Part I Introduction

Chapter 1

Anatomy and Physiology of the Male Reproductive System

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The male reproductive system is an incredibly complex yet balanced network of central nervous system circuits and internal and external pelvic organs. The feedback circuit composed of the hypothalamic–pituitary–gonadal (HPG) axis leads to reproductive tract formation and development during embryogenesis, sexual maturation at puberty, and testosterone and sperm production by the testis. The HPG axis continues to stimulate androgen production throughout adulthood to maintain adequate testosterone and sperm production. This axis and the internal and external pelvic organs are the key components in the male reproductive system. This chapter outlines the anatomy and physiology of the male reproductive system, including the HPG axis, control of testosterone production and spermatogenesis within the testis, maturation of sperm within the epididymis, and the transportation of sperm from the distal epididymis through the ejaculatory duct during seminal emission (Figure 1.1).

1.1 Hypothalamic–Pituitary–Gonadal Axis

1.1.1 Basic Hormone and Feedback Concepts

The HPG axis plays an essential role in development, sexual maturation, and maintenance of the male

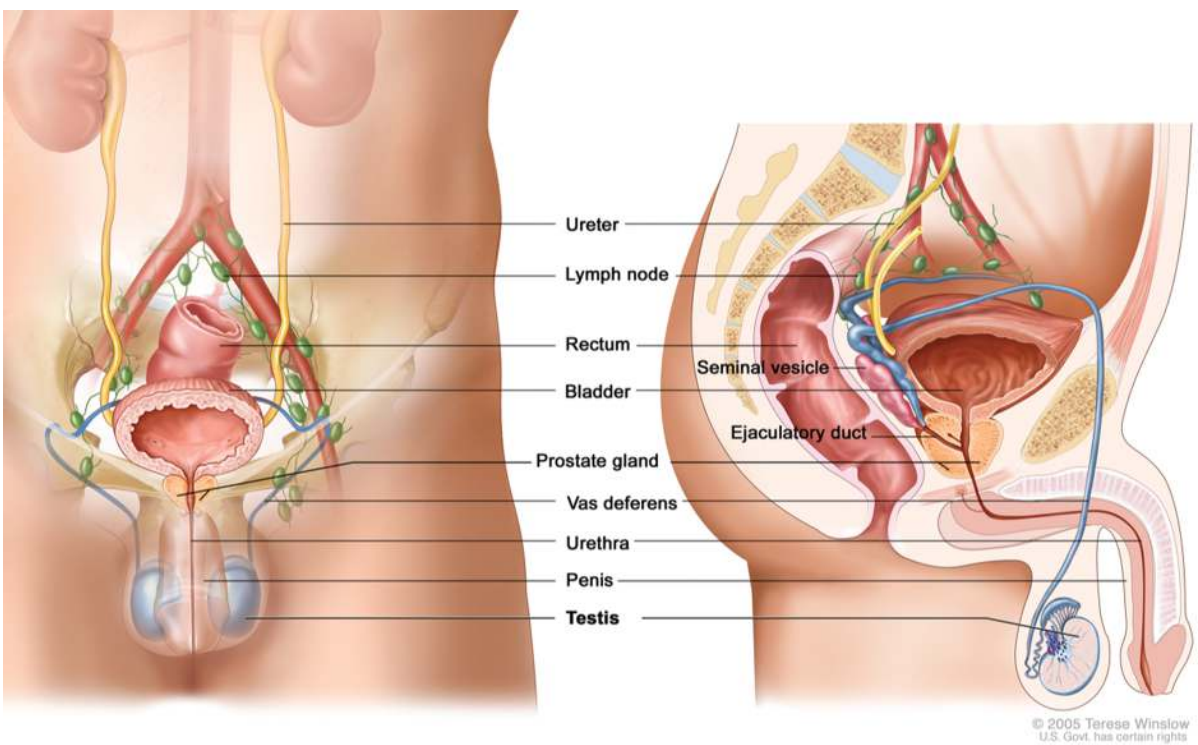

Figure 1.1 Anatomy of the male reproductive and urinary systems. Reprinted by permission of Terese Winslow

