* gene product includes the SOX9 and steriodogenesis factor (SF1). These classified products stimulate the differentiation of sertoli cells and leydigs in the testes and also in the formation of tunica albuginea.

3. **External genital development:** There are two primitive structures of the reproductive anatomy that give rise to the external genitalia in both sexes. This includes the genital tubercle and the Urogenial sinus. However, the masculinisation of these structures to form the penis, scrotum and prostate gland depends on the secretion of testosterone by the fetal testes unless stimulated by androgens; these structures develop into the female external genitalia (clitoris, labia, vagina opening etc). When there is insufficient androgen in male embryos or too much androgen in female embryos, differentiation is incomplete and the external genitalia are ambiguous. Differentiation of the masculine external genitalia depends on the dehydrotesterone rather than testosterone. The mechanism through which this occur is via the conversion of testosterone into dihydrotestosterone (DHT) by an enzyme called 5α-reductase

$$\text{testosterone} \xrightarrow{5?\text{alpha reductase}} \text{dihydrotestosterone} \quad (1)$$

4. **Brain development:** Sex hormone such as testosterone and estradiol exert their influence during development of the fetus. Testosterone secreted into the blood reaches the brain and gets converted into estradiol by an enzyme called Aromatase. The estradiol is what actually help in the masculanization of the human brain. In the female the estradiol secreyed by the ovaries binds to a particular protein called α-fetoprotein and therefore prevent its entering into the brain to protect the female brain from being masculanized by estradiol.

$$\text{testosterone} \xrightarrow{\text{Aromatase}} \text{estradiol} \quad (2)$$

5. **Neural development:** Neural development is one of the earliest systems to begin and the last to be completed after birth. This development generates the most complex structure within the embryo and the long time period of development means in utero insult during pregnancy may have consequences to development of the nervous system. The early central nervous system begins as a simple neural plate that folds to form a neural groove and then neural tube. This early neural is initially open initially at each end forming the neuropores. Failure of these opening to close contributes a major class of neural abnormalities (neural tube defects). Within the neural tube stem cells generate the 2 major classes of cells that make the majority of the nervous system: neurons and glia. Both these classes of cells differentiate into many different types generated with highly specialized functions and shapes.

7. The physio-anatomy of the testes

In adult males, the testis is a strong oval-shaped male gonad, about 4 cm long and 2.5 cm wide in size. Testes are located in the scrotum that regulates its temperature below the normal body temperature to approximately 23°C [1, 14]. There are normally two testis, each weighing about 11–17 g with the right one usually slightly larger and heavier than the left one weighing about 963 + 0 [1]. A testis (singular) is surrounded by a saccular extension, called tunica vaginalis, of the peritoneum inside the scrotum. Underneath the tunica vaginalis, Tunica albuginea is contained and forms the testis' white fibrous capsule [8]. Tunica albuginea is subsequently thickened, assembling the testis mediastinum from which the fibrous septa penetrates the testis and divides into about 200 to 300 wedge-shaped lobules.

There are one to four tightly coiled seminiferous tubules in each testicular lobule where sperm is produced [8]. Testis seminiferous tubules consist of two main types of cells, the germ cells and the supporting cells or Sertoli cells. In the seminiferous epithelium, the Sertoli cells are uniformly distributed along with developing germ cells and they nourish the germ cells during their growth. A basal lamina, which includes peritubular myoid cells, lines the seminiferous tubule. Myoid cells constitute a barrier of partial permeability by preventing large molecules from entering the germinal epithelium. The close and gap junctions that exist between the adjacent Sertoli cells, however, form the main exclusion barrier. The seminiferous epithelium is divided into two distinct compartments by these inter-Sertoli cell junctions, called the blood testis barrier: the basal and the adluminal compartments. Spermatogonia and early spermatocytes live in the basal compartment and are readily available for systemic circulation. The adluminal compartment is sequestered from the systemic circulation, containing meiotic and post-meiotic spermatocytes, and is only exposed

to the components transported by Sertoli cells [9]. The undifferentiated spermatogonia that reside in the basal compartment of the seminiferous epithelium undergo a series of mitotic divisions during the process of spermatogenesis to form primary spermatocytes.

The primary spermatocyte is then moved to the adluminal compartment and this requires comprehensive restructuring of the inter-Sertoli closed junctions. The spermatocytes undergo two consecutive meiosis rounds in the adluminal compartment to form mature haploid spermatids. In addition to offering physical support to germ cells, Sertoli cells provide a special atmosphere in the adluminal compartment, which is responsible for transporting sperm from the testis to the epididymis by providing a specialized testis. Development factors and nutrients that are essential for the survival of germ cells are important functions of the testis [15]. Germ cell variables, on the other hand, also play an important role in regulating the behavior of the Sertoli cells. For successful spermatogenesis, the interactions between germ cells and Sertoli cells are important. The interstitial compartment of the testis are made of steroid-secreting Leydig cells, blood and lymphatic vessels, nerves, macrophages, fibroblasts and loose connective tissues. However, the principal cells of this compartment are the Leydig cells of interstitial.

8. Epithelial cells of the testes

8.1 Sertoli cells (also called substantial cells)

Sertoli cells are large, irregularly shaped somatic cells. Sertoli cells are bound by tight junctions to each other at their base. Sertoli cells, as shown by their close contact, are essential to the formation of germ cells. A Sertoli cell can be connected to as many as 6 to 12 spermatids. Sertoli cells assist in the spermiation process, where the final detachment of mature spermatozoa into the seminiferous tubule lumen takes place [16]. Excess cytoplasm resulting from the transition of spermatids to spermatozoa, as well as damaged germ cells, are also targeted and phagocytized by sertoli cells. Moreover, for germ cells, the Sertoli cells also provide structural support and nutrition, secreting fluid. In the seminiferous epithelium of adult rats, the columnar cells stretching from the basal to the luminal compartment are found to occupy a volume of approximately 17–19 percent. Sertoli cell secretes inhibin, which is a gonadal-origin nonsteroidal pituitary receptor [9]. The tight junctions around the circumference of each tubule that lead to the blood-testis barrier were created by a continuous layer of non-germinal Sertoli cells. Via the cytoplasm of Sertoli cells, molecules from the blood join germinal cells. A protein called androgen-binding protein is also secreted into the lumen of the seminiferous tubules by Sertoli cells. The Sertoli cell cytoplasm spreads from the periphery to the tubule lumen and envelops the developing germ cells. It helps to protect the seminiferous tubules from immune attack; on the surface of T lymphocytes, the Sertoli cells generate FAS ligand that binds to the FAS receptor. In this way, by inducing apoptosis of T lymphocytes, it avoids the immune attack of the developing sperm [3]. Sertoli cells refer to the testes' somatic cells, which are important for testes to develop and also for spermatogenesis. Via direct interaction and regulation of the environment inside the seminiferous tubules, these cells (Sertoli) promote the progression of germ cells to spermatozoa. The blood testes barrier (BTB), which is produced near the basement membrane by adjacent Sertoli cells, acts as a "gatekeeper" to prevent harmful substances from reaching germ cells, especially during postmeiotic spermatids. The BTB also divides the seminiferous epithelium into the basal and luminal (apical) compartments to allow the growth of postmeiotic spermatids,

namely spermiogenesis, to take place in the apical compartment behind the BTB in a specialized microenvironment. The BTB also contributes to the immune privilege status of the testis, at least in part, so that anti-sperm antibodies against antigens that are transiently expressed during spermatogenesis are not produced [10]. Sertoli cells have become incredibly difficult to remain morphologically stable because during the 14 phases of the epithelial cycle they have a continuously evolving, three dimensional relationship with growing germ cells. There have been many Sertoli cell functions identified, most of which are directly related to the production and movement of germ cells. These include 1) the provision of structural support; 2) the production of an impermeable and immunological barrier; 3) involvement in the movement and spermation of germ cells; 4) nutrition of germ cells through their secretory products [10].

8.2 Leydig cells (or interstitial cells of the leydig)

Leydig cells are polygonal in form and are the main type of cell inside the interstitial tissue where they are mostly located adjacent to the seminiferous tubules and blood vessels. Other cell types, such as fibroblasts, macrophages and a limited number of mast cells, are also present in the interstitial space, in addition to Leydig cells. The primary source of testosterone in the systemic circulation of males is the Leydig cells. The Leydig cell cytoplasm contains a lot of mitochondria, a granular endoplasmic reticulum, lipid droplets and occasionally some protein crystals [10]. Leydig cells do not have follicle stimulating hormone (FSH) receptors. Therefore their growth is influenced indirectly rather than directly by the FSH. FSH activates the Sertoli cell development growth stimulators, which in turn stimulated the growth of the Leydig cells that were growing. In addition, the proliferation of developing Leydig cells can also be stimulated by the androgens. However, proliferation and activity of these cells are reduced by the Estrogen receptors that are present in the Leydig cells. Leydig cells have LH receptors, and inducing androgen secretion through a cAMP-dependent mechanism is the main effect of the luteinizing hormone (LH). Testosterone is the primary product of Leydig cells, but dehydroepiandrosterone (DHEA) and androstenedione, two other androgens of less biological activity, are also a product of Leydig cells [17]. However, now that human testes live in the scrotum, they have adapted to this cooler climate and are unable to generate sperm at the 37°C core body temperature. There are three mechanisms in the scrotum to control test temperature:

Cremaster muscle: The cremaster muscle consists of strips that enmesh the spermatic cord of the internal abdominal obligue muscle. The cremaster contracts and pulls the testicles closer to the body when it is cold to keep them warm. The cremaster relaxes when it is warm and the testicles are suspended further from the body.

