Male Reproductive System—Anatomy and Physiology
ABSTRACT

Basic understanding of the male reproductive system is fundamental in effective evaluation and treatment of male infertility. This chapter is a concise introduction to the male reproductive anatomy and the intricately designed process of spermatogenesis along with its hormonal control.

INTRODUCTION

Understanding the fundamentals of anatomy and physiology of male reproductive system is a key to effective evaluation and treatment of male infertility. It comprises of the hypothalamic-pituitary-testis axis, epididymis, vas deferens, seminal vesicles, prostate and urethra.

ANATOMY OF MALE REPRODUCTIVE SYSTEM

Development

The male urinary and reproductive systems share a common developmental origin. The testes and extratesticular ducts arise from three different tissues: intermediate mesoderm, mesodermal epithelium and primordial germ cells.

• The intermediate mesoderm forms a urogenital ridge that gives rise to testicular stroma and the mesonephric (Wolffian) duct.

• The mesodermal (coelomic) epithelium gives rise to Sertoli cells and the paramesonephric duct.

• The primordial germ cells migrate from yolk sac and give rise to the spermatagonia.

Sexual differentiation occurs in the seventh week of gestation in embryos carrying the Y-chromosome.

Transcription of the SRY gene present on the Y-chromosome leads to synthesis of testis-determining factor (TDF) protein. Secretion of TDF protein stimulates the nascent Leydig cells to produce testosterone, causing development of the mesonephric duct. It also stimulates Sertoli cells to secrete Mullerian-inhibiting factor (MIF), which leads to the regression of the paramesonephric duct. This cascade of events leads to the formation of male internal genital organs. Conversion of testosterone to dihydrotestosterone (DHT) induces the urogenital sinus to form the male external genitalia, prostate and urethra.

First step in testicular development is the formation of tunica albuginea. This layer of fibrous connective tissue separates the seminiferous cords (also known as sex cords) from the surface epithelium. These seminiferous cords are separated from one another by mesenchyme, which eventually produces the Leydig cells.

Leydig cells produce testosterone, which bind to receptors in the mesonephric duct. It helps maintain the presence of the mesonephric ducts as opposed to the female embryo where these ducts degenerate. Meanwhile, the renal corpuscle degenerates, allowing the tubules of the mesonephros to connect with the rete testis. This results in the formation of ductuli efferentes. These tubules are continuous with the mesonephric duct, and form what is known as the epididymis.

The seminiferous cords also play an important role in male differentiation. The cords contain no lumen and remain solid until puberty. They are comprised of many highly proliferative Sertoli cells that secrete...
anti-mullerian hormone. This hormone inhibits the paramesonephric ducts resulting in their degeneration at approximately ninth week of development. A lumen develops in the seminiferous cords at puberty and they become seminiferous tubules.1

Structure-testis, Epididymis and Vas Deferens

The testes are the male gonads, similar to ovaries in females. The human testes are two glandular, ovoid organs that lie in the scrotum enveloped by a strong connective tissue covering, the tunica albuginea. Early in the embryonal life, testes lie retroperitoneally in the abdominal cavity. Before birth, the testes and spermatic cord descend through the inguinal canal into the scrotum.1

Each testis contains about 370 seminiferous lobules measuring about 180 µm in diameter each. These lobules lie between the fibrous septa extending between the mediastinum testis and the tunica albuginea. They are enclosed by connective tissue containing Leydig cells, blood vessels, lymphatics and nerves.

Along the posterior border, the testes are loosely connected to the epididymis, a narrow, tightly-coiled tube that connects the efferent ducts from the back of each testis to its vas deferens. Spermatozoa produced in the testis are stored in the epididymis to be carried away by the vas deferens. Smooth muscles in the wall of the epididymis contract to thrust the spermatozoa forward into the prostatic urethra. Here sperms mix with secretions from accessory glands including the prostate, seminal vesicles and bulbourethral gland2,3 (Figures 1.1 and 1.2).

