Section 1 **Anatomy and Physiology of the Male Reproductive System**

Chapter 1

Anatomy and physiology of the male reproductive system

Ray Costabile

The male reproductive hormonal axis

Maintenance of normal reproductive function is dependent on the coordinated release of hormones in the hypothalamic–pituitary–testis cascade. Gonadotropin-releasing hormone (GnRH) is released in a pulsatile pattern into the pituitary portal blood system from neuroendocrine cells in the basal hypothalamus and acts to stimulate gonadotropes in the anterior pituitary to synthesize and release two peptide hormones, follicle-stimulating hormone (FSH) and luteinizing hormone (LH) into the circulation. Once in the bloodstream these hormones reach the testis, where **LH stimulates testosterone production by the Leydig cells in the interstitium while FSH supports spermatogenesis in the seminiferous epithelium by stimulation of the Sertoli cells.** A focused network of negative feedback relationships finesse testosterone secretion and sperm production. This cascade is maintained by steroid and peptide feedback within the testis as well as the hypothalamic and pituitary gland (see Figure 1.1).

Hypothalamus

The hypothalamus is located in the lower aspect of the third ventricle of the brain. It is a complex region in the brain, which responds to different signals generated externally and internally as it is richly connected by neural projections to other parts of the brain including the amygdala as well as the olfactory bulbs. The output of GnRH is influenced by three different rhythms including seasonal, circadian, and pulsatile, leading to peak levels during the spring, the early morning hours as well as every 90 to 120 minutes. The precursors of GnRH neurons migrate to their position in the hypothalamus from the olfactory placode during embryonic development.

Pituitary

The pituitary body is found in the hypophyseal fossa inferior to the hypothalamus. It is divided into two distinct lobes: anterior and posterior. The posterior lobe is known as the neurohypophysis and is stimulated by neurons from the hypothalamus to secrete both oxytocin and vasopressin. The anterior lobe, also known as the adenohypophysis, in contrast communicates via blood-borne factors secreted by the hypothalamus. These neuropeptides are transported by the portal blood system to the anterior lobe where they stimulate synthesis and secretion of adenohypophyseal hormones. **Including the gonadotropes, LH and FSH, the anterior pituitary also secretes other glycoprotein hormones, corticotropin-related peptides, and somatomammotropin hormones.** Prolactin and growth hormone have a significant contribution to male reproductive function.

Steroid feedback loop

Testosterone provides negative feedback suppression of the release of GnRH through androgen receptors in the pituitary and hypothalamic neurons. Testosterone is also readily metabolized to dihydrotestosterone and estradiol by 5α-reductase and aromatase, respectively, in the testis and peripheral tissues. **Both testosterone and estrogen play important roles in the regulation of reproductive function at the cellular and tissue levels.** This can be demonstrated clinically by individuals with genetic mutations resulting in partial or complete loss of function in androgen and estrogen receptors with increased pituitary release of LH [1]. Stimulation of the Sertoli cell by FSH results in production of inhibin, a glycoprotein hormone, which suppresses FSH secretion by gonadotropes. Regulation of gonadotropin secretion exists for different steroids. While the negative effect of testosterone on LH secretion is primarily mediated by the androgen itself, the effect of testosterone on FSH secretion is mediated by estradiol [2].

Development of the male reproductive axis

Testosterone, dihydrotestosterone, and müllerian inhibiting substance from the fetal testes are important determinants of sexual phenotype. Sertoli cell precursors secrete müllerian inhibiting substance (also known as anti-müllerian hormone) which prevents the development of the female reproductive tract structures leading to a male phenotype [3]. Secretion of testosterone by the fetal Leydig cells stimulates differentiation of the wolffian duct system, which later develops into the vas

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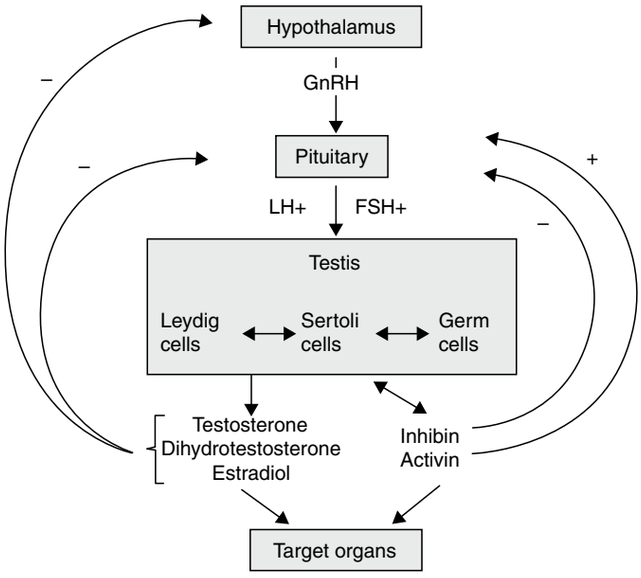

Figure 1.1 Diagram of the hypothalamic–pituitary–testis axis.