Darto muscle: A subcutaneous layer of smooth muscle is the darto muscle (tunica dartos). When it is cold, it, too, contracts, and the scrotum becomes taut and wrinkled. The scrotum 's teaching helps to keep the testes snugly against the warm body and decreases the scrotum's surface area, thus decreasing heat loss.

The pampiniform plexus is an extensive network of veins in the spermatic cord from the testes that surround the testicular artery. These converge as they pass through the inguinal canal to form the testicular vein, which emerges into the pelvic cavity from the canal. Warm arterial blood will heat the testicles and prevent spermatogenesis without the pampiniform plexus. However, by serving as a countercurrent heat exchanger, the pampiniform plexus avoids this. Such a process in the spermatic cord eliminates heat from the descending arterial blood, so this blood is 1.5c to 2.5c cooler than the core body temperature by the time it enters the testicles.

Most fish and amphibians do not have seminiferous tubules. The sperm is instead formed in the spherical form known as sperm ampullae. These are seasonal structures, which during the breeding season release their material and are then reabsorbed by the body. Fresh sperm ampullae begin to develop and ripen before the next breeding season. In higher vertebrates, with the same variety of cell types, the ampullae are otherwise virtually similar to the seminiferous tubules.

9. Testicular temperature regulation of testes

The testes perform best at temperature slightly lower than the core body temperature. At lower and higher temperatures, spermatogenesis is less effective [11]. This is possibly why the testicles are found outside of the body. To hold the tests at the optimum temperature, there are various mechanisms [11].

10. Testicular development

The germ cells migrate from the yolk sac to the genital ridge during the 3rd week of development after fertilization. In male embryos, testes develop from the genital ridges from the 4th to the 8th week, and primordial germ cells migrate from the wall of yolk sacs to the gonads. The Leydig cells of the developing testis are starting to evolve under the influence of human chorionic gonadotropin. Testosterone is secreted. The labioscrotal swellings merge at around week 9 to form the scrotum. In order to form the epididymis, vas deferens and seminal vesicles, testosterone also induces mesonephric (Wolfian) duct production [11]. The gubernaculum shortens and pushes the testes, the deferent duct, and its vessels downward between the 7th and the 12th week. The testes remain in the area of the inguinal canal between the 3rd and 7th months so that they may enter into it. Under the control of the androgen hormone, they enter the scrotum at roughly the time of birth. The vaginal process appears as an outpouching of the parietal peritoneum at about 13 weeks of development. The testis stays for 10 to 12 weeks at the beginning of the vaginal process, the internal inguinal ring. This patent herniation mechanism is at least partially dependent on the musculature of the abdominal wall to produce an elevated intra-abdominal input. The patent processus vaginalis does not advance through the inguinal canal if the abdominal muscles are unable to raise intra abdominal pressure, and the testis may not descend into the scrotum. Each testis is formed from three sources: First, in the 7th week of intrauterine life, the production of testes becomes apparent. The medulla of the undifferentiated genital ridge, and the cortex of which regresses, is the base of each testis. The proliferation of coelomic mesothelium covering the medial surface of the mesonephric ridge forms the genital ridge. From the proliferation of the endoderm of the dorsal wall of the hind intestine, primitive sex cells or gonocytes are produced and appear in the genital ridge through active dorsal and sephalic migration between the primitive dorsal mesentery layers of the gut. From the surface of the genital ridge, multiple solid cellular testis cords emerge and project into its interior. Within the testis cords, primitive sex cells are inserted. A cellular plexus and the rete cord, which is located near the blind ends of the mesonephric tubules, are connected by the inner ends of the testis cords to form. Invading the genital ridge, the mesenchymal cells of the mesonephrc ridge spread under the surface, later disconnecting the peripheral ends of the testis cords from the surface. Tunica albuginea forms this portion of the invaded cells. Some of the mesenchymal cells between the testis cords project inwards and persist as a septa testis, and the interstitial cells are formed from the

mesenchymal cells that are detached. The testis cords and rete cords are canalized during the 7th month of intrauterine life and form the seminiferous tubules and the rete testis, respectively. Secondly, efferent testis ductules are created to form the proximal 12–15 of the persistent menosephric tubules that form secondary ties with the rete testis. Epididymis and vas deferens are formed from the mesonephric duct in the third channel. The epididymis precedes the testis into the processus vaginalis at 26 to 36 weeks of growth. These structures descend into the scrotum and are fused with the scrotum 's posterior layers, providing an anchor that prevents the movement of the testis. The vaginal process closes at 37 to 40 weeks (full term), preventing all contact between the peritoneum and the inguinal canal or scrotum. A proximal remnant (or more than one remnant) may persist as a small appendage, the appendix epididymis, as the mesonephric duct evolves into the epididymis. Most frequently, this tissue is connected to the caput (most proximal and cephalad portion) epididymis. Such an appendix can sometimes twist and become inflamed. The paramesonephric structures (Müllerian) simultaneously regress under the influence of the Müllerian inhibiting substance (MIS) secreted from the developing testis by the Sertoli cells.

11. Blood neurovascular supply of the testes

The survival of the cells in target organs depends on the delivery of nutrient-rich, oxygenated blood and the removal of metabolic waste. In addition, neural signaling is required for most organs to perform specific duties. In terms of the testes, each of the spherical reproductive organs is supplied by a rather basic bilateral neurovascular network. The extensive vascular supply of the testes serves a variety of functions in addition to supplying oxygen, nutrients, and eliminating waste from the area. This is due to the organs' temperature-sensitive functionality, as well as their dual roles as endocrine glands and reproductive organs.

11.1 Arterial supply

The testicular arteries are a pair of arterial structures on either side of the abdominal aorta that branch straight from it. They arise at the level of the base of the L1-L2 vertebra from the anterolateral surface of the massive artery caudal to the renal vessels. The right testicular artery travels inferolaterally, medial to the right testicular vein and the proximal section of the right ureter, after crossing the inferior vena cava anteriorly. The artery crosses the ureter anteriorly and continues its inferior path on the body of the psoas major. The left testicular artery runs medial to the testicular vein on the left side.

In comparison to the right testicular artery, it has a more vertical proximal path. It also passes anteriorly through the left ureter. The common and external iliac vessels are served by both the left and right testicular arteries. Only when they enter the inguinal canal via the deep inguinal ring do they cross the external iliac vessels (at which point the external iliac vessels become the femoral vessels). They run lateral to the vas (ductus) deferens and its artery within the canal. The testicular artery gives a branch to the epididymis after it enters the scrotum before bifurcating into lateral and medial branches. These two branches further split to perforate the organ's material directly. There are also three noteworthy vascular anastomotic connections formed with the testicular artery. Each of the cremasteric arteries originates on the anteromedial side of its corresponding inferior epigastric artery (branch of the external iliac artery) and forms an anastomosis with the testicular artery as it passes through the spermatic cord (in the inguinal canal). The inferior vesical artery, which

is supplied by the anterior segment of the internal iliac artery, gives birth to the ductus deferens artery. It also connects to the testicular artery via an anastomosis.

11.2 Venous drainage

Around the testicular artery, a venous plexus is formed by a dense network of connected veins. The pampiniform plexus is a network that travels cranially with cooler, deoxygenated, nutrient-poor blood. The plexus' branches continue to consolidate as it leaves the scrotum and enters the spermatic cord, eventually becoming four branches. Two branches join at the deep inguinal ring, on either side of the testicular artery. As a result, each testicular artery has two valvular testicular veins that run alongside it to their drainage locations. The two veins then merge to produce a single testicular vein that flows laterally alongside the testicular artery across the psoas muscles anterior surface. The neurovascular supply to the testes is definitely not a light topic, but interactive anatomy can definitely make it easier to study. Each testicular vein crosses its corresponding ureter on the front surface of the psoas muscles about the level of the L3 vertebra. The left testicular vein then travels almost vertically to pierce the left renal vein, passing between the testicular artery on the medial side and the ureter on the lateral side. The right testicular vein, on the other hand, goes practically vertically on the left side, then obliquely on the right side (also with the ureter lateral and the testicular artery medial) before draining straight into the inferior vena cava.