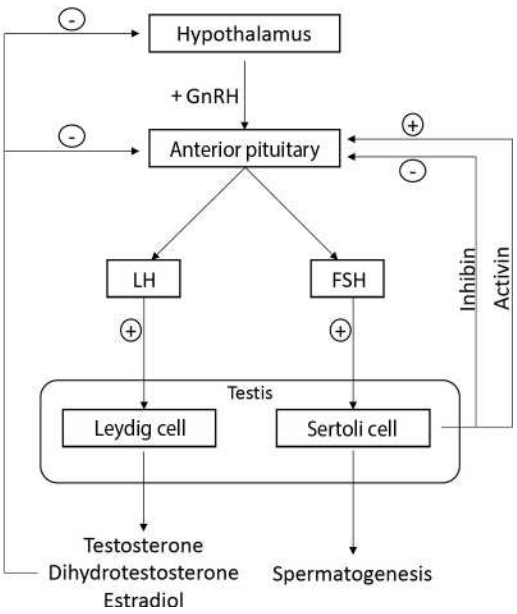

Figure 1.2 Diagram of the HPG axis in males. +, positive feedback; –, negative feedback.

reproductive system. The hypothalamus, anterior pituitary, and gonads each secrete hormones necessary for communication between the individual components of this axis (Figure 1.2). The hormones secreted by the HPG axis come in two flavors: peptide and steroid hormones. Peptide hormones are small, hydrophilic proteins that are unable to cross the plasma membrane; they exert their effects via cell surface receptors and signal transduction. Examples of peptide hormones include gonadotropin-releasing hormone (GnRH), follicle-stimulating hormone (FSH), and luteinizing hormone (LH). Steroid hormones are lipophilic hormones derived from cholesterol that are able to freely diffuse across the plasma membrane and bind to intracellular receptors in the cytoplasm and nucleus. This steroid hormone–receptor complex is able to bind directly to DNA and operate as a transcription factor for gene expression. Examples of peptide hormones include estrogen and testosterone.

1.1.2 Components of the Reproductive Axis

1.1.2.1 Hypothalamus

The hypothalamus is connected to a variety of areas in the central nervous system and has many functions. The most notable function of the hypothalamus is its central neuroendocrine function, and its main role in the HPG axis is to transport hormones to the anterior pituitary for stimulation of peptide hormone release and gonadal regulation. Gonadotropin-releasing hormone is the most important hypothalamic hormone for reproduction. It is a 10-amino acid neuropeptide hormone produced by hypothalamic neurosecretory cells. It is released in a pulsatile manner into the hypophyseal portal circulation, where it is delivered directly to the anterior pituitary gland and stimulates LH and FSH production and secretion [1]. When GnRH pulses do not occur at the appropriate amplitude or frequency, possible complications include hypogonadism and decreased plasma gonadotropins.

1.1.2.2 Anterior Pituitary

The anterior pituitary is the target site of GnRH released from the hypothalamus, and stimulation of the anterior pituitary by GnRH results in production and release of adenohypophyseal hormones. Release of LH and FSH from the anterior pituitary is essential for regulation of testicular function. Both LH and FSH are released in a pulsatile manner, and negative feedback from estrogen and testosterone affect the secretion of these hormones by the anterior pituitary. In the testis, LH acts on Leydig cells to stimulate the production of testosterone, whereas FSH acts on Sertoli cells within the seminiferous tubules to initiate spermatogenesis during puberty and maintain spermatogenesis throughout adulthood.

1.1.2.3 Testis

The human testis is essential in steroidogenesis and the production of spermatozoa. Once LH acts on the Leydig cells and testosterone is produced, the active testosterone metabolites dihydrotestosterone and estradiol are formed to act on target organs. After FSH acts on Sertoli cells, various proteins and growth factors are produced, leading to seminiferous tubule growth during development and sperm production at puberty. The testis also produces other regulatory proteins such as inhibin and activin. Inhibin is produced by the Sertoli cells in response to FSH stimulation, acting as a negative feedback inhibitor at the anterior pituitary, whereas activin has a stimulatory effect on FSH production [2]. Testosterone and estrogen are also capable of regulating hormone production via feedback suppression on the hypothalamus and anterior pituitary.