Supporting Cells

- Leydig cells
- Sertoli cells

**Leydig Cells**

Leydig cells, named after the German anatomist Franz Leydig who first identified them in 1850, are somatic cells lying in the testicular interstitium. These are irregularly shaped cells containing granular cytoplasm and are often seen in clumps within the connective tissue. Leydig cells of testis are the main site of synthesis and secretion of androgens, including testosterone, the primary male sex hormone.1 Luteinizing hormone (LH) secreted by the pituitary, stimulates the Leydig cell to produce testosterone, which is then accumulated in the interstitium and seminiferous tubules.

**Sertoli Cells**

The Sertoli cells line the seminiferous tubules and are the ‘nurse’ cells of the testes. Their main function is to nurture the developing germ cells during various stages of spermatogenesis.4 Sertoli cells communicate with germ cells through multiple sites for the maintenance of
spermatogenesis. Sertoli cells also form tight junctions that divide the seminiferous tubules into two compartments for the spermatozoal development. The basal compartment below the tight junctions is in contact with the circulatory system and is the site where spermatogonia develop into primary spermatocytes. The tight junctions open at specific times and allow progression of spermatocytes to the adluminal compartment, where meiosis is completed. In the adluminal compartment, spermatocytes are protected by a blood-testis barrier formed by tight junctions between the Sertoli cells.

The principal functions of Sertoli cells are as follows:
• Provide support for germ cells, forming an environment in which they develop and mature.
• Provide the signals that initiate spermatogenesis and sustain spermatid development.
• Regulate pituitary gland function and, in turn, control of spermatogenesis.
• Secrete aqueous secretion into the lumen to aid sperm transport.

**SUMMARY**

**Testis**
- 90% seminiferous tubules (Sertoli and germ cells).
- 10% interstitial (Leydig cells, connective tissue, blood supply).
- Two functions:
  - Spermatogenesis—in the seminiferous tubules.
  - Biosynthesis of testosterone (T)—Leydig cells.

**Accessory Glands**
- Seminal vesicle—60% of semen.
  Contain fructose which is the energy source for sperm; and prostaglandins that react with cervical mucus and induce peristaltic contractions up the tract.
- Prostate—20% of semen.
  Alkaline solution; contain citrate, cholesterol, and prostaglandins.
- Bulbourethral glands
  Buffers to neutralize the acidic environment of the reproductive tracts; contain phosphate and bicarbonate.

*Biosynthesis of Testosterone (T)—Leydig Cells*
- Synthesized from cholesterol.

**Spermatogenesis**
Spermatogenesis is the process by which male spermatogonia develop into mature spermatozoa.
During this complex process, primitive totipotent stem cells divide to produce daughter cells, which, over a span of approximately 70 days mature into spermatids. The process involves both mitosis and meiosis and is regulated by Follicle Stimulating Hormone (FSH) and Luteinizing Hormone (LH) from the anterior pituitary.
Spermatogonia divide by mitosis and differentiate until they become primary spermatocytes, which remain dormant until puberty.
The process of spermatogenesis can be best understood by discussing individual stages.
The first stage of formation of spermatozoa is spermatocytogenesis. During this stage, stem cells divide to produce a population of cells destined to become mature sperm cells and to replace themselves. Spermatocytogenesis occurs in the basal compartment. Spermatogonium is of three functional types (Figure 1.3)

![Figure 1.3: Spermatocytogenesis](image)
Type Ad “dark”
Type Ap “pale”
Type B
Type Ad cells maintain the initial pool of spermatogonium. These cells do not take part directly in the process of spermatid formation but ensure a continuous supply of stem cells for spermatogenesis. Type Ad cells are capable of dividing into—Type Ap and Type Ad cells itself.

Type Ap spermatogonia undergo repeated mitotic divisions to produce a clone of cells. These cells are tethered together with cytoplasmic bridges that allow synchronized development. The resultant cells differentiate into Type B spermatogonia.

Type B spermatogonia undergo mitosis to produce diploid intermediate cells, the primary spermatocytes. The primary spermatocytes are arrested in the prophase of the first meiotic division until puberty and thus have the longest life span of all types of spermatagonia. At puberty, the diploid (2N) primary spermatocytes enter meiosis I and divide by to become haploid (N) secondary spermatocytes.