11.3 Innervation

The sympathetic nerve fibers that innervate the testes come from the T10 spinal segment. The lesser splanchnic nerves carry them to the celiac ganglion, where they synapse. The testicular artery is then followed along its route to its place of innervation by the post-ganglionic fibers. Sensory root fibers follow a similar path, passing information to the T10 segment's dorsal root ganglion cells. The testes' tunica vaginalis receives sensory innervation from the genital branch (L2) of the genitofemoral nerve (L1, L2) of the lumbar plexus.

11.4 Lymphatic drainage

The testes are the only structures in the male external genitalia that do not leak into the inguinal lymph nodes. Its lymphatics follow the path of the testicular veins until they reach the para-aortic lymph nodes at the L2 vertebral level.

12. Male reproductive functions

The male reproductive organs are specialized for the following functions:

- Spermatogenic function; for sperm production,
- maintainance and transport of sperm (the male reproductive cells and protective fluid semen)
- Sperm Discharge function; for discharging sperm inside the female reproductive tract.
- Hormonal function; for producing and secreting male sex hormones like testosterone.

12.1 Spermatogenic functions

12.1.1 Semen

Sperm cells and secretions of the seminal vesicles, prostate, Cowper's gland and, perhaps, urothral glands are included in the fluid that is ejaculated in time of organism. It has a fixed gravity (1.028), a bright, opalescent fluid and a PH of 7.35–7.50 of it. For each ejaculation, the approximate volume of semen is 2.5 to 3.5 ml after several days of consistency [18]. The seminal vesicles contain the bulk of this secretion or fluid (about 60 percent), and the prostate gland contributes the remainder (about 40 percent). Components of seminal vesicle secretion include fructose, phosphorylcholine, ergothioneine, ascorbic acid, flavins and prostaglandins, while spermine, citric acid, cholesterol phospholipids, fibrinolysis, fibrinogenase, zinc, and acid phosphate are components of prostate secretion. Semen is also known to contain buffers (phosphate and bicarbonate) and hyaluronidase. The volume of the semen containing sperm decreases rapidly with repeated ejaculation. The sperm in human males ranges between 60 and 150million per millimeter in the ejaculated semen (which accounts for about 20% of the semen volume), even though it takes just only one sperm to fertilize the ovum. Human sperm moves through the female genital tract at a rate of about 3 nm/min and reaches the uterine tubes 30–60 minutes after copulation (sexual intercourse).

A sperm concentration below about 10 millimeter is termed oligospemia, and is associated with decreased fertility. Various factors, including heat from a sauna or hot tub, various prescription medications, lead and assenic poisoning and illicit drugs such as marijuana, cocaine and anabolic steroids, may cause oligospermia. In addition to low sperm counts, some men and women have antibodies against sperm antigens as a cause of infertility (this is very common in men with vasectomy). These antibodies do not tend to influence well being; however they decrease fertility. Secretion from the epididgmins, seminal vesicles, prostate gland and bulbourethral glands along with sperm composition makes up just 1 percent of the semen or seminal fluidsperm, the rest is made up of accessory gland fluids. Semen is over 90% water but contains many substance, most notably energy rich fructose, the known vitamins which include Vitamins C and inositol and the trace elements which include Calcium, Zinc, Magnesinm, copper and sulfur. Semen also contains the highest concentration of prostaglandin in the body. The consistency of semen varies from thick and viscous to almost watery fluid. Primordial germ cells are the first cells destined to become semen. They are produced in the sac of the yolk, a membrane connected with the embryo that is developing. They move into the embryo itself in the fifth to sixth week of development and colonize the seminiferous tubule, beyond the blood-test barrier (BTB). By mitosis, spermatogonia multiplies, producing two types of type A daughter cells and type B spermatogonia. Type A cells remain beyond the barrier of blood tests and begin to multiply from puberty until death. Therefore, men never exhaust their supply of gametes and typically remain fertile in old age. Spermatogonia type B migrates closer to the lumen of the tubule and differentiates into slightly large cells known as primary spermatocytes. These cells must pass through the membrane of the blood testicles and travel into the tubule lumen.

The tight junction between two sustentacular cells is usually dismantled ahead of the primary spermatocyte, while a new tight junction is forms on the other side. The primary spermatocyte undergoes mitosis 1, which gives rise to two equal- size, haploid secondary spermatocytes. Each of these undergoes meiosis II, dividing into two spermatid or a total of four for each spermatogomia. Each stage is a little bit closer to the tubule than the previousr stages. All stages on the luminal side of the blood testies

barrier are bound to the sustentacular cells by the tight junctions and gap junction and are closely enveloped in tendrils of the sustentacular cells. Throughout this meiotic division, the daughter cell, remain connected to each other by means of narrow cytoplasmic bridges and do not completely separated. Hence, the rest of spermatogenesis is called spermiogenesis. It does not involve further cell division, but a gradual transformation of each spermatid (immature sperm) into a matured spermatozoon.

12.1.2 Spermatogenesis

The cellular divisions and developmental changes that occur within the seminiferous tubules of the testes are termed spermatogenesis, and it consists of two major parts (**Figure 3**). In part 1, spermatocytogenesis occurs in which it starts with spermatogonia which involve mitotic division of stem cells to form spermatocytes that take place in the early stage, followed by meiosis where the number of chromosomes is reduced to form spermatids. In part 2, spermiogenesis occurs in which the spermatids are transformed in regards to metamorphic changes to sperm [19]. Spermatogenesis is a highly organized but complex process and it normally continuous throughout life [20]. The above description categories spermatogenesis into

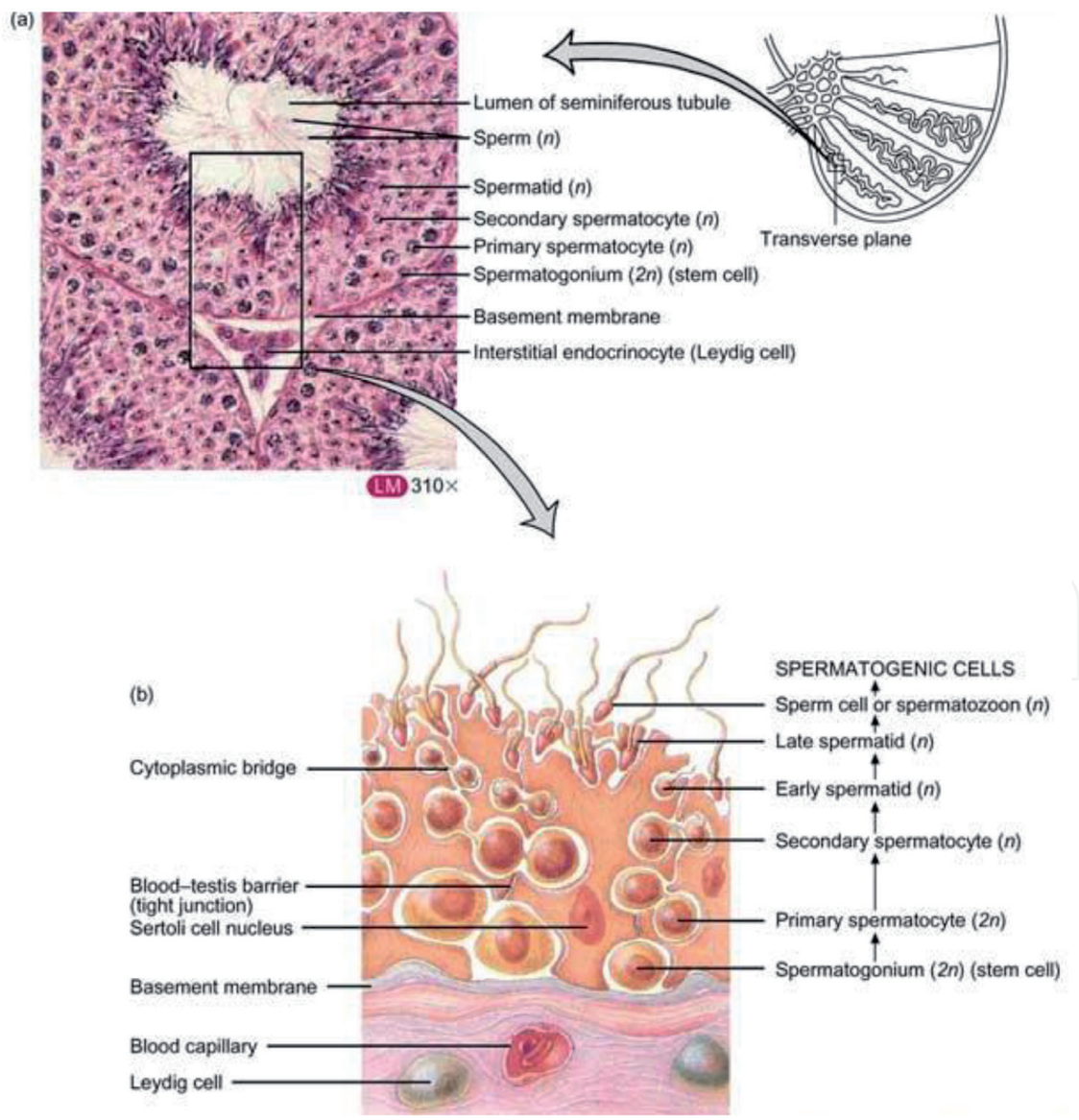

Figure 3.
Showing the Microscopic anatomy of the seminiferous tubules.