1.2 The Testis

1.2.1 Testis Structure and Function

1.2.1.1 Testicular Parenchyma

The human testis is an external, ovoid organ that hangs from the inguinal canal by the spermatic cord and is located within the scrotum. Each testis has a volume of 15–30 ml and measures 3.5–5.5 cm in length by 2.0–3.0 cm in width [3]. Each testis contains two compartments: an interstitial compartment made up of Leydig cells that are responsible for testosterone production and secretion, and a seminiferous tubule compartment that is made up of Sertoli cells and germ cells, where spermatogenesis occurs. Approximately 80 percent of testicular volume is dedicated to spermatogenesis. Figure 1.3 represents a lateral cross-section view of the human testis.

1.2.1.2 Testicular Vascular Supply and Innervation

Arterial blood supply to the testis originates from three sources: the testicular artery, which arises from the abdominal aorta; the cremasteric artery, which arises from the inferior epigastric artery; and the deferential artery, which arises from the superior or inferior vesical arteries. The pampiniform plexus is an intricate venous network responsible for venous return from the testes to the testicular vein and temperature regulation of the testis. It is this countercurrent heat exchange that is necessary for maintaining a testicular temperature lower than normal body temperature that is ideal for sperm maturation. The testis is innervated by the intermesenteric nerves and renal plexus [2].

1.2.1.3 Interstitium

The main component of the testis interstitium is Leydig cells, which are responsible for testicular androgen production. Cholesterol is the precursor to testosterone synthesis within the Leydig cells and undergoes several enzymatic reactions once inside the cells to be converted into testosterone. Regulation of androgen synthesis is controlled by numerous factors. The feed-forward mechanism of testosterone synthesis involves hypothalamic GnRH stimulation of the anterior pituitary, which leads to LH release and activation of testosterone production in Leydig cells. The other important regulatory mechanism of testosterone synthesis is via negative feedback of peptide and steroid hormones produced by

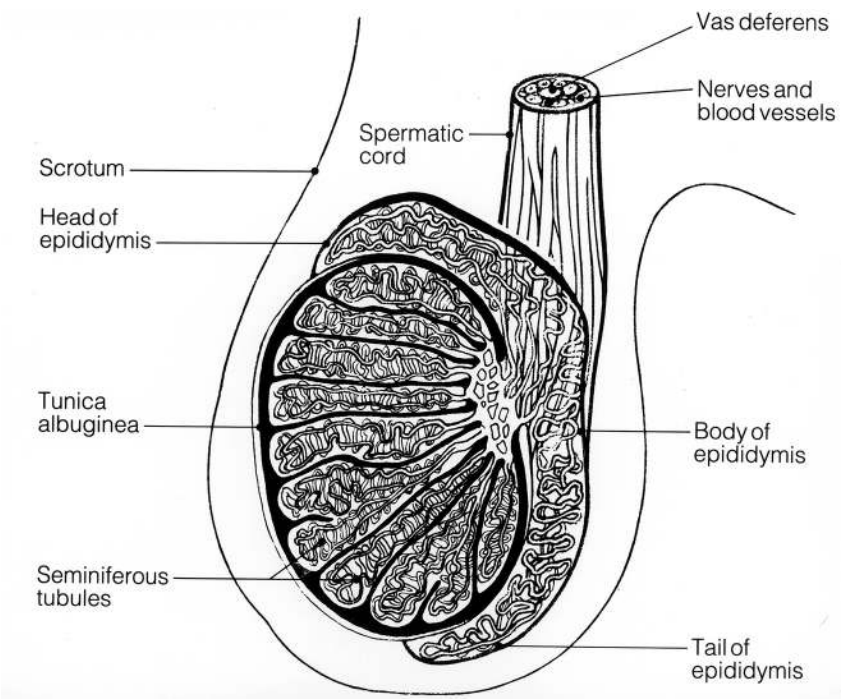

Figure 1.3 Lateral cross-section view of a human testis. Courtesy of the National Cancer Institute

the testis. Testosterone and estradiol act at the hypothalamus and the anterior pituitary to inhibit GnRH and gonadotropin secretion [3].

1.2.1.4 Seminiferous Tubules

The seminiferous tubule compartment of the testis is composed of Sertoli cells and germ cells, where spermatogenesis occurs. Sertoli cells have many functions, most of which are associated with germ cell development and movement. The following are some of the most important functions of Sertoli cells: (1) provide structural support; (2) create tight junctions that form an immunological blood–testis barrier; (3) contribute to germ cell migration and spermiation; and (4) nourish germ cells via secretory products [4].

