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# 1

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## *The Pathophysiology of Male Infertility*

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Pallav Sengupta and Chak-Lam Cho

### KEY POINTS

- Pathophysiology of male infertility involves complex multivariate mechanisms.
- Dysregulations of hormonal axes and endocrine cross-talks adversely affect male reproductive functions.
- Testicular disruptions directly impair semen parameters.
- Posttesticular impairments afflict spermatozoal maturation and transport.

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### Introduction

The male reproductive system apparently possesses simplistic functions so as to produce sperm and testosterone, but the underlying mechanisms are far more complex and yet to be completely revealed. Such elusive mechanisms of male reproductive functions have led to poor understanding of the actual causatives of male infertility in about 50% of the cases [1]. Disruption of male fertility may be reflected by impaired sperm parameters through multivariate factors at different levels [2,3,4]. Etiologies of male infertility may act at the pretesticular or neuroendocrine regulatory levels. Other factors may directly affect intratesticular sites, thereby afflicting the functions of Sertoli cells, Leydig cells, and germ cells. Disruptions can also occur at the posttesticular strata, impairing sperm maturation and transport. Besides the conventional concept of pathophysiology of male infertility, there is advent in male reproductive immunology as well as reproductive genetics and epigenetics, modulations of which may induce varying forms of impairment to the male fecundity. Proper evaluation of male infertility at different levels is essential for its effective management. Targeted treatment to specific male factor with or without assisted reproductive techniques (ART) may be adopted for management of male infertility [5].

This chapter is a concise synopsis of the pathophysiology of male infertility merging the classical and modern postulations. It summarizes the concepts of male reproductive functions and their regulatory

factors. Finally the mechanisms by which impairment of the reproductive functions or their regulators, individually or in concert, leading to male infertility are illustrated.

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## Male Reproductive Physiology: An Overview

Pristine perception of both morphology and physiology of male reproductive system facilitates conceptualization of the complex pathophysiological mechanisms of male infertility. The male reproductive system has three fundamental functions: Production of spermatozoa (spermatogenesis) and hormones (steroidogenesis), as well as storage followed by ejaculation of the sperm into the female reproductive tract [6]. However, accomplishment of these functions require orchestrated action of the testicular cells including the germ cells, Sertoli cells, and Leydig cells in response to the endocrine regulation. The male reproductive system along with its regulatory entity comprises of brain centers, which regulate pituitary release of gonadotropins and sexual behavior; a pair of testes, which produce sperm and hormones; a ductal system (vas deferens and epididymis), which stores and transports sperm; accessory sex glands (seminal vesicles, prostate, and bulbourethral glands) to support sperm viability; and the penis [7].

Spermatogenesis and steroidogenesis are under endocrine regulation via the pituitary gonadotropins, luteinizing hormone (LH) and follicle-stimulating hormone (FSH) [8]. The hypothalamus is known to be the center of information processing as per external and internal cues. Via the pulsatile release of gonadotropin-releasing hormone (GnRH), it stimulates the secretion by anterior pituitary, LH and FSH, which binds to receptors on the Leydig cells, and Sertoli cells, respectively. Leydig cells reside within the interstitial compartments and produce testosterone. Sertoli cells lie along the lining of the seminiferous tubules, supporting the germ cells to develop through the stages of spermatogenesis. Sertoli cells have receptors for both FSH and testosterone and produce estradiol at low levels. Another contribution of the Sertoli cells is the productions of glycoprotein hormones (inhibin, activin, and follistatin) that modulate FSH secretion [9]. Testosterone is the main androgen that sends feedback to the hypothalamus and pituitary, regulates spermatogenesis directly, monitors sexual behavior, and serves as the primary male sex hormone that aids primary and secondary sex development.

The duct system, comprising of epididymis, vas deferens, and urethra, stores the sperm until they acquire the capability to fertilize with sufficient motility and then transports them to the female genital tract through the penis [6].

Alterations in one or more of the components of the reproductive system are accompanied by modulations in other reproductive organs and their endocrine regulations.

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## Etiologies of Male Infertility

The clinical definition of “infertility” itself not only often poses a conceptual enigma that both subfertile and infertile couples are put under the same category but also refers to failure in attaining pregnancy within the first year of unprotected intercourse. However, many subfertile couples actually may not conceive within this stipulated time and are included under the definition of being infertile [10]. In addition, among all the cases of male infertility, about 60%–75% are idiopathic and remain undiagnosed

[11]. Diagnosis of male infertility probably covers a number of different etiologies, which again is a mechanistic paradox and several hypotheses attempt to explain the multivariate causes of the same. The physiological disruptions resulting in male infertility may be related to failure in sperm production, impaired sperm morphology and functions, problems in transmission along the duct system through the penis during ejaculation, secretory disturbances of the accessory glands, and endocrine imbalances. There lies an array of concepts to justify these events individually or in combinations and most of the time, the exact mechanism is difficult to specify. In many cases, male infertility remains just a mystery. The contributing factors ranges from severe to moderate pathological conditions, systemic causes, environmental factors, lifestyle factors, and metabolic distress to oxidative stress (Figure 1.1). This chapter aims to address the perplexity unveiling the physiological mechanisms paving the way to male infertility, explaining every strata of male reproductive functions at the pretesticular, testicular, and posttesticular levels.