major three divisions; spermatocytogenesis, meiosis and spermiogenesis respectively. The process begins from spermatogonial stem cells that are found on the basement membrane of the seminiferous tubules, which usually proliferate for self-renewal and reproduced to a progeny of the differentiating spermatogenic cells such as (1) primary spermatocytes, (2) secondary spermatocytes, (3) spermatids and (4) spermatozoa [21]. The spermatogonia are duplicated mitotic division, one of the duplicate member called primary spermatocyte undergoes meiotic division in order to form secondary spermatocytes. When the spermatogonia (which are a diploid primary spermatocyte) complete the first meiosis, two daughter haploid cells will be produced, a result which is known as secondary spermatocytes. By the end of the second (2nd) meiotic cell division, each of the two (2) secondary spermatocytes formed two (2) haploid spermatids [3]. In the beginning, the spermatids will still pose the normal characteristics of epithelioid cells, however, they differentiate and elongate into matured spermatozoa. A matured spermatozoon comprises of a tail and a head which contains a condensed nuclear material, a thin cytoplasm and a surrounding membranous layer [22]. The major features of spermiogenesis includes the formation of the acrosome derived from the Golgi apparatus, condensation, elongation of the nucleus, formation of the flagellum and extensive shedding of the cytoplasm of the spermiated, spermatozoa consists of a head, middle piece and tail (**Figure 4**) [23].

12.1.3 Structure of mature spermatozoa and its membrane

The sperm consists of a head, a centerpiece, and a tail. The head comprises nuclei surrounded by an acrosome of tightly packed chromatin. The acrosome

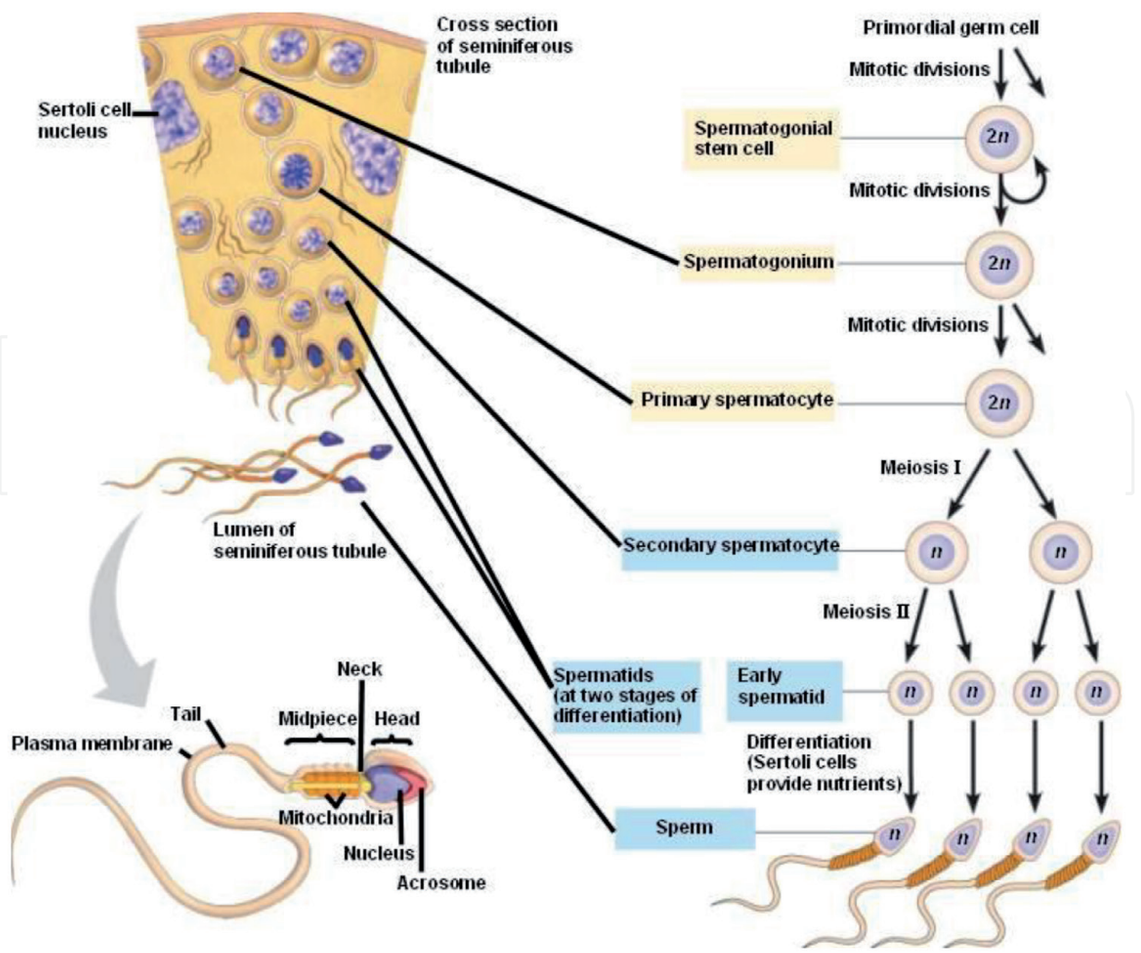

Figure 4.
Showing an overview of spermatogenesis (adapted from bio1151.nicerweb.com).

includes enzymes that are used for oocyte penetration. A special arrangement of mitochondria spiraling around the middle part of the sperm is used for the production of ATP for the passage of the sperm through the female reproductive tract. Spermatozoa are driven by the tail or flagellum of the spermatozoa. Axoneme is the microtubule and related protein bundle that forms the center of the flagellum of eukaryotic sperm and is responsible for movement. Sperm cells and secretions of the seminal vesicles, prostate, Cowper's gland and, perhaps, urothral glands are included in the fluid that is ejaculated in time of organism.

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During sperm passage through the epididymis, spermatozoa collected or derived from the testis do not show progressive motility or capacitate, but developed these abilities [24]. Dynamic morphological and metabolic changes leading to the development of active sperm capable of fertilizing the ovum are referred to as sperm maturation. These processes are called maturation. The completion of nuclear condensation and changes in the distribution and expression of molecules on the surface of the sperm are all part of sperm maturational changes. Phospholipid hydroperoxide glutathione peroxidase (GPx4) may be used as an alternative reductant to glutathione in the sperm nucleus by the thiol groups in nuclear proteins. ROS lipid peroxide generation could provide GPx4 with a substrate to drive the oxidation of these proteins and promote nuclear condensation, while providing protection against oxidative DNA damage at the same time [25]. By enhancing cyclic adenosine monophosphate (cAMP) synthesis and protein phosphorylation at the time of ejaculation, reactive oxygen species could also be involved in motility initiation [26]. For successful fertilization, the membrane structure of spermatozoa plays a pivotal role, as both the acrosome reaction and sperm-oocyte fusion are membrane-associated events; in fact, the spermatozoa membrane lipids are essential for spermatozoa fluidity and flexibility. These lipids, however, along with membrane proteins, are also the key substrates for peroxidation that can cause serious sperm functional disorders [27]. High oxidant concentrations have been shown to provoke sperm pathology such as ATP depletion, leading to inadequate axonemal phosphorylation, lipid peroxidation and loss of motility and viability. The adverse influence of reactive oxygen species (ROS) is due to the sperm plasma membrane's peroxidative damage. In addition, in a high proportion of infertility patients, oxidative stress-mediated damage to the sperm plasma membrane can account for defective sperm function observed. In spermatozoa maturation, capacitation and the initiation of the gamete interaction process, ionic environment and ionic fluxes through the membrane are extremely significant. In the mammalian sperm plasma membrane, various kinds of ion channels are found, indicating a number of different functions in sperm physiology and gamete interaction.

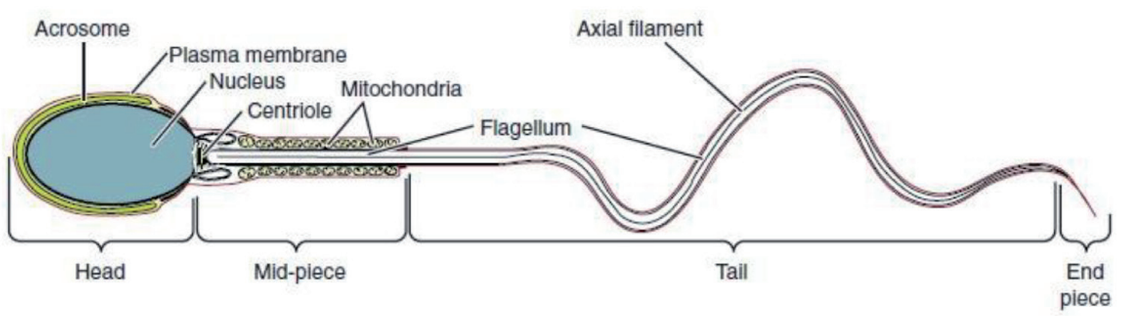

Figure 5.
Structure of a mature spermatozoon (adapted from [24]).