Germ cells are located within the seminiferous tubules of the testis and give rise to spermatozoa for male reproduction. Germ cell lines are established by week four of embryogenesis, and somatic cells surrounding the germ cells lead to germ cell differentiation into the male or female pathway. In males, these somatic cells that lead to germ cell differentiation are the Sertoli and Leydig cells. Once directed down the male path, the gonocytes migrate to the basal membrane and become spermatogonia around six months after birth, remaining dormant until puberty [5].

Surrounding the seminiferous tubules are multiple layers of tissue, called peritubular tissue, which contains peritubular myoid cells that are thought to have various functions within the testis. Peritubular myoid cells are believed to create a smooth muscle layer surrounding the tubules that exerts a contractile force to traffic spermatozoa throughout the testis. In addition, myoid cells within the peritubular tissue are also responsible for maintaining spermatogonial stem cells. Studies have shown that peritubular myoid cells secrete GDNF (glial cell derived neurotrophic factor) during spermatogenesis, leading to signaling of a co-receptor RET, which leads to upregulation in Src family kinase (SFK) signaling and eventually self-renewal of spermatogonial stem cells via activation of genes encoding transcription factors [6]. Knockout studies of the GDNF pathway have demonstrated loss of spermatogonia and infertility, and overexpression studies of GDNF have revealed buildup of spermatogonial stem cells with no differentiation, leading to the conclusion that GDNF signaling is crucial for maintaining spermatogonial stem cells [6].

The blood–testis barrier is the barrier between the seminiferous tubules and the blood vessels within the testis. This barrier is actually composed of the Sertoli cells of the seminiferous tubules, which is why it is also referred to as the Sertoli cell barrier. The blood–testis barrier is composed of four separate cell junctions – tight junctions, ectoplasmic specializations, desmosomes, and gap junctions – which are all present between Sertoli cells and create two separate compartments within the blood–testis barrier: the basal and adluminal compartments [7]. This allows germ cells to be isolated from blood vessels and the lymphatic systems within the adluminal compartment, creating a microenvironment necessary for the completion of meiosis without a normal immune response from the male's immune system acting against the newly created sperm [7].

1.2.2 Spermatogenesis

Spermatogenesis is the process by which spermatozoa are produced from germ cells within the seminiferous tubules of the testis. This process takes place at puberty and continues throughout adulthood. Spermatogenesis in humans occurs in three stages: (1) a mitotic phase known as spermatocytogenesis in which stem cells divide to produce Type A spermatogonia that replace themselves or Type B spermatogonia that go down the differentiation path into spermatozoa; (2) a meiotic phase in which primary spermatocytes undergo division to produce haploid spermatids; and (3) a metamorphic phase known as spermiogenesis in which spermatids become spermatozoa. As mentioned previously, it is believed that Sertoli cells are responsible for structural support and germ cell nourishment throughout spermatogenesis. The entire process takes approximately 74 days to complete and happens at different times in different parts of the testis. This creates an overlapping production cycle in which spermatogonia can be found at different states of maturation throughout the testis.

1.2.2.1 Testis Stem Cells

In order for normal spermatogenesis to occur, testis stem cells must migrate correctly during embryogenesis, undergo renewal to replace themselves during spermatocytogenesis, and proliferate to produce daughter cell lines capable of forming mature spermatozoa. Gonocytes migrate and become spermatogonia around

six months of age, remaining dormant until puberty. Once puberty occurs, mitotic division results in two separate cell lines, and GDNF secretion during spermatogenesis aids in the maintenance of spermatogonial stem cells. These separate cell lines lead to the proliferation of Type A spermatogonia that replenish themselves, or Type B spermatogonia that differentiate into spermatozoa.