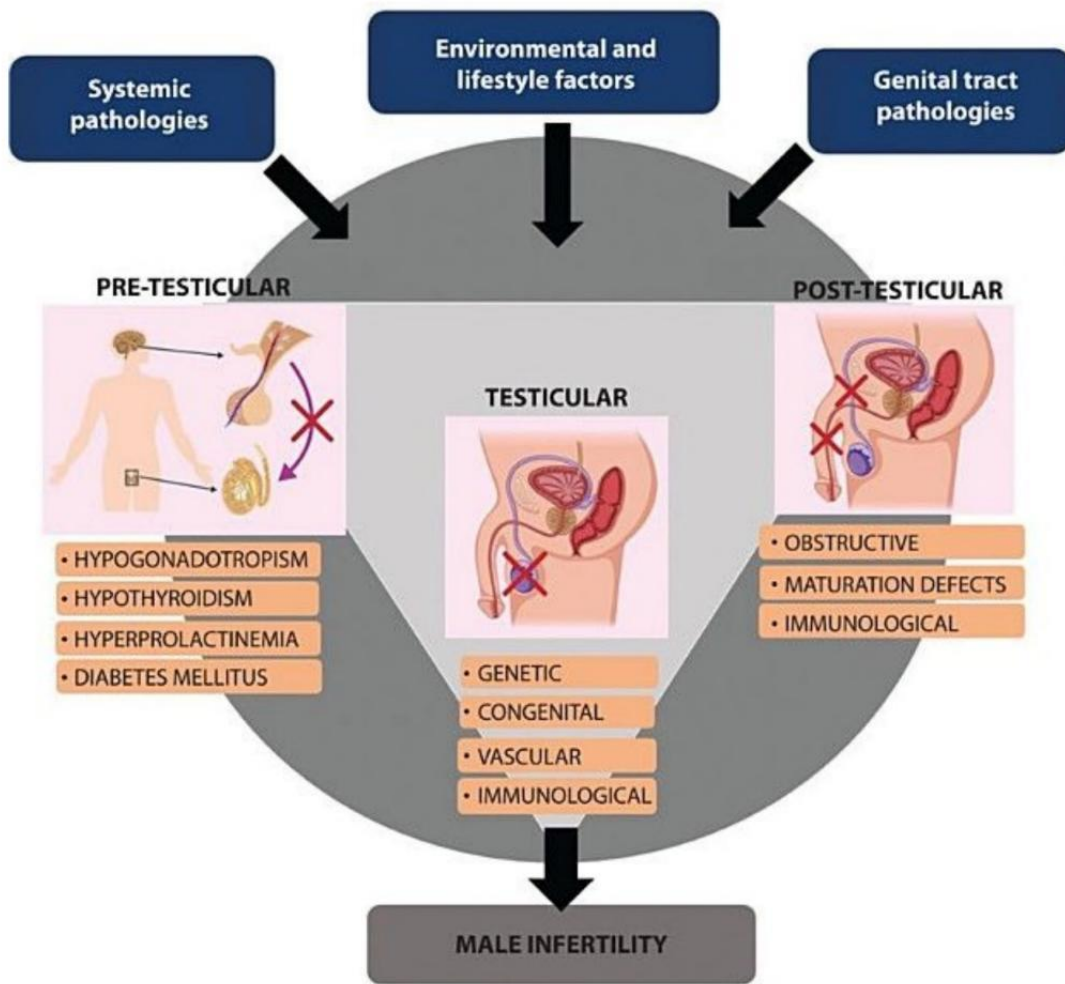


FIGURE 1.1 Common pretesticular, testicular, and posttesticular causes of male infertility.

### Pretesticular Pathophysiology

Immaculate coordination of the hypothalamic-pituitary-testicular axis with other related hormones determine functioning of the male reproductive system. The hypothalamus via its pulsatile secretion of GnRH stimulates the pituitary gonadotropins, LH, and FSH, which regulate testicular steroidogenesis and spermatogenesis. Inhibin and activin from the testes in turn operate feedback mechanisms that influence the secretion of both hypothalamic GnRH and subsequent pituitary gonadotropins [12].