The plasma membrane integral enzymes in most animal cells are Na^+/K^+-ATPase (E.C. 3.6.1.9) and Ca^{2+}-ATPase (E.C. 3.6.1.3) and are important components involved in ionic homeostasis. Changes in the surrounding of the sperm membrane and thus in fluidity change the activities of these enzymes, requiring the existence of phospholipids closely linked to their structure. The Na + pump is a heteromeric protein consisting of several isozymes and is not only responsible for maintaining cell osmotic equilibrium, volume and pH, but also for maintaining the capacity of the cell resting membrane and supplying chemical energy across the cell membrane for the secondary Na + −coupled transport of other ions, solutes and water. The Ca^{2+} pump, on the other hand, is responsible for the homeostasis of calcium that is central to normal cell function. In particular, a distinctive Na^+/K^+-ATPase isoform expression profile has been found in the mammalian testis with regard to the Na^+ pump. Sanchez *et al.* stated that the human Na^+/K^+-ATPase 4 isoform has different functional properties and plays a primary role in the motility of sperm. Sulphydryl (SH) containing enzymes are considered to be both ATPases and their thiol groups may be the target for both nitric oxide (NO) and its derivatives such as peroxynitrite (ONOO-). In fact, it has been clearly shown that NO and NOderived reactive nitrogen species modulate the activity of different enzymes and can thus damage cells, causing sperm dysfunction by increasing lipid peroxidation, complete depletion of the sulphydryl group and formation of nitrotyrosine or by inactivating proteins, damaging nucleic acids, which in turn leads to to alteration or disturbances in membrane structure and function. The development of several disease states in humans is the accumulation of this oxidative damage and, in particular, the progressive oxidation of sperm thiols to disulphides is involved in sperm chromatin condensation and stabilization of the tail structure needed for the subsequent initiation of motility. In particular, it has been revealed that peroxynitrite inhibition of Na^+/K^+-ATPase activity is followed by a reduction in the number of protein thiol groups and a shift in the enzyme's substrate dependency curve [28, 29]. This means that the blockade of Na^+/K^+-ATPase ATPase SH-groups is responsible for its inhibition [29]. The pattern of this inhibition is consistent either with the oxidation of thiol groups directly involved in the binding of ATP but in a way that cannot be resolved by raising the concentration of the substrate ('noncompetitive') or with the oxidation of SH groups located outside the enzyme's active site but essential for the enzyme's activity.

12.1.4 Capacitation and acrosome reaction

Capacitation is a morphological transition that spermatozoa are subjected to by hyperactivation and acrosome reaction sequence to gain the capacity to fuse with an ovum [30]. Sperm motility hyperactivation is characterized by a high amplitude, asymmetrical sperm tail beating pattern and enables the sperm to enter the ovum zone pellucida. It is accompanied by the acrosome reaction where acrosin and other enzymes are released by the head of the mature spermatozoa to digest the cumulus cells and break through the zona pellucida [24]. Research has shown that O2-plays an extremely important regulatory function in promoting both hyperactivated motion and acrosome reaction induction [24, 31]. Increased membrane fluidity, increased tyrosine phosphorylation, increased pH levels, increased intracellular cAMP, and calcium influx are characterized by capacitation. Substances present in semen, progesterone, peroxiredoxin-4 and other substances secreted by the oocyte cumulus complex [29] can regulate capacitation, but can also occur spontaneously under sufficient in vitro conditions. Moreover, through the redox regulation of tyrosine phosphorylation, ROS produced by mammalian spermatozoa can play a physiologically important role in driving the complex process of capacitation.

The mechanism that support this redox-effect on protein tyrosine phosphorylation include a number of additional signal transduction stalls, such as sarcoma and extracellular kinase regulated signal mediation pathways, stimulation of inhibition of tyrosine phosphatase activity by cAMP generation. Capacitation is therefore carried out by increasing membrane fluidity, cholesterol efflux, ion fluxes leading to sperm membrane potential alteration, increased protein phosphorylation of tyrosine, hyperactivation induction, and acrosome reaction. Reactive oxygen species function alongside other factors including bicarbonate, membrane cholesterol loss, and increased intracellular Ca^{2+} resulting in activation of the cyclase of adenyl (AC), leading to cAMP production and activation of protein kinase A (PKA) and the phosphorylation of tyrosine proteins. Lewis and Aitken proposed that adenyl cyclase is activated by superoxides, while Rivlin *et al.* [32] proposed that cyclase is activated by hydrogen peroxides that may substitute for bicarbonate. Increased cAMP activates PKA, which activates tyrosine kinases and, by unknown mechanisms, inhibits tyrosine phosphatassase (TP). The participation of PKA with the PKA inhibitor (H89) was confirmed. Hydrogen peroxide stimulates TK directly and inhibits TP. The main driving force of capacitation and conduct to hyperactivation, zone binding and acrosome reactions is the increase of the tyrosine phosphorylation induced by such changes [33]. The increase of fertilization by 50 percent by induction of mild LPO using a mixture of ferrous ion and ascorbic acid was seen in vitro studies performed on mouse sperm. The study shows that a strongly hydrogen peroxide-induced OS activates sperm activity and improves fertilization rate. Superoxide anion induces capacitation in incubation conditions by the effects of an oxidase. Further stimulation of the development of ROS; superoxide anion, hydrogen peroxide induce the release from plasma of these cells of unesterified fatty acid.

12.1.5 Sperm abnormalities

Sperm anomalies, which are usually based on sperm concentration, motility, and morphology, include: oligospermia (sperm concentration lesser than 20 million/ml). This is supported by Iammarrone *et al.* [34], which showed low conception rate in human sperm counts with a concentration lesser than 20 million/ml. A complete lack of spermatozoa in an ejaculate is termed azoospermia and such is found to accounts for 10–15 percent of male infertility cases. Partial obstruction of sperm duct also influenced sperm concentration [35]. Asthenospermia (poor sperm motility), is a condition in which spermatozoa are too slow in movement, not able to strive in a straight line along the cervical mucus within the female reproductive tract and or fertilize the egg. When 60% or more sperm actively move in a straight line, the percentage motility is said to be normal, and quality is at least average. In cases where percentage motility is less than 40%, the sperm the condition is as less qualitative. Genetic or otherwise sperm defects may be responsible for sluggishly sperm movement and this may render them incompetent of fertilizing the egg. Poor sperm motility associated with DNA fragmentation can increase the risk of genetic diseases transmitted to offspring. Sperm motility is rated in two ways: percentage of the total motility (general motility), or the individual forward progressive sperm movement (progressive motility) [36]. The latter is a grade dependent on the pattern of the majority of motile sperm. It ranges from null indicating (no movement) to four (suggesting excellent forward progression). Notably, a sperm sample needs to have at least 50% progressive motility. Teratospermia or morphologic abnormalities are usually categorized based location of the deformity of a spermatozoon, whether it is on the head, neck (midpiece), or tail.

Primary and secondary anomalies are the most important classification scheme types: primary abnormalities are structural defects in the location affecting head, midpiece and tail. While the sperm was still inside the seminiferous epithelium of

the testis, a more primary serious defect is thought to originate while secondary defects are considered less extreme and thought to occur during the passage through the epididymis or by mishandling after ejaculation (sperm). The heterogeneous state of teratozoospermia includes changes in the form of various components of sperm. There is a strong connection between morphological defects and the potential for sperm fertilization, since mature spermatozoa structures have the best organization to serve specific functions. Teratozoospermia can therefore be considered to be a mixture of morphological defects with associated sperm function impairments [36].

12.1.6 Factors influencing spermatogenesis

The spermatogenesis process is highly sensitive to environmental fluctuations, especially hormones and temperatures. In order to sustain the process, which is accomplished by bidding testosterone with androgen binding protein present in the seminiferous tubules, testosterone is needed at large local concentrations. Testosterone is produced by interstitial cells that reside adjacent to the seminiferous tubule, also referred to as ledig cells. In humans and certain other animals, the seminiferous epithelium is susceptible to elevated temperatures and can be adversely affected by temperatures as high as average body temperature; therefore, the testes are found in a skin sack called the scrotum outside the body. At 20°C (Man) -80°C (mouse) below body temperature, the optimum temperature is preserved. This is accomplished by controlling blood flow and by placing the cremasteric muscle and dartos smooth muscle towards or away from the body heat. A nutritional deficiencies (such as vitamins B, E, and A), anabolic steriod, metals (Cadmium and lead), X-ray exposure, dioxin, alcohol, drug toxicant and diseases of pathogens may also adversely affect the rate of spermatogenesis [29, 37].