1.2.2.2 Meiosis

Meiosis consists of a first and second cellular division, during which primary and secondary spermatocytes are produced, respectively. When normal spermatogonia first enter meiosis, their karyotype is originally 46,XY; however, after the second cellular division and completion of meiosis, haploid spermatids are produced containing a 23,X or 23,Y karyotype. This entire process from Type B spermatogonia to haploid spermatids last approximately 24 days in humans, and adjacent spermatocytes remain attached to one another via cytoplasmic bridges to allow for the sharing of mRNA and coordinated progression throughout meiosis [8]. Genetic recombination occurs during the pairing of homologous chromosomes in prophase, allowing for the exchange of DNA between maternal and paternal homologues, which results in genetic variation in subsequent generations.

1.2.2.3 Spermiogenesis

Throughout spermiogenesis, the spermatids produced during meiosis undergo various changes to mature into spermatozoa. The sperm head is reshaped, DNA undergoes condensation, cytoplasm is reduced, the acrosome is formed from the Golgi complex, and the axoneme is formed from centrioles and continues to grow [8]. At the end of spermiogenesis, mature spermatozoa are eventually released from the Sertoli cells into the seminiferous tubule lumen in a process known as spermiation.

1.3 The Epididymis

1.3.1 Epididymal Structure

The epididymis is the transport duct for spermatozoa between the testis and vas deferens. It is divided into three parts: a head (caput), a body (corpus), and a tail (cauda). As sperm travel throughout the epididymis, they undergo final maturation processes allowing for increased motility and fertility.

1.3.1.1 Vascular Supply and Innervation

The head and body of the epididymis both receive blood supply from a branch of the testicular artery, whereas the tail of the epididymis is supplied by the deferential artery of the vas. The epididymis is innervated by the intermediate spermatic nerve, which arises from the superior portion of the hypogastric plexus, and inferior spermatic nerve, which is a branch of the pelvic plexus [2].

1.3.1.2 Epididymal Epithelium

The epithelium of the epididymal tubule consists of principal, basal, apical, and clear cells [9]. Principal and basal cells make up the majority of the epididymal tubule cells, and the principal cells with their long stereocilia are responsible for resorption of testicular fluid and secretion of nutrients for sperm maturation. The basal cells are located at the base of principal cells and are undifferentiated precursors of principal cells. Apical and clear cells are the remaining groups of cells found within the epididymal epithelium. Apical cells are more commonly found within the head of the epididymis and contain an abundance of mitochondria, whereas the clear cells are more commonly found within the tail and contain a large number of endocytic vesicles and lipid droplets [9].

1.3.1.3 Epididymal Contractile Tissue

Just as there is a smooth muscle layer surrounding the seminiferous tubules to traffic spermatozoa throughout the testis, similar contractile tissue surrounds the epididymis. As a sperm traverses from the head to the tail of the epididymis, the amount of smooth muscle surrounding the epididymal tubule increases along its course. This allows for increased peristalsis to advance the sperm along the length of the epididymis toward the vas deferens.

1.3.2 Epididymal Function

Aside from serving as the transport system for spermatozoa between the testis and vas deferens, the epididymis also has two other functions: (1) to act as a reservoir for sperm storage during the process of spermatogenesis; and (2) to assist in sperm maturation and promote increased motility and fertility via several biochemical changes.

1.3.2.1 Sperm Transport

It has been estimated that sperm transport through the human epididymis ranges anywhere from 2 to 12

days, and this transport time is independent of a male's age [10]. Prior to Johnson and Varner's studies, it was thought that humans had delayed epididymal transit times to accommodate for the slow process of spermatogenesis and sperm maturation; however, Johnson and Varner's research contested these claims and showed that men with greater rates of daily spermatozoan production have faster epididymal transit times, with some having a transit time of just two days, indicating maturation may occur very rapidly within the epididymis [10].

1.3.2.2 Sperm Storage

After sperm traverse through the head and body of the epididymis, a large majority are retained in the tail for storage. Several findings support the fact that the caudal epididymis is the spermatozoa storage site: (1) following repeated ejaculation, sperm were expelled from the caudal epididymis, but the rate of sperm transit throughout the caput and corpus remain unchanged; (2) the ducts proximal to the cauda epididymis have neuromusculature that results in slow, regular contractions, whereas the cauda epididymis normally has a neuromusculature that is relatively dormant but produces nerve-mediated, short, forceful contractions; and (3) spermatozoa in the vas deferens following ejaculation return to the cauda epididymis [11]. Although the exact amount of time that sperm can remain fertile within the cauda is unknown, some studies have indicated that caudal sperm can preserve their capability of fertilizing an egg for up to three weeks, and their motility is maintained for twice as long as their ability to fertilize [11].