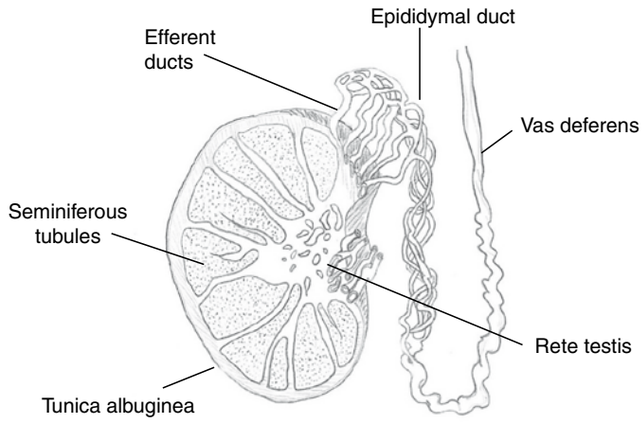

Figure 1.2 Schematical drawing of the human testis showing seminiferous tubules, epididymis, and vas deferens.

deferens, epididymis, and sex accessory glands. **Events of early testis differentiation are controlled by the sex-determining region on the Y chromosome (SRY) gene.** The SRY gene acts synergistically with other transcription factors to initiate male sex differentiation [4].

Aging of the male reproductive system

Epidemiologic studies have demonstrated that with age, circulating levels of testosterone progressively decline [5]. This decline in androgen levels is associated with modifications in body composition, diminished energy, muscle strength and physical function, reduced sexual function, and depressed and decreased cognitive function [6]. This age-related decline of testosterone levels is complex involving both intrinsic and extrinsic factors to the Leydig cell. The brown Norway rat has become a well established model for human reproductive aging, and studies have reported that the number of Leydig cells per testis remains unchanged compared to younger controls [7]. These findings suggest that functional changes to the Leydig cells rather than their loss account for the reduction in testosterone [8]. High testicular concentrations of testosterone are essential to maintain spermatogenesis and men older than age 40 years have been shown to have significantly lower fecundity [9]. Further studies are likely to center on investigation of the intracellular molecular mechanisms leading to decreased Leydig cell steroidogenesis. These may lead to the discovery of potential methods by which to ameliorate the decline of testosterone synthesis in the aging male, which may have an impact on male infertility.

Macroscopic anatomy of the testis

The ovoid testis in young healthy males has a volume of 15 to 25 mL and a longitudinal length of 4.5 to 5.1 cm [10]. A capsule made up of three distinct layers surrounds the parenchyma of the testis: the tunica vaginalis, tunica albuginea, and the tunica vasculosa. The testes receive their blood supply from the testicular arteries, the cremasteric arteries, and the deferential arteries. The testicular artery arises from the abdominal aorta just below the renal artery and becomes a component of the spermatic cord above the internal inguinal ring as well as being intimately associated with a network of anastomotic veins, which eventually form the pampiniform plexus. A counter current heat exchange in the spermatic cord provides blood to the testis that is 2 to 4°C lower than the rectal temperature in a normal male [11]. The testicular arteries penetrate the tunica albuginea and then travel inferiorly along the posterior surface of the testicle and eventually ascend onto the anterior surface with several branches that course into the parenchyma. The location of these vessels should be considered as they may be injured during biopsy or orchidopexy. The medial and lateral aspects of the superior pole have the lowest density of superficial vessels compared with the inferior and anterior portions of the testicle.

The testicle is divided into compartments by septa, which are projections of the tunica albuginea. Each septum separates the seminiferous tubules, as well as the interstitial tissue which is composed of Leydig cells, blood vessels, lymphatics, mast cells, nerves, and macrophages. **The seminiferous tubules are the site of germ cell production.** They are looped tubules continuous at their ends with the rete testis, a network of collecting tubes that eventually coalesce to form efferent ducts that provide a conduit for collecting the testicular fluid and spermatozoa to the caput epididymis. The seminiferous tubule is made up primarily of Sertoli cells, germ cells, and peritubular myoid cells (see Figure 1.2).