12.2 Testicular steroidogenesis

For both spermatogenesis and the development of secondary sex characteristics, steroidogenesis, which involved the production of testosterone (T) and dihydrotestosterone (DHT) from cholesterol by a series of P450 enzymes in the Leydig testis cells, is essential. The differentiation of the Wolffian ducts into the epididymides, vasa deferentia, seminal vesicles, and the development of the levatorani-muscle and bulbocavernosus gland (the LABC complex) is the responsibility of T in utero (produced locally by the interstitial Leydig cells regulated by LH). DHT (produced locally in the testis by T conversion using the 5-alpha-reductase enzyme) is responsible for differentiating the genital tubercle from the external genitalia and the urogenital sinus into the glands of the prostate and Cowper and for regression of nipple anlagen in the male fetuses. According to the receptors to which they attach, steroid hormones can be classified into five distinct groups: mineralocorticoids, glucocorticoids, androgens, estrogen and progestagen. Cholesterol, the basic precursor for biosynthesis of all steroid hormones, is integrated by receptor-mediated endocytosis into the Leydig cell from low-density lipoproteins or is synthesized de novo from acetate within the cell. In cytoplasmic lipid droplets, cholesterol is contained in an ester form and the number of droplets in Leydig cells is regarded to be inversely proportional to the rate of androgen synthesis [38]. LH-induced cholesterol ester hydrolase activation hydrolyzes cholesterol ester during steroidogenesis, which is transported into the mitochondria of Leydig cells. The StAR protein is used to transport cholesterol from the outside to the inner mitochondrial membrane. The exact mechanism by which cholesterol is transported by StAR protein to the mitochondria, however, remains uncertain. StAR protein is regulated acutely, and protein expression is critically dependent on stimulation of trophic hormones

(e.g. LH and ACTH). This makes it sensitive to toxicants from the environment: several xenobiotics [e.g. 4-tert-octylphenyl and pesticides Lindane (1,2,3,4,5,6-hexachlorocyclohexane) and glyphosate Roundup (2-(phosphonomethylamino) acetate)] have been reported to interfere with StAR protein expression inhibitor Steroidogenesisby [39, 40]. The condition lipoid congenital adrenal hyperplasia (lipoid CAH) is believed to be caused by mutations in the StAR gene. Lipoid CAH is an autosomal recessive lethal condition in which cholesterol and cholesterol esters accumulate and a sufficient amount of steroids can not be synthesized by the newly born child. In humans, StAR knockout mice display a phenotype that is very similar to lipoid CAH, providing a clear model for studying the mechanism of the important contribution of StAR protein to steroidogenesis and endocrine production. In the inner mitochondrial membrane, the cytochrome P450scc side chain cleavage enzyme, which belongs to the monooxygenase family, transforms cholesterol to pregnenolone. Three successive monooxygenations are involved in this step: 22-hydroxylation, 20-hydroxylation and C20-C22 bond cleavage. Pregnenolone then diffuses across the mitochondrial membrane and is translocated to the endoplasmic reticulum, where it undergoes a series of testosterone-forming biochemical reactions. Pregnenolone undergoes C17 hydroxylation in the Delta 5 pathway to form 17 alpha-hydroxypregnenolone, which is then split between C17 and C20 bonds to form DHEA. The cytochrome P450 17 alpha-hydroxylase/ C17, 20 lyase catalyzes these reactions [41]. DHEA could be transformed by the action of 3β-HSD to androstenedione and then 17β-HSD to testosterone. The equilibrium between these androgens depends on the present activity and type of 17b-HSD. Types 3 and 5 of 17b-HSD catalyze the conversion of androstenedione to testosterone and are expressed in Leydig testis cells, while the opposite reaction occurs in type 2 (found among others in prostate and placenta) [42].

In steroidogenic and non-steroidogenic tissue such as asthetes, prostate, skin and brain, the enzyme 3β-HSD is commonly expressed. Four 3β-HSD isozymes exhibiting differential and tissue-specific expression were characterized in the rat. The spermatic vein transports testosterone into circulation. Testosterone synthesis is governed by LH in Leydig cells. Testosterone biosynthesis is also regulated by other factors, such as FSH, insulin-like growth factor-1 and cytokines [43]. By paracrine regulation of testicular functions, FSH also regulates spermatogenesis (**Figure 6**).

12.3 Sperm discharge function

The discharge of semen into the reproductive tract of female has to do with the following steps;

a. **Libido:** This is the biological need (sexual drive) for sexual activity and is often expressed as conduct that seeks sex. Its strength is variable over a given time between people and within an person. In stable older but not younger men, higher serum testosterone tends to be associated with greater sexual action.

b. **Erection:** The enlargement and firm state of penis is the erection of the penis. The dynamic interaction of psychological, neuronal, vascular and endocrine factors are some of the factors it depends on. When two tubular structures running the length of the penis, the corpora cavernosa, are engorged with venous blood, a penile erection occurs. This can result from any of the different physiological stimuli. The corpus spongiosum is a single tubular structure situated just below the cavernosa corpora, which comprises the urethra from which, during urination and ejaculation, urine and semen move through. This may often be slightly engorged with blood, but less so than the penile erection of the

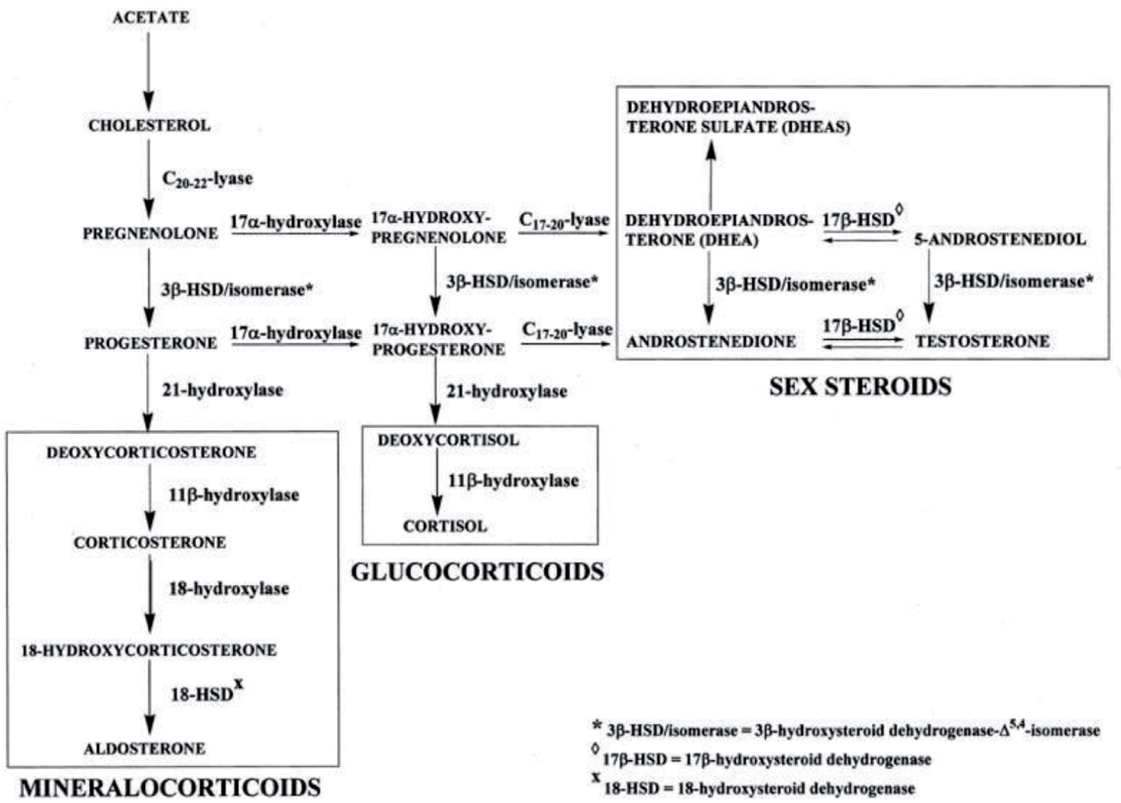

Figure 6.
Showing the major pathways in steroid biosynthesis.

corpora canvernosa normally results from sexual arousal and/or excitement, but can also occur due to triggers such as a full urinary bladder or spontaneously over the course of a day or at night, often during romantic or wet dreams. Swelling and enlargement of the penis results from an erection. Although it is not necessary for all sexual activities, erection makes sexual intercourse and other sexual activities (sexual functions).

c. **Ejaculation:** Ejaculation and erection must take place for sperm to deliver into the female genital tract (without technical assistance). Two occurrences or events should really be considered during ejaculation, the first being semen deposition into the posterior urethra, called seminal emission, and the second being semen expulsion from the urethra. The sympathetic nervous system controls emission and ejaculation of sperm. Emission includes the intense contraction of the vas, ampulla of the vas, seminal vesicles and prostate covering muscle and myoid complexes. Ejaculation, along with contraction of the periurethral muscles, mainly the bulbocavernosus muscle, requires closure of the bladder neck to avoid or prevent retrograde semen flow.

d. **Orgasm:** Organsm, or orgasm, is an intense, pleasurable feeling that typically happens at the height of sexual arousal, accompanied by a decrease in sexual tension. Not all sexual arousal results in orgasm, because in order to have an orgasm, people need various circumstances and different forms and quantities of stimulation. Orgasm is made up of a rhythmic contraction series. In the pelvic organs and genital area. Throughout the body, breathing rate, heart rate, and blood pressure increase dramatically. The general contraction of the muscles can lead to facial contortions and muscle contractions in the extremities, back, and buttocks. Organism occurs in two phases in men. First, at the

base of the urethral, the vas deferens, seminal vesicles, and prostate contract, sending seminal fluid to the bulb, and the man feels a sense of inevitability of ejaculation, a sensation that ejaculation is just about to happen or happen and can not be prevented. Second, a mechanism called ejaculation is closely related to the urethra bulb and penis rhythmically contracting, expelling the sperm, but some men experience organism separately from ejaculation.