1.3.2.3 Sperm Maturation

As sperm pass through the epididymis, they must undergo maturation processes to increase motility and fertility. In previous studies, spermatozoa released from the caput epididymis were immotile or displayed weak, beating movements that did not result in forward movement; however, motile spermatozoa with strong, beating, forward movements were first identified in the corpus, and an even larger population was found in the cauda [12]. Some studies have questioned the claims that epididymal maturation is necessary in humans, noting that spermatozoa aspirated from the efferent ducts or from blocked ducts has led to fertilization *in vitro*, and some patients are capable of conceiving after anastomosis of the rete testis or seminiferous tubule to the vas deferens [11]. In men with nonobstructive azoospermia, finding sperm within the testis during a procedure known as testicular sperm extraction allows those sperm to be used for *in vitro* fertilization (IVF) with intracytoplasmic sperm injection, further questioning the need for epididymal maturation, at least in the artificial setting of IVF. The maturation mechanisms for gaining motility may be extraordinarily different when comparing normal physiological conditions versus abnormal tract conditions. In addition to gaining motility, sperm must undergo changes that increase their ability to fertilize an oocyte. *In vivo* and *in vitro* studies have yet to show that testicular spermatozoa are capable of fertilizing an oocyte, and additional reports show that spermatozoa must pass through a proximal portion of the epididymis in order to bind the zona pellucida and penetrate the oocyte [11]. Several important biochemical changes take place that allow for better migration through the female reproductive tract and improved zona pellucida adherence: (1) the spermatozoan membrane gains a net negative charge; (2) disulfide bonds are formed in the nucleus and perinuclear matrix, leading to increased structural stability during egg penetration; and (3) exchange of glycosylated proteins and sterols in the sperm plasmalemma [12]. These maturation processes observed in the epididymis are necessary for males to achieve paternity without assisted reproductive means.

1.4 Vas Deferens

1.4.1 Vas Deferens Structure

The vas deferens is a tubular organ derived from the mesonephric duct and functions as a transport system between the epididymis and ejaculatory ducts. The vas deferens is approximately 30–35 cm long, 2–3 mm in diameter, and has a luminal diameter of 300–500 μm [9]. In cross-section, the vas deferens is composed of an outer adventitial sheath containing nerves and blood vessels, a muscular wall composed of inner and outer longitudinal and circular smooth muscle, and an inner mucosal layer composed of pseudostratified columnar epithelium with stereocilia [9]. The three-layered muscular wall gives the vas deferens the greatest muscle-to-lumen ratio compared to any other hollow organ in the human body. Its arterial blood supply is derived from the artery of the vas deferens, and the veins of the vas deferens drain into the pelvic venous plexus.

1.4.2 Vas Deferens Function

The vas deferens serves two functions in the male reproductive system: (1) transport of sperm from the epididymis to the ejaculatory ducts; and (2) absorption and secretion of various substances to create a viable environment for the sperm.

1.4.2.1 Sperm Transport

The most widely understood function of the vas is to act as a conduit for sperm between the epididymis and ejaculatory ducts. Peristaltic contractions of the thick muscular layer surrounding the vas deferens aids in this transport.

1.4.2.2 Absorption and Secretion

After complex studies of the vas deferens using light and electron microscopy, the absorptive and secretory functions of the human vas were discovered based on the epithelial morphology. Electron micrographs of principal cells discovered that these particular cells are capable of synthesizing proteins and glycoproteins, and additional studies revealed that the endocytotic invaginations of the principal cell membranes, the phagolysosomes, and the small, coated vesicles in the cytoplasm are important for protein absorption from the lumen [13]. Two other interesting findings were discovered in Hoffer's studies: (1) the presence of mitochondrion-rich cells and dense inclusion bodies in the nuclei of principal cells; and (2) mitochondrion-rich cells that appear near puberty. Although the function of these cells is still in question, it is hypothesized that the mitochondrion-rich cells are involved in the acidification of seminal plasma, and the inclusion bodies may be androgen-dependent structures within the vas deferens with an unknown function [13]. These additional discoveries have brought into question the previous belief that the vas deferens was only a transport duct for sperm.