The Leydig cell

Leydig cells can be identified by their location in the interstitium of the testis. They are distinguished by the presence of a

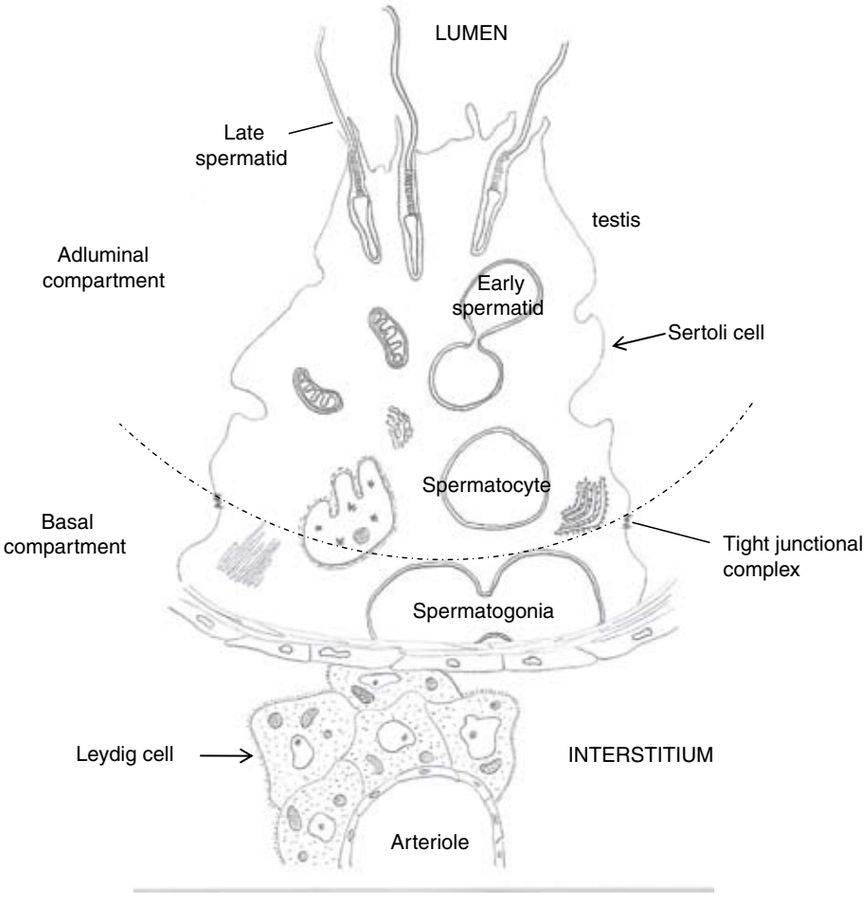

Figure 1.3 A diagrammatic representation of the seminiferous tubule and the interstitium of the testis.

round nucleus, prominent nucleolus, and Reinke crystals in the cytoplasm. Numerous gap junctions allow direct communications between Leydig cells. The Leydig cell is responsible for the majority of androgen steroid production. The potency of the steroid hormones secreted by Leydig cells is reflected by the small percentage of the human testis occupied by Leydig cells [12]. Circulating levels of testosterone in the serum dramatically fluctuate in a life cycle. The maximal concentration of testosterone is reached during the second and third decade of life, reaches a plateau, and then starts to decline thereafter. Leydig cell function is regulated by pituitary hormones, paracrine factors secreted by cells within the seminiferous tubules, as well as autoregulatory factors.

The Sertoli cell

The Sertoli cell is a non-dividing somatic cell of epithelial origin that rests on the basement membrane and forms the wall of the tubule. An irregularly shaped nucleus, prominent nucleolus, low mitotic index, Sertoli–germ cell connections, as well as unique tight junctional complexes between adjacent Sertoli cell membranes characterize this unique cell. Surface processes from the Sertoli cells extend outward to surround germ cells as this provides an arrangement such that each germ cell is supported by a number of adjacent Sertoli cells [13]. **The Sertoli cell has several distinct functions that facilitate the maturation of the germ cells. First, it provides a physical scaffold upon which the germ cells develop and migrate towards the lumen of the tubule. Second, the Sertoli cell forms the blood–testis barrier with specialized tight junctions that exist between these cells. Third, Sertoli cells create the focused microenvironment essential for germ cell maturation.** These distinctive functions also encompass phagocytosis, fluid secretion, and production of a variety of molecules (see Figure 1.3).

The quest for a Sertoli cell product as a marker of Sertoli cell function that is helpful in the evaluation of an infertile patient has yet to be elucidated. Androgen-binding protein was one of the first extracellular protein markers identified in the 1970s and since then a myriad of other secretory products have been discovered as well. Inhibin is a glycoprotein hormone secreted primarily by the Sertoli cells and suppresses FSH secretion. Some have proposed that serum inhibin B could possibly be an independent marker of impaired testicular function, as well as a predictor of the presence of sperm in the testes of infertile men [14].