Research since the last decade, procures that besides the pivotal classical scheme of the hypothalamic-pituitary-gonadal (HPG) axis, there are several other components playing vital roles in the regulation of male reproductive functions. Among these are the groups of small RFamide peptides consisting of the motif Arg-Phe-NH<sub>2</sub> at C-terminus, namely, gonadotropin-inhibiting hormone (GnIH) and its related peptides [8]. Another essential 54-amino-acid peptide, Kisspeptin, encoded by the *KISS1* gene, has been identified. This peptide, which activates the G protein-coupled receptor (GPR54) in the hypothalamus, is reportedly a major trigger for puberty and can supposedly even kindle precocious puberty in men [13].

HPG axis may be disoriented by the influence of an inestimable number of internal and external cues, the most common being via the stress hormones, several adipokines, and the opioid system. A disrupted HPG axis results in inadequate sex steroids and inhibin production and in turn, loss of negative feedback to regulate hypothalamus and pituitary secretions. Consequently, there is an increase in serum activin and unregulated release of GnRH and gonadotropins [14]. This undesired elevation of LH and FSH culminates in male reproductive dysfunctions [15]. Hence, dysregulation of the HPG axis actually modulates concentrations of gonadal hormones and alters the sensitivity of their respective hippocampal receptors, resulting in disoriented hormone-receptor signaling and abnormal elevation in neuronal GnRH, LH, and activin signaling [16]. Stress may also induce elevated levels of reactive oxygen species (ROS), which may trigger oxidative stress (OS). This may lead to lipid peroxidation (LPO) in Leydig cells and germ cells, disrupt lipoproteins, fragment proteins, and inhibit steroidogenic enzyme activities [17]. OS mediates its detrimental effects on male fertility by reduction in testosterone production by affecting Leydig cells or indirectly via disruptions in endocrine regulations of hypothalamus or anterior pituitary [18].

Interruption or ceased GnRH release and subsequent inhibition of LH and FSH secretions lead to hypogonadotropic hypogonadism (HH). Secondary and tertiary HH owing to hypothalamic and pituitary hormones deficiencies, respectively, are different from primary or testicular dependent factors. Secondary or tertiary HH is characterized by normal or low gonadotropin levels with low testosterone concentration [12]. Congenital abnormalities resulting from GnRH deficiency can either occur singly (normosmic congenital HH) or along with hyposmia or anosmia, which is called Kallmann syndrome. Besides testosterone insufficiency, fertility problems, and anosmia, patients with Kallmann syndrome often experience other neurologic and cardiac disorders. Hypogonadism is thus a threat to male fecundity and systemic functions and can be caused by various factors including aging [19], obesity [20], and type 2 diabetes mellitus [21]. Steroidogenesis gradually declines with aging and reports suggest men older than 60 years generally possess serum testosterone levels less beyond the lower limits of a young sexually matured adult [19]. Obesity is another worldwide prevalent metabolic disorder that severely impairs the hormonal profile and alters several metabolic hormone profiles, including those of adiponectin, leptin, ghrelin, obestatin, and orexin, which individually or in concert may affect HPG axis or directly alter testicular functions. An increased number or size of adipocytes

owing to obesity leads to both physical and hormonal changes that affect male fertility. Physical alterations may comprise increased scrotal temperature and thus affect spermatogenesis and erectile function (ED). Hormonal disturbances include elevation in the levels of adipokines (leptin is the mostly reported), estrogen, and insulin, and diminution of testosterone levels. These alterations contribute to male fertility complications like azoospermia, oligozoospermia, increased sperm DNA fragmentation (SDF) index, and a reduction in semen qualities [22].

Androgen insensitivity syndrome is another severe male hormonal incompetency, which is an X-linked disorder triggered by mutations in the androgen receptor gene causing resistance to any androgenic actions for normal reproductive functioning [23].

### Testicular Pathophysiology

Spermatogenesis is a continuous process throughout a man's lifetime after puberty with individual germ cells requiring about 72–74 days to reach maturity. The optimum temperature for spermatogenesis is about 34°C. The process occurs within seminiferous tubules, where the Sertoli cells support the development, and the Leydig cells produce the required testosterone. Disruptions in spermatogenesis may lead to inadequate sperm count (oligozoospermia) or absolutely no sperm production (azoospermia) and also may result in defects in sperm morphology or motility.