13. Endocrine and neuroendocrine factors regulating testicular functions

The brain (on stimulation), the master endocrine gland, and local factors generated by the testes finely regulate the spermatogenic and steroidogenic functions of the testes. The proliferation of primitive germ cells and the development of the testes are carefully regulated by testosterone (secreted by the legdig cell on activation by placenta released human chorionic gonadotropin (HCG)) during intrauterine life [44]. The hormonal control of testes ceases after birth and the testes remain quiet until the beginning of puberty [45]. The testicular function setting is triggered at puberty by certain cells in the hypothalamus that activate GnRH secreting cells (**Figure 7**). These cells are referred to as kisspeptin secreting cells found in the periventricular nucleus (PVN), preoptic nucleus (PN) and arcuate nucleus (ARC) and in the anteroventral perivetricular nucleus (AVPV) [44].

Steroids, leptin, and other systemic factors are believed to have effect on the testicular functions by binding on receptor located on these kisspeptin secreting cells [44]. Kisspeptin stimulates GnRH cells to release gonadotropin releasing hormone via the median eminence (**Figure 8**). The cells that secrete GnRH are under the regulation of kisspeptin because they express the GPR54 receptor on their cell membrane that bind to kisspeptin released by kisspeptin secreting cells. This hormone is carried to the anterior pituitary through the hypothalmo-hypophyseal portal system. There the gonadotropes are stimulated by GnRH to release follicle stimulating hormone (FSH) and luteinizing hormone (LH) which are the tropics for leydig and sertoli cells respectively. This is the neuroendocrine axis of testicular regulation. The gonadotropes in the adenohypophysis, on stimulation, releases LH, FSH and growth hormone that regulate the functions of the testes. This is the endocrine axis of

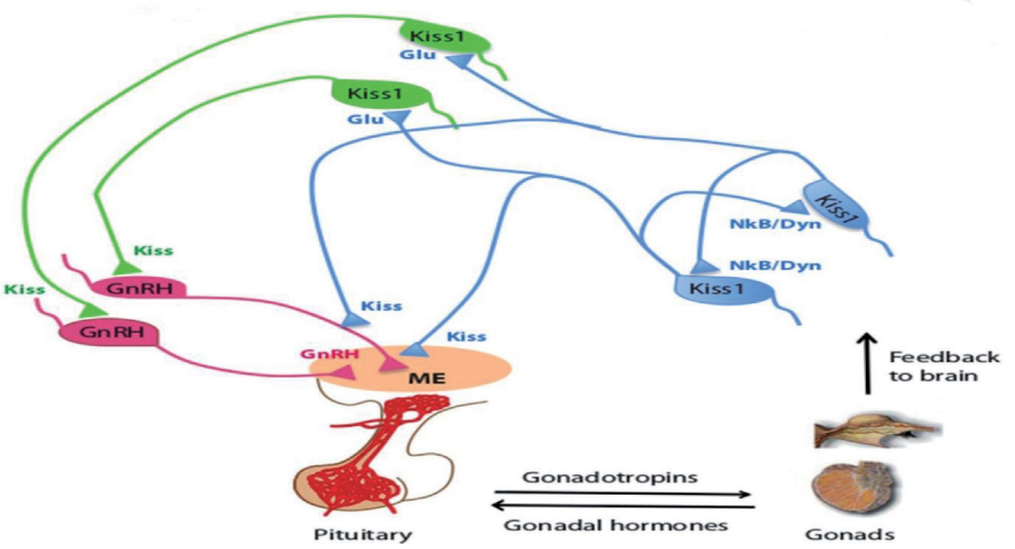

Figure 7.
Showing kisspeptin cells connections with GnRH cells (source: www.wikipedia.org).

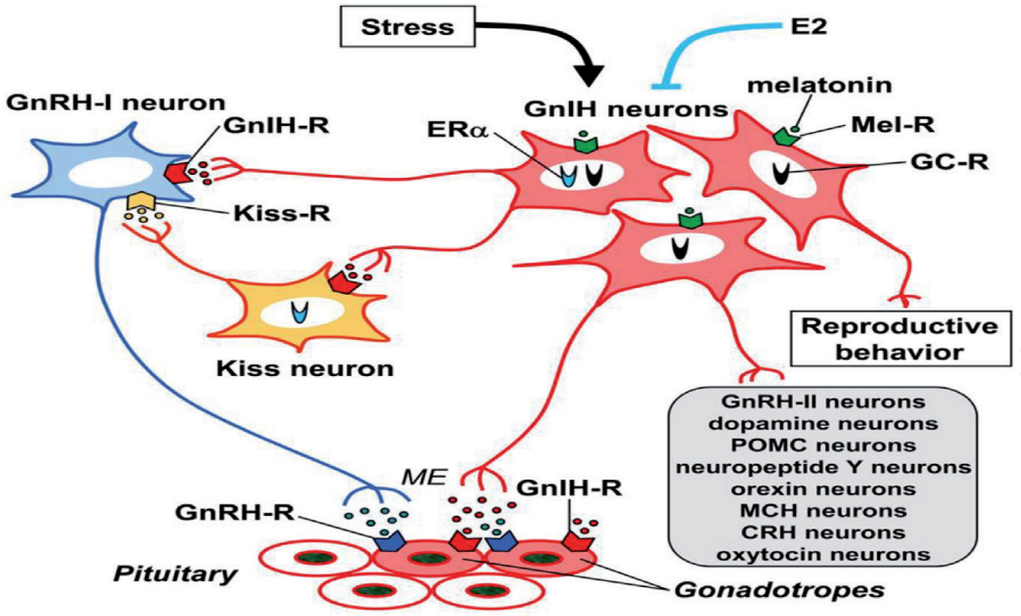

Figure 8.
Regulation of kisspectin-GnRH axis (Wikipedia.org.) It is through this kisspeptin-GnRH axis that factor such as steroids stress, leptin light and dark etc. influence the functions of the testicles [46].

testicular regulation. Spermatozoa development is based on pituitary gonadotropins, LH and FSH, which are released in response to hypothalamic GnRH pulsatile release.

The testes as an endocrine gland secrete steroid and other local factors that regulate its function through autocrine and paracrine mechanism. The steroids and inhibin synthesized by leydig and sertoli cells respectively regulate the neuroendocrine and endocrine factors via negative feedback mechanism. Abnormalities in these levels of testicular regulation results to male reproductive dysfunctions [29, 37]. This is hypogonadotropin-hypogonadism due to misdirection in GnRH cells migration from the olfactory cells during development [44].

GnRH act via interacting with a particular receptor found on the cell membrane of gonadotropes. These receptors are G-protein - coupled receptors that interact with the hormone to form a hormone receptor complex. This results in the interaction of phosphoinositide with Gp protein hydrolysis and the release of diacylglycerol and inositol triphosphate, resulting in the mobilization of calcium from intracellular stores and the inflow of extracellular calcium into the cell. The release of gonadotropin from gonadotropes into the general circulation results from this calcium influx [44].