The blood–testis barrier

Within the testis there exists a functional blood–testis barrier. This barrier, made up of specialized junctions, creates a division in the seminiferous epithelium between adjacent Sertoli cells that forms a basal compartment and an adluminal compartment [15]. The basal compartment is accessible to blood-borne substances via the extracellular spaces; however, due to the occluding nature of the barrier these substances are prevented from directly reaching the adluminal compartment. The adluminal compartment contains mature germ cells, while the basal compartment contains spermatogonia and young spermatocytes. The different functional components of the blood–testis barrier include the tight junctional complexes between Sertoli cells, peritubular myoid cells, as well as the endothelial cells in the nearby capillaries [16]. The clinical significance of this barrier is reflected by post-pubertal protection of the adluminal (inferior) compartment of the testis from post-pubertal testicular insults and the lack of development of antisperm antibodies unless this barrier is breached.

Spermatogenesis

Spermatogenesis is an elaborate process of cell differentiation concluding with development of the fully differentiated highly specialized haploid motile spermatozoa. Spermatogonia, the most immature germ cells, reside along the basement membrane of the seminiferous tubule in the basal compartment. **The slow evolution of spermatogonia into highly specialized spermatozoa requires approximately 64 days** [17]. The first mitotic divisions occur in the fetal testis generating the spermatogonia and primary spermatocytes that are present at birth. There appears to be very little activity in further development until the onset of puberty. There are three types of spermatogonia: the dark type A, the pale type A, and the type B spermatogonia. These cells undergo several mitotic divisions to produce a large number of cells that will either participate in stem cell renewal or go on to create daughter cells, which will later become spermatocytes.

Primary spermatocytes are unique in that they undergo two successive cell divisions that produce the spermatids. This process, called meiosis, comprises two cell divisions following replication of the chromosomes, generating haploid germ cells. It is the fusion of the haploid spermatozoon with an equally haploid ovum that restores the diploid number of chromosomes in the cells of the embryo. There are two meiotic divisions involving primary and secondary spermatocytes. Each meiotic division is comprised of four distinct phases including prophase, metaphase, telophase, and anaphase. Primary prophase I is long and subdivided into five stages: leptotene, zygotene, pachytene, diplotene, and diakinesis. **Spermiogenesis refers to the dramatic metamorphosis that a round spermatid undergoes to become an elongated flagellar cell capable of motility.** This transformation includes the development of the acrosome, condensation of chromatin, formation of the flagellum, and migration of cytoplasmic organelles [18].

The sperm head consists principally of a nucleus, which contains the condensed chromatin material as well as the acrosome. The acrosome is a membrane-bound organelle that contains the hydrolytic enzymes necessary for penetration of

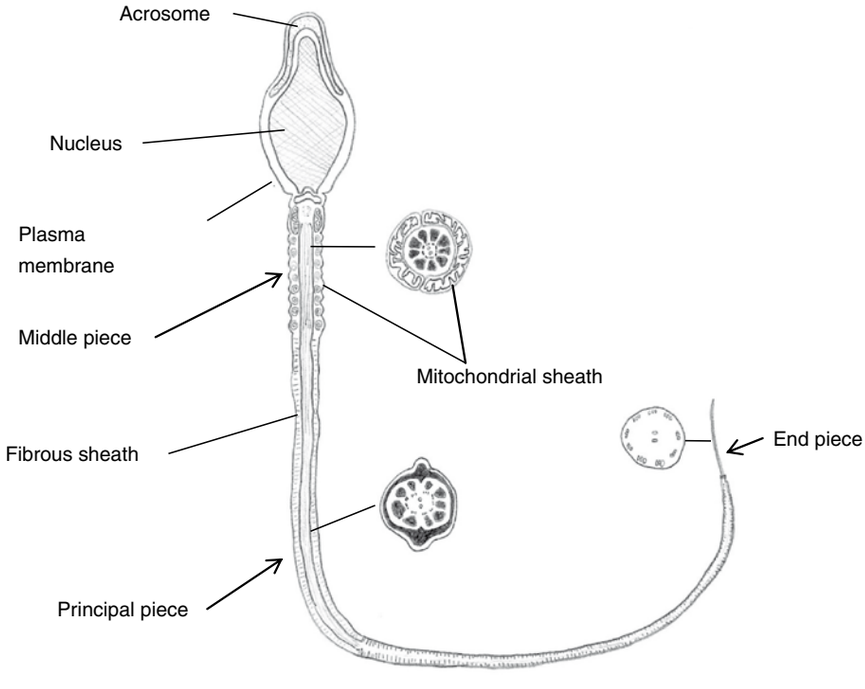

Figure 1.4 Diagram of a typical mammalian spermatozoon. Cross-sectional insets show the orientation of the internal cell structure.