Spermatogenesis disorders may be evaluated by testicular biopsy, and oftentimes, spermatozoa are procured for ART. In this regard, the pathological observations mostly reveal either “mixed atrophy” (tubules having different spermatogenic phases), several forms of developmental or morphological defects in spermatozoa (e.g., round spermatid or meiotic arrest), or even “Sertoli cell-only syndrome” (SCOS, where absolute absence of germ cells can be observed). These characteristics of spermatogenesis disorders can be global, which involve all the seminiferous tubules or focal with a number of tubules suffering from quantitative or qualitative spermatogenesis defects [2]. The pathophysiology of spermatogenic impairment from a molecular perspective is still arduous. This is due to lack of detailed functional concepts on the testes, which do not simply comprise the two established compartments: The interstitial part (containing the most prominent testosterone-producing Leydig cells, among other underdiscussed components) and seminiferous tubules (with the germ cells and supporting Sertoli cells). Moreover, spermatogenesis itself is an intricate differentiation process, completely transforming spermatogonia to mature spermatozoa via various stages. Such continuous coordinated processes are being mediated via integration of neuroendocrine and genetic dispositions, amid other physiological regulations and is reportedly orchestrated by almost 2,000 genes, of which more than 600 are supposedly expressed in the male germline [3,4,24,25].

General causatives of impaired spermatogenesis are scrotal heat, endocrine and genetic disorders, drugs, and toxins [26]. Endocrine disorders may include abnormalities in the HPG axis, adrenal gland disorders, thyroid dysfunctions, hyper-prolactinemia, and hypogonadism. The genetic defects may lead to gonadal dysgenesis, Klinefelter syndrome (KS), while severe spermatogenesis impairment has been observed due to microdeletions of the Y chromosome sections. Genitourinary disorders may also afflict spermatogenesis, among which cryptorchidism or undescended testis is one of the most prevalent congenital disorders [27]. Other important genitourinary disorders include infection, injury, testicular atrophy, as well as varicocele, which will be discussed in details in the following sections. Exposure to

excessive heat due to excessive physical activities, tight clothing, and exposure to radiation may increase scrotal temperature, affecting spermatogenesis.

Sertoli cells, supportive cells present in the epithelium of the seminiferous tubules, are critical players in spermatogenesis, providing nourishment, physical support, and hormonal signals required for successful spermatogenesis. Sertoli cells support the germ cells through the developing stages. They have FSH receptors that enable FSH to act upon them for progression of spermatogenesis. They also produce vital hormones, activin, and inhibin, which mediate the feedback regulations of hypothalamic GnRH and pituitary gonadotropins. These LH and FSH in turn determine the testosterone production by the Leydig cells and initiation of spermatogenesis via acting on Sertoli cells, respectively [28]. Therefore, Sertoli cells and their ability to support spermatogenesis act as a limiting factor for spermatogonial proliferation [29]. Disruption of Sertoli cell function leads to irreversible testicular atrophy [30]. Sertoli cell toxicants are more severe than germ cell toxicants because the latter fails to deplete the entire stem cell mass, and the damage caused are thus reversible with the seminiferous tubules repopulating the germinal epithelium with due period [31]. Disruptors or toxicants may induce morphological defects by vacuolation of the cytoplasm and shedding of apical germ cells [30]. Seminiferous tubule fluid (STF), secreted by the Sertoli cells, is responsible for the required nutritional and hormonal microenvironment for normal spermatogenesis, and STF may also be depleted following exposures to toxicants or testicular injury, which precedes bulk necrosis of the germ cells [32]. Decrease or prevention in production of proteins inhibin B and androgen-binding protein (ABP) by the Sertoli cells have also been documented that link to depletion of specific spermatogonia [33,34]. For this association, serum inhibin B measurement serves as a noninvasive means of the assessment of male fertility [35].

Leydig cell disruptions lead to male infertility because testosterone production is inhibited, causing stage-specific degeneration of the germ cells. This is usually a reversible condition with cessation of exposure to the particular disruptors [36]. Endocrine disruptors or toxicants can disrupt Leydig cell functions either by morphological alterations, degenerations of the Leydig cells, modulating the activities of the marker enzymes of the Leydig cells, namely,  $3\beta$ -hydroxy steroid dehydrogenase ( $3\beta$ -HSD) and esterase and, thus, adversely affecting the steroidogenesis [36,37]. These effects either singly or cumulatively lead to insufficient testosterone needed for successful spermatogenesis [31,36,37].

Varicocele is the most common vascular disease and accounts for 35% of the overall male infertility cases [38]. Varicocele is characterized by defects in the testicular venous drainage system with abnormal dilations and torsions in the veins of the pampiniform plexus. The etiology of varicocele is based on several hypotheses: Valvular insufficiency of the internal spermatic veins and the “nutcracker phenomenon” are among the most commonly discussed ones. Research in recent years support that OS is a key player in the pathophysiology of varicocele-mediated infertility. A strong association between varicocele and OS was evidenced through elevated levels of ROS, nitric oxide, and LPO products among infertile men with varicocele as compared to infertile men without varicocele [39,40]. Besides varicocele, some of the other vascular disorders that attract the attention of researchers and clinicians in