Male Endocrine Dysfunction

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KEYWORDS

• Male • Endocrine • Dysfunction • Fertility • Spermatogenesis • Hypogonadism • Sperm • Review

KEY POINTS

- Endocrine dysfunction, as it pertains to the infertile male, centers around the role of intratesticular testosterone, which is vital for sperm growth and maturation. This is under the primary control of the hypothalamic-pituitary-gonadal (HPG) axis.
- Understanding how feedback inhibition in the androgenic axis may cause dysfunction and how the subsequent manipulation of these endocrine systems may improve spermatogenesis.
- Multiple endocrine systems at various levels of the HPG axis act to modulate spermatogenesis.
- Current treatments focus on increasing intratesticular testosterone, although may expand to other hormones in the future.

INTRODUCTION

Male endocrine assessment is an integral part of the evaluation of the infertile couple. This article discuss the various modalities available to diagnose endocrinopathies affecting male factor infertility. Although male endocrine dysfunction is a significant part of the evaluation of the infertile male, a primary hormonal cause is found in less than 3% of infertile men.[1] Conversely, 30% to 70% of men with male infertility have some degree of concurrent endocrine dysfunction.[2,3] Thus, in the treatment of the infertile male, endocrine evaluation has historically been one of the first avenues in patients seeking evaluation. As our knowledge of male androgenic hormonal dysfunction expands, so too will our armamentarium of potential treatments. The different physiologic mechanisms involved in male infertility are discussed in this article, as well as current and promising new treatments based on an ever-evolving foundation of knowledge that may aid the specialist in treatment.

Although some have denigrated the role of the endocrine evaluation in male factor infertility, it is only through a rigorous epidemiologic, genetic, and environmental assessment of perturbations of the male endocrine axis that the causes of male infertility will be truly unraveled. As mathematician Blaise Pascal stated, "we may have three principal objects in the study of truth: one to discover it when it is sought; another to demonstrate it when it is possessed; and a third, to discriminate it from the false when it is examined." Currently, endocrine evaluation of the infertile male excels at discovering truth when it is sought but falls far short from discriminating it from the false on further examination. Gross abnormalities can be demonstrated such as in hypogonadotropic hypogonadism but how a myriad of genetic and environmental factors combine to render the male endocrine axis incapable of facilitating normal spermatogenesis has not been elucidated.

MALE ENDOCRINE PHYSIOLOGY