the egg before fertilization [19]. The flagellum forms at the lower pole where the mitochondria coalesce and generate the energy needed for motility. The mitochondria are arranged in a helical pattern surrounding a set of outer fibers and the characteristic 9 + 2 microtubular structure of the axoneme (see Figure 1.4)

The initiation and maintenance of normal spermatogenesis is dependent on the synergistic effect of FSH and testosterone [20]. While germ cells require these hormones they do not possess receptors for either FSH or testosterone. Sertoli cells possess both these receptors and it is thought that the actions of FSH and testosterone are mediated by the Sertoli cell.

Genetic factors critical for spermatogenesis are being rapidly elucidated. **Investigations in men with severely impaired spermatogenesis led to the discovery of submicroscopic deletions of a region of the Y chromosome** [21]. These regions are referred to as the **a**zoospermic **f**actor (AZF) a, b, and c with distinct genes that have been deleted in azoospermic men such as the DAZ (deleted in azoospermia) gene found in the AZF_c region. Localization of specific genes that are critical for spermatogenesis remains the subject of active investigation.

Epididymis

Spermatozoa acquire the capacity to become fully motile as well as the ability to recognize and fertilize an egg within the epididymis. These transformations of spermatozoa are called sperm maturation. Sperm motility and fertilization capacity are both androgen-dependent processes. The loss of androgens results in the loss of epididymal weight, as well as changes in the components of the epididymal fluid secretions [22]. The epididymis, derived from the wolffian (mesonephric) duct, is an organ consisting of a single highly convoluted duct, which the testicular sperm must pass through. It is attached to the superior and inferior pole of the testis and is closely applied to the posterior aspect. The epididymis is divided into three major regions: caput, corpus, and cauda. The caput epididymis overlies the superior pole of the testis and the cauda overlies the inferior pole of the testis. The intervening region is referred to as the corpus.

The epididymis is surrounded by the visceral layer of the tunica vaginalis, except over the posterior aspect, which is attached to the scrotum and spermatic cord by a fibrofatty connective tissue. **Approximately 10 ductuli efferentes arise from the rete testis that eventually come together to form a single epididymal duct. In humans, the epididymal tubule is approximately 3 to 4 m in length** [23]. The vascular supply to the epididymis is from two sources. The caput and corpus are supplied from the superior and inferior epididymal branches of the testicular artery. The cauda is supplied from the branches of the deferential artery. This blood supply is characterized by tortuosity of the vessels as well as a large number of anastomotic communications [24]. While the venous drainage of the epididymis may vary, the veins of the caput and proximal corpus communicate directly with the pampiniform plexus. The veins arising from the cauda and distal corpus eventually communicate with the deferential or cremasteric veins.

Functions of the epididymis

The three primary functions of the epididymis are sperm maturation, sperm transport, and sperm storage. Maturational changes allow sperm the capacity to become motile and fertilize as they transit from the testis, through the epididymis to the vas deferens. It has been shown that as human spermatozoa migrate through the epididymis they develop increased motility. In comparison to the caput epididymis the more distal portions of the epididymis house a higher percentage of spermatozoa capable of efficient motility [25]. While the exact mechanisms that detail sperm maturation are not fully understood, the consensus is that these processes are potentiated through the interaction with the epididymis during migration into more distal regions of the duct.

The transit time of the sperm in the human epididymis averages 12 days but is highly variable, with some sperm moving ahead through the epididymis in as little as 2 days [26–28]. Transport through the proximal epididymal duct is principally due to spontaneous, peristaltic contractions of the smooth muscle that surrounds the epididymal duct. Other contributing factors that aid in the transport of sperm include motile cilia as well as the flow of the secreted testicular fluid. Sperm transport time through the epididymis has also been shown to vary with age and sexual activity with a direct correlation to the differences in daily rate of sperm production [29].

In humans the major storage site of spermatozoa is the cauda epididymis where approximately half of the total number of spermatozoa are stored [26]. It has been suggested that preservation of sperm viability and motility in humans is not as efficient as it is in other species [30]. While there are numerous studies using experimental animals, the fate of unejaculated sperm is still unknown.