Secondary spermatocytes have the shortest life span (1.1 to 1.7 days) of all types of spermatagonia.

Secondary spermatocytes undergo meiosis II to yield spermatozoa (N) with half the DNA material of the primary spermatocytes from which they originated. The process begins with one primary spermatocyte containing double genetic material, which divides into two haploid secondary spermatocytes, each containing normal complement of genetic material and finally resulting in four spermatids, each containing half of the genetic material from the original spermatocyte (Figure 1.4).

Once the process of meiosis is completed, the final stage of spermiogenesis, begins. During this stage the spermatids develop into mature, motile spermatozoa (Figure 1.5). This occurs in deep folds of cytoplasm of the Sertoli cells. The maturation of spermatids to spermatozoa depends on the action of androgens on the Sertoli cells in which the developing spermatozoa are embedded. FSH acts on the Sertoli cells to facilitate the last stages of spermatid maturation.

Six different stages in the process of spermatid maturation are described by morphology:

- Sa-1 and Sa-2
  - Golgi complex and mitochondria are well developed and differentiated.
  - The acrosomal vesicle appears.
- Sb-1 and Sb-2
  - Acrosome formation is completed.
  - Intermediate piece is formed.
- Sc-1 and Sc-2
  - Tail development is completed during Sc stage.

During the post meiotic phase, progressive condensation of the nucleus occurs with inactivation of the genome, the histones convert to transitional proteins, and protamines convert to well-developed disulfide bond.
Mature spermatozoa are released from the Sertoli cells and become free in the lumen of the tubules. This process is **spermiation**.

The newly released sperm are non-motile. They are suspended in a fluid secreted by the Sertoli cells and are transported to the epididymis by peristaltic contraction of the myoid cells present in the walls of the tubules. The spermatozoa reach the epididymis by passing through the efferent ductules, the first segment of the extratesticular duct system. Within the epididymis, activation of the CatSper protein localized in the principal piece of the sperm tail develops the progressive motility of the sperm. This protein appears to be a Ca\(^{2+}\) ion channel that permits cAMP-generated Ca\(^{2+}\) influx. Smooth muscle peristalsis transports the sperm through the remainder of the male reproductive system.

**Spermatozoa**

Each sperm is an intricate motile cell, rich in DNA, with a head comprised mostly of chromosomal material (Figure 1.6). Sperm are highly specialized, differentiated and condensed cells that do not divide. Approximately 60 µm long and 1 µm wide, each sperm is composed of the head, midpiece (body), and tail.

**Head**

The normal head of the spermatozoa is oval and measures about 3.0-5.0 µm in length and 2.0-3.0 µm in width with a thickness of 1.5 µm (Mortimer). The normal length-to-width ratio is about 1.50-1.75 (Anibal AA). The head contains the nuclear material for the fertilization process. The acrosome covers the sperm head like a cap. This lysosome-like organelle is rich in enzymes which mediate the penetration of ovum by the sperm.

**Neck**

The neck is the junction between the head and tail. The presence of decapitated spermatozoa is a common abnormality.
Tail

The tail contains the locomotory flagellum, divided into middle, principal and end pieces. The middle piece has the flagellum, surrounded by a sheath of mitochondria that provide the energy for movement.

Thermoregulation of the Scrotum

The male gonads lie in the scrotum which is a characteristic feature of almost all mammals. Human testicular temperature is physiologically maintained within a range of 32-35°C. The location of testes in the scrotum facilitates the production of viable and mature spermatozoa in a comparatively cooler environment than the rest of the body.6

Impairment of spermatogenesis by elevation of testicular temperature is now a widely accepted phenomenon.7 Mieusset et al reported that an increase of 1.5-2°C in scrotal temperature inhibited spermatogenesis. In man, dangling scrotum helps thermoregulation by allowing the heat produced during spermatogenesis to dissipate. Other supporting features of the scrotum such as thin skin with high vascularization, scanty hair, abundant sweat glands and absence of subcutaneous fat also facilitate the heat dissipation. Excessive heat in the testes or exposure to warm, ambient temperature cause the scrotal skin to loosen, thus increasing its surface area; and the scrotal muscles to relax so as to take the testes away from body thereby preventing sperm damage. On exposure to cold, the scrotal surface area is minimized by rugosities, and cremaster muscles lift the testes closer to the abdomen in order to conserve heat and protect the sperm. The absence of spermatogenesis in cryptorchidism where the testes is retained intraabdominally has been attributed to supraphysiological temperatures.