1.5 Seminal Vesicle and Ejaculatory Ducts

1.5.1 Seminal Vesicle Structure

The seminal vesicles are paired glands located at the base of the prostate, measuring approximately 5–10 cm in length and 3–5 cm in diameter, with an average volume of 13 ml [9]. Each seminal vesicle is a coiled tube with diverticula scattered throughout its wall, and the wall of each vesicle is composed of three layers: an external connective tissue layer, a middle smooth muscle layer, and an inner mucosal layer lined with cuboidal and pseudostratified columnar epithelium and protein-secreting cells [9]. The primary blood supply of the seminal vesicles comes from the vesiculodeferential artery, which is a branch of the umbilical artery, and venous drainage occurs via the vesiculodeferential vein [14]. The seminal vesicles are innervated by parasympathetic input from the pelvic plexus, and sympathetic input from the hypogastric nerves.

1.5.2 Ejaculatory Duct Structure

The lower pole of the seminal vesicle consists of a straight duct that merges with the ampulla of the vas deferens to form the ejaculatory duct. Each ejaculatory duct is roughly 2 cm in length, extending from the base of the prostate toward its opening on the verumontanum [9]. The ejaculatory duct walls are thin and consist of three layers: an outer fibrous layer, a thin layer consisting of smooth muscle fibers, and a mucosal layer lined by columnar epithelium [9].

1.5.3 Seminal Vesicle and Ejaculatory Duct Function

Approximately 80 percent of seminal fluid is secreted by the seminal vesicles; however, this portion of the seminal fluid is rarely seen in the first ejaculate fractions, which contain high concentrations of spermatozoa and prostate secretions [2]. The fluid secreted by the seminal vesicles is yellowish in color with a neutral to alkaline pH and contains a high concentration of fructose, coagulation proteins, and prostaglandins [9]. After fluid is produced by the seminal vesicles, it progresses through the ejaculatory ducts and empties into the prostatic urethra. The exact function of this fluid is unknown, but some studies indicate that the fructose may provide a nutrient-rich environment for spermatozoa and the coagulation proteins may assist in sperm motility and suppression of immune response in the female reproductive tract [2]. Ejaculatory duct obstruction is a rare but potentially reversible cause of obstructive azoospermia.

1.6 Spermatozoa

1.6.1 Anatomy and Physiology

The spermatozoon is a motile sperm cell that joins with an ovum to form a zygote. The human

spermatozoon is approximately 60 μm in length and is composed of three units: a head, a neck, and a tail [2]. The ovaloid head is approximately 4 × 3 μm, containing condensed chromatin, nucleoproteins, and an acrosomal cap with enzymes essential for oocyte fertilization [9]. The neck contains centrioles that are necessary for connection of the sperm head to the tail. The sperm tail is divided into the middle, principal, and end pieces. The middle piece of the tail comprises the axoneme, which is composed of two central microtubules that are surrounded by nine microtubule doublets (9 + 2 microtubule arrangement), and a spiral mitochondrial sheath that generates the energy necessary for motility [3]. The principal and end pieces of the tails are both surrounded by a fibrous sheath [2]. The axoneme is the most important structure necessary for sperm motility. The microtubule doublets of the axoneme are all connected by dynein, and the ATPase function of dynein in conjunction with hundreds of other enzymes and structural proteins leads to the characteristic sperm flagellar movement [2]. Defects can occur in this microtubule structure, leading to poor sperm motility and infertility issues. Primary ciliary dyskinesia is a rare autosomal recessive genetic disorder that causes defects in the action of all cilia in the body, including flagellum of sperm.

1.7 Summary

The male reproductive system is a complex balance of hormonal regulation and pelvic organs. Spermatogenesis is regulated by pulsatile secretions of GnRH, LH, and FSH and feedback regulation on the HPG axis. Mitosis, meiosis, and spermiogenesis lead to the production of immotile spermatozoa within the seminiferous tubules of the testis. During transport through the epididymis, sperm undergo maturation processes to increase motility and fertility. Sperm are transported through the ejaculatory ducts and into the urethra during ejaculation, combining with the seminal fluid that provides a nutrient-rich environment, assists in sperm motility, and suppresses the immune response in the female reproductive tract.

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