Ductus vas deferens

The vas deferens is a thick muscular tube that measures approximately 30 to 40 cm from the cauda epididymis to the point of fusion with the seminal vesicle and ejaculatory ducts. Five portions have been previously described: epididymal, scrotal, inguinal, pelvic, and ampulla. The vas deferens, like the epididymis and seminal vesicle, is derived from the mesonephric duct. The ability to propel sperm forcefully is dependent on a three-layered muscular coat, with an inner and outer longitudinal layer and a middle circular layer. While the vas deferens receives nerve fibers from both the sympathetic and parasympathetic nervous system, the rich supply of adrenergic fibers contributes to the efficiency of sperm transport. The vas deferens receives its blood supply from the deferential artery via the inferior vesical artery, and the deferential vein accompanies it.

Pearls

- LH stimulates testosterone production by the Leydig cells in the interstitium while FSH supports spermatogenesis in the seminiferous epithelium by stimulation of the Sertoli cells.
- The hypothalamus is a complex region in the brain that responds to different signals generated externally and internally as it is richly connected by neural projections to other parts of the brain including the amygdala as well as the olfactory bulbs.
- Apart from the gonadotropes, LH and FSH, the anterior pituitary also secretes other glycoprotein hormones, corticotropin-related peptides, and somatomammotropin hormones.
- Both testosterone and estrogen play important roles in the regulation of reproductive function at the cellular and tissue levels.
- Events of early testis differentiation are controlled by the sex-determining region on the Y chromosome (SRY) gene.
- The ovoid testis in young healthy males measures 15 to 25 mL in volume and has a longitudinal length of 4.5 to 5.1 cm [10].
- A counter current heat exchange in the spermatic cord provides blood to the testis that is 2 to 4°C lower than rectal temperature in a normal male.
- The medial and lateral aspects of the superior pole have the lowest density of superficial vessels compared with the inferior and anterior portions of the testicle.
- The seminiferous tubules are the site of germ cell production.
- The Sertoli cell has several distinct functions that facilitate the maturation of the germ cells. First, it provides a physical scaffold upon which the germ cells develop and migrate towards the lumen of the tubule. Second, the Sertoli cell forms the blood–testis barrier with specialized tight junctions that exist between these cells. Third, Sertoli cells create the focused microenvironment essential for germ cell maturation.
- The slow evolution of spermatogonia into highly specialized spermatozoa requires approximately 64 days [17].
- Spermiogenesis refers to the dramatic metamorphosis that a round spermatid undergoes to become an elongated flagellar cell capable of motility.
- The initiation and maintenance of normal spermatogenesis is dependent on the synergistic effect of FSH and testosterone [20].
- Investigations in men with severely impaired spermatogenesis led to the discovery of submicroscopic deletions of a region of the Y chromosome [21].
- Spermatozoa acquire the capacity to become fully motile as well as the ability to recognize and fertilize an egg within the epididymis.
- Approximately 10 ductuli efferentes arise from the rete testis that eventually come together to form a single epididymal duct. In humans, the epididymal tubule is approximately 3 to 4 m in length [23].
- The three primary functions of the epididymis are sperm maturation, sperm transport, and sperm storage.
- The transit time of the sperm in the human epididymis averages 12 days but is highly variable, with some sperm moving ahead through the epididymis in as little as 2 days [26–28].
- The vas deferens is a thick muscular tube that measures approximately 30 to 40 cm from the cauda epididymis to the point of fusion with the seminal vesicle and ejaculatory ducts.

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Section 2

Evaluation

Chapter 2

History and physical examination of the infertile male

Moshe Wald

Introduction

The evaluation of the infertile male consists of a variety of components, which include a detailed medical, surgical, developmental, and reproductive history, as well as a careful physical examination, semen analyses and possibly other laboratory tests, all performed in concert with the evaluation of the female partner. The history and physical examination, along with appropriately obtained semen analyses, represent the core of the evaluation of the infertile male. In fact, the need for different laboratory tests is determined by the history and physical examination findings. For example, a cystic fibrosis screen, which is not part of the routine male infertility evaluation, should be ordered when a vas deferens can not be palpated on physical examination, a finding concerning for congenital absence of the vas deferens (CBAVD). This chapter will provide a comprehensive review of the history and physical examination of the infertile male as well as the indications and recommended timing for the performance of each component.

History

Obtaining a thorough medical and reproductive history that explores all aspects potentially related to fertility is a key component of the evaluation of the infertile male [1]. While the detailed history focuses on the male partner, pertinent information regarding the reproductive status of the female partner and the couple's fertility efforts should also be gathered.