Varicocele, a tortuous dilation of testicular veins resulting in stagnation of venous blood in the pampiniform plexus, is the leading causes of secondary male infertility. Hyperthermia has been identified as one of the major factors contributing to sperm damage in varicocele. Although controversy exists behind this hypothesis, but the scientific evidence is strong.

Functions of the Epididymis in Spermatogenesis

Sperm maturation is defined as the development of the ability of spermatozoa to fertilize eggs as they progress through the epididymis. The epididymis has been shown to play an important role in sperm maturation, serving as the motility gaining site.

Several small water-soluble components of epididymal fluid (myo-inositol, L-carnitine, taurine, glutamate) are taken up by spermatozoa during post-testicular maturation, to function as a reserve of intracellular osmolytes against the osmotic challenges that spermatozoa experience later at ejaculation. As a result, the composition of the fluid environment within the epididymis differs significantly from that of plasma. Inorganic ions, rather than organic compounds, seem to be the major osmolytes. The effects of high osmolality in dehydrating spermatozoa as a means of enforcing sperm quiescence have been proposed, although this implies that the solutes remain extracellular. Several proteins also are found within the lumen, some of which have are known to play a role in sperm maturation. For many others, their role is still undefined.

Transport through the epididymis takes approximately a week. The transport is achieved by contraction of smooth muscles around the epididymal epithelium, aided by continuous fluid movement. The sperm attain different functions at different parts of the epididymis. Motility is attained as spermatozoa pass through the caput (head) region, and fertilizing ability is achieved as the spermatozoa pass through the corpus (body).3 Considerable absorption of water occurs in the proximal region. The cauda region stores the spermatozoa until ejaculation. This is the site of aspiration of sperm for ICSI (Figure 1.7).

Tight junction complexes between the epididymal cells form the blood-epididymis barrier, an important

Figure 1.7: Percutaneous epididymal sperm aspiration
physiological and anatomical barrier that also gives immunological protection to the spermatozoa. Spermatozoa are immunogenic and must be protected from the immune system.

The epididymis also possesses the ability to protect spermatozoa from oxidative attack while stored in the cauda region, through the local actions of antioxidants such as catalase, superoxide dismutase (SOD), glutathione peroxidase (GPX) and glutathione reductase (GRD). The eventual result of activity within the epididymis is the production of fully viable spermatozoa capable of fertilizing the ovum.9

### HORMONAL REGULATION OF SPERMATOGENESIS

Spermatogenesis is regulated by hormones secreted by the hypothalamic-pituitary-gonadal axis. Spermatogenesis is regulated by negative feedback mechanism.

Hypothalamus secretes gonadotrophin releasing factor (GnRH) in the hypothalmo-hypophyseal portal circulation. This factor stimulates synthesis and releases the gonadotrophins, FSH and LH, by the pituitary gland into the systemic circulation.

LH acts on the Leydig cells stimulating the production of testosterone. FSH acts on the Sertoli cells and is important for the development of the Sertoli cells that are vital for spermatogenesis. Sertoli cells under the influence of the FSH secrete androgen binding protein, inhibin and plasminogen activator. Androgen binding protein (ABG) is necessary to maintain high levels of the androgens locally which is important for spermatogenesis. The plasminogen factor helps in spermiation and inhibin has a negative feedback effect on the FSH secretion by the anterior pituitary gland.10

Testosterone is the principle androgen produced by the Leydig cells in the testis under the influence of LH.

### Functions of Testosterone

- Differentiation, development and maturation of internal and external reproductive organs in male.
- Stimulation of spermatogenesis.
- Regulation of accessory sex gland functions.
- Development of the secondary sex characters.
- Regulation of gonadotrophin secretion by negative feedback mechanism.

### REFERENCES