14. Clinical implications of gonadotropins and steroidogenic hormones

LH binds to the receptors located on the Leydig cells in the testis and induces testosterone synthesis, which in turn could adversely affect the release of hypothalamic and pituitary hormones. FSH targets the receptors on the Sertoli cells and induces androgen-binding protein production, which helps to transport testosterone via the Sertoli cells' tight junction complexes. Sertoli cells are also activated by FSH to secrete inhibin and activin, both of which have a negative effect on hypothalamus and pituitary hormone release. The primary endocrine hormone involved in testicular function control is FSH. FSH has a central role to play in regulating the Sertoli cell populations, which in turn modulates the number of germ cells proceeding through the mitotic and meiotic spermatogenesis phases. In mitotic and meiotic spermatogonia, FSH handles or regulate DNA synthesis and also prevents apoptosis induction in

round spermatids [47]. It has been shown that FSH stimulates the release of various products from Sertoli cells. Sertoli cell products have been reported to play a role in the regulation of the functions of Leydig cells. For successful spermatogenesis and steroidogenesis, the ability of LH to function on the LH receptors present on Leydig cells is essential. LH controls the growth of Leydig cells, the number of Leydig cells, the biosynthesis of testosterone and its secretion. The removal of testosterone has been shown to induce spermatid detachment from Sertoli cells, resulting in full spermatogenesis stoppage. To initiate, sustain, and restore spermatogenesis, testosterone works synergistically with FSH. In particular, testosterone contributes to the blood-testis barrier development, the maintenance of interactions between Sertoli and germ cells, and the release of mature sperm from Sertoli cells). The blood-testis barrier formation is weakened in the absence of testosterone and germ cells are released from the Sertoli cells prematurely.

Estrogens, localized in Leydig and Sertoli testis cells, efferent ductules and epididymis also play a significant role in spermatogenesis control. Evidence suggests that estrogen is secreted into the seminiferous tubular fluid by germ cells, which may be essential for the efferent ductules and epididymis functions. It is stated that estrogen has a stimulatory and inhibitory effect on the proliferation and differentiation of germ cells. It has been shown that administration of aromatase inhibitors to male monkeys induces decreased spermatogenesis and sperm concentrations, suggesting estrogen 's crucial role in sustaining spermatogenesis. In proliferating Sertoli cells, high estrogen levels are present and their levels decrease as Sertoli cells avoid differentiation and start maturation. Estrogens control the expression of the molecule of cell adhesion, neural cadherins, involved in the maintenance of cell adhesion of germ cells-Sertoli.

Environmental estrogens is known to have a deleterious effects on male fertil¬ity and it has been shown that neonatal exposure to exogenous estrogens induces irreversible alteration of gene expression in the reproductive tract. Testicular steroidogenesis in adulthood has been shown to impair neonatal sensitivity to diethylstilbestrol, a synthetic estrogen. Administration of 17β-estradiol to adult rats has been shown to induce a decrease in basal and stimulated testosterone production of 33–48 percent. Adult male rats showed a substantial decrease in circulating FSH

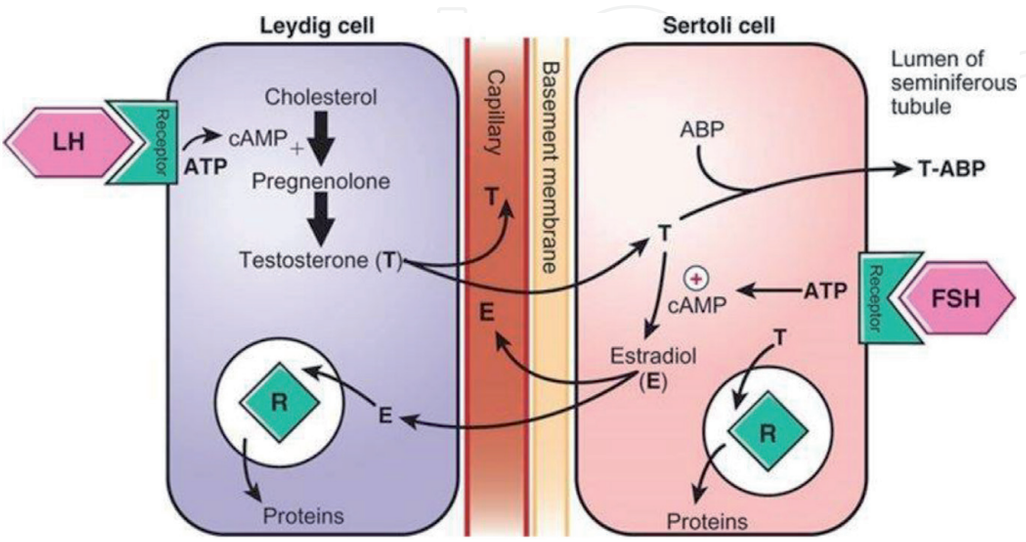

Figure 9.
Showing the main product of Leydig cells (e.g testosterone), Regulation, hormonal products, Leydig and Sertoli cells interaction. AB (androgen binding protein); ATP (adenosine triphosphate); cAMP (cyclic adenosine monophosphate); E (estradiol); FSH (follicle-stimulating hormone); LH (luteinizing hormone); T (testosterone) [17].

and LH concentrations when treated with estradiol, which subsequently contributed to reductions in serum and testicular testosterone levels. Several other factors, apart from hormones, have also been shown to affect testicular functions (**Figure 9**).

15. Other factors necessary for male reproductive functions

- **Growth Hormone:** This hormone is usually synthesized by the anterior pituitary (AP) and has effect on virtually all tissues and organs of the body. It is essential for the general metabolic processes in the testes. It is also necessary for proliferation of spermatogenesis, and plays a key role in the proliferation, growth and maturation of spermatids [45].

- **Local Factors:** Some of the most important local factors produced in the testes by the leydig cells are testosterone and insulin-like factor while that of sertolin cells of thae testes are inhibin, growth factor. Stem cell factors, immunological factors, opioids, oxytocin, vasopressin, peritubular cell modifying factors, rennin, angiotensin, GnRH, CRH, ACTH, GHRH, calmudilin, pasminogen activator, metalloproteases, dinophin, PACAP etc. are some of the other local factors that are believed to have effects on the functions of the testes [44]. Apart from these factors, glucose has also been shown to be important for proper functioning of testis.

- **Insulin signaling and glucose transport:** Apart from these factors, glucose has also been shown to be important for proper functioning of testis. Glucose is very critical for high-energy, challenging testicular spermatogenesis and steroidogenesis to be successfully accomplished. It has been shown that cytochalasin B, a glucose transport inhibitor, competitively binds to proteins that are involved in Leydig cells' facilitated glucose absorption, and inhibits testosterone synthesis stimulated by LH. In the presence of glucose, high testosterone production has been observed, suggesting the need of this compound for testosterone production in addition to LH, and it has also been shown that there is no testosterone production in the absence of glucose. The family of facilitative glucose transporter (GLUT) proteins carries out glucose transfer through the plasma membranes. There are 13 GLUT protein families that have been identified to date. Glucose transporter-1 to −3 expressions in different types of rat testicular cells has been demonstrated. Mature spermatozoa also express glucose transporters because they require glucose for basic cell activity as well as for specific functions such as motility and fertilizing capacity [48]. One of the recently cloned members of the GLUT family, GLUT-8 is known to be the leading transporter of glucose in the testis. In the heart, skeletal muscles, brain, spleen, prostate and intestine, GLUT-8 is expressed, but its expression was found to be highest in the testis relative to all other tissues [49, 50], thus indicating the involvement of GLUT 8 in glucose transport for steroidogenesis of Leydig cells [51–53]. In addition, in testicular cell types, GLUT-2 has also been shown to be abundantly expressed. The high expression in the testis of insulin signaling molecules and glucose transporters suggests the high energy expenditure of contractile testicular cells and the dependency on glucose as an energy source. The insulin receptor family also plays an important role in the development of gonads in the testis. The differentiation of the testis is caused by the sex-determining region Y (SRY) expression present in somatic progenitor cells intended to become Sertoli cells. Sertoli, Leydig, interstitial and myoid cells have been shown to express IRS-1 and IRS-2, suggesting the reliance of

these cell types on insulin. Sperm motility, progressive motility and acrosome reaction of human spermatozoa have been reported to increase by insulin and leptin, thereby improving their fertilizing ability. In addition, it has been shown that human spermatozoa releases pulsatile insulin, which is autocrine-regulated, and it has been hypothesized that insulin derived from sperm can play a role in sperm capacitation [54]. Therefore, insulin plays an important role in the proper functioning of the testis and in preserving the capacity of spermatozoa to fertilize. Insulin signaling and glucose transport in the body are known to be affected by many factors. Of the different variables, as one of the main regulators of glucose homeostasis in the body, reactive oxygen species (ROS) are involved. While low ROS levels are important for the signaling of insulin, increased ROS could have a negative impact on homeostasis of glucose.

Author details

Oyovwi Mega Obukohwo[1*], Nwangwa Eze Kingsley[2], Rotu Arientare Rume[3] and Emojevwe Victor[4]

1 Department of Hunan Physiology, Achievers University, Owo, Ondo State, Nigeria

2 Faculty of Basic Medical Science, Department of Physiology, Delta State University, Abraka, Nigeria

3 Department of Physiology, University of Ibadan, Ibadan, Oyo State, Nigeria

4 Department of Physiology, University of Medical Sciences, Ondo, Ondo State, Nigeria

*Address all correspondence to: megalect@gmail.com

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