Sexual and reproductive history

Duration of infertility and previous fertility should be determined, including details of any prior pregnancies achieved. Frequency of sexual intercourse and masturbation should be recorded, as well as the timing of coitus. It is important to determine whether the couple attempts to time intercourse with ovulation, and whether this is done in an effective manner that could optimize the chances of conception. As sperm remain viable within the cervical mucus and crypts for 48 hours or longer, the timing of sexual intercourse does not have to coincide exactly with ovulation, but most experts recommend vaginal intercourse every 2 days near the time of ovulation, ensuring the presence of viable sperm in the female reproductive tract during the critical 12- to 24-hour period in which the oocyte is within the fallopian tube and is capable of being fertilized [2]. While exceedingly frequent intercourse may result in inadequate numbers of sperm being deposited in the vagina, conversely, ovulation could be missed with infrequent sexual activity. The use of vaginal lubricants during intercourse should also be determined, as some of these substances, such as Astroglide® (BioFilm, Inc., Vista, CA), K-Y Jelly® (McNeil-PPC, Inc., Skillman, NJ), Surgilube® (Fougera, Melville, NY), and saliva, have been reported to negatively affect sperm motility [3,4,5]. Decreased libido, as well as erectile or ejaculatory dysfunction should be noted, as these could be associated with hypogonadism or other systemic disorders. While a history of absent or noticeably low ejaculate volume could also be part of the clinical picture of hypogonadism, it also suggests the possibility of other conditions, including retrograde ejaculation, ejaculatory duct obstruction, or congenital absence of the vas deferens.

Genitourinary infections

Information regarding any previous urinary tract infections or sexually transmitted diseases should be obtained. A history of prostatitis may lead to ejaculatory duct obstruction, and previous pyospermia may represent an inflammatory process with an adverse effect on sperm production. However, the direct causative relationship of these conditions to infertility has not been confirmed [2,6]. A history of previous epididymitis should also be noted, given its possible sequelae of epididymal obstruction.

Mumps orchitis and other forms of viral orchitis may develop in post-pubertal patients. In cases of previous mumps infection, it is important to confirm that the disease involved the testicles, as only 10–30% of pubertal patients who acquire mumps develop mumps orchitis [7]. Bilateral involvement has been reported in 20% to 60% of cases [2].

Childhood illnesses and developmental history

Delayed or absent puberty may indicate an endocrine disorder or an androgen receptor abnormality [8]. A history

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of gynecomastia may be associated with testis cancer, hyperprolactinemia, or estrogen abnormalities [9]. While unilateral cryptorchidism has been reported to only slightly decrease fertility, bilateral cryptorchidism results in a significant reduction in fertility [10,11].

Past surgical history

Various surgical procedures could potentially disrupt the physiologic regulation of different functions of the male reproductive tract, as well as damage the anatomic integrity of this system at different sites along its course. Surgery or trauma of the brain or pituitary could impair the hormonal regulation of spermatogenesis and testicular testosterone production. Pelvic or retroperitoneal surgery may affect erectile and ejaculatory function. For example, retroperitoneal lymph node dissection for testis cancer may involve sympathetic nerve injury, resulting in failure of emission or retrograde ejaculation. Bladder neck surgery may also result in retrograde ejaculation. Inguinal hernia repair may be associated with damage to the vas deferens, by inadvertent direct injury or compromising its blood supply. Additionally, the vas deferens may be entrapped in dense fibrosis associated with hernia repair using mesh, leading to vasal obstruction. Finally, scrotal surgery such as hydrocelectomy, spermatocelectomy or orchidopexy for torsion may result in injury and obstruction of the vas deferens and/or the epididymis. Testicular trauma or torsion may result in testicular atrophy or scarring. Furthermore, these events may lead to the formation of antisperm antibodies, possibly due to the disruption of the blood–testis barrier.

Systemic medical illnesses

Erectile dysfunction, retrograde ejaculation, and other ejaculatory abnormalities may develop in patients with diabetes mellitus or multiple sclerosis. Many other systemic disorders could have a negative effect on spermatogenesis. A febrile illness, even if associated with a disease that does not directly involve the genitourinary tract, could cause spermatogenesis impairment for up to 3 months [12]. End-stage renal disease has been reported to be associated with male infertility [2]. Men with testicular cancer or lymphoma may have fertility difficulties even before initiation of treatment, as low sperm concentrations have been reported in 60% or more of patients at the time of diagnosis [13,14,15]. Obviously, chemotherapy or radiotherapy administered for these conditions or other cancers may impair spermatogenesis. While these treatments may result in permanent azoospermia, return of spermatogenesis is possible under certain circumstances, although it may take up to 4 to 5 years to occur after completion of treatment [15,16,17]. Spermatogenesis recovery following radiation therapy or chemotherapy varies, depending on the specific agents used, doses, and duration of treatment [17].

A history of frequent or chronic respiratory tract infections in the setting of male infertility and lack of sperm motility should raise the suspicion for immotile cilia (or Kartagener's) syndrome, which also includes situs inversus [18]. Frequent respiratory infections associated with azoospermia suggests the possibility of Young's syndrome, in which epididymal obstruction is caused by inspissation of secretions [19]. A personal or familial history of cystic fibrosis (CF) is of importance, as almost all male patients with clinical CF have bilateral congenital absence of the vas deferens [20,21].

Prolactinoma or other pituitary tumors should be suspected with a history of severe headaches, galactorrhea, or impaired visual fields. Anosmia associated with male infertility should raise the possibility of Kallmann syndrome, a congenital form of hypogonadotropic hypogonadism.

Medications, recreational drugs, and gonadotoxin exposure

Certain medications, including nitrofurantoin, cimetidine, and sulfasalazine, have been reported to impair spermatogenesis [2]**.** A similar effect has been attributed to certain recreational drugs, including cocaine [22,23] and marijuana [24], as well as to anabolic steroid and chronic alcohol abuse [25]. **Additionally, the androgenic effect of steroids may cause hypogonadotropic hypogonadism, which is usually but not always reversible after the discontinuation of these agents** [26]**.** While the effect of cigarette smoking on spermatogenesis is unclear, it has been suggested that smoking could possibly be a cofactor in male patients with other causes of infertility [27].

Occupational or environmental exposure to pesticides or other toxic chemicals should be noted, as these substances may have a deleterious effect on sperm production or function. Additionally, a history of excessive heat exposure, either occupational or secondary to the frequent use of saunas and hot tubs is of relevance, as experimental hyperthermia and the frequent use of hot tubs have been shown to cause impaired semen quality and spermatogenesis [2].

Family history

The family history of the infertile male should focus on the phenotype of the maternal uncles, as the androgen receptor gene, as well as multiple other genes affecting male reproduction, is located on the X chromosome.

Physical examination

General examination

The physical examination of the infertile male should not be limited to a genital examination, and should include a detailed general examination, which can reveal identifiable abnormalities that may be associated with infertility and its underlying causes. The patient's habitus should be noted, as alterations of the normal male appearance may be associated with chromosomal or endocrine disorders that have an impact on fertility as well as on other health issues. For example, a eunuchoid appearance could be associated with Klinefelter syndrome or

Figure 2.1 Calipers used for measuring long and short testicular axis.

Figure 2.2 Orchometer used for measuring testicular volume. Image reproduced with kind permission from Prader.

hypogonadotropic hypogonadism. Additionally, abnormalities of the secondary sex characteristics and changes in the pattern of virilization, such as lack of temporal pattern balding, may also indicate a congenital endocrine disorder. Other pertinent findings on the general physical examination include gynecomastia, which is suggestive of either an imbalance between estrogen and androgen levels or increased prolactin levels, as well as situs inversus, which may be part of Kartagener's syndrome, a congenital disorder associated with immotile cilia leading to absent sperm motility.

Genital examination

A careful genital examination is a critical part of the evaluation of the infertile male. This examination can allow for identification of the cause of infertility, such as in cases of bilaterally absent vasa deferentia or clinically evident varicoceles, and may also direct the clinician toward the next steps of the evaluation that are required for a given scenario. For example, the absence of any palpable vas deferens on both sides suggests the diagnosis of congenital bilateral absence of the vas deferens (CBAVD), a condition closely associated with cystic fibrosis, and should prompt genetic testing for cystic fibrosis.

The entire genital area should be inspected for any findings concerning for sexually transmitted diseases, such as warts, sores, herpetic-like lesions, and any urethral discharge. The penis should be examined for any curvature or plaques, which could suggest Peyronie's disease. The possible presence of severe chordee should also be noted. The location of the urethral meatus should be determined, since significant hypospadias, as well as severe penile curvatures and chordee could interfere with proper deposition of semen in the vagina.

The examination of the scrotum should be performed with the patient both supine and standing in a warm room to allow for relaxation of the cremaster muscle. Use of a heating pad to relax the scrotum prior to examination is very effective without overheating the examiner or the patient. **The testicles should be carefully palpated to assess their consistency and to rule out the presence of an intratesticular mass. The dimensions of the testicles should be measured, using either calipers** (Figure 2.1) **for determination of the long and short testicular axis, or an orchidometer for assessment of testicular volume** (Figure 2.2) [**28**]. Testicular measurement by calipers should be done carefully, to avoid painful squeezing of the testicles. Interestingly, variations in the normal range for testicular dimensions between different ethnic groups have been reported. While the normal adult testis is greater than 4×3 cm in its greatest dimensions or greater than 20 mL in volume for Caucasians and African-Americans [29], Asian men normally have smaller testicles but higher sperm production per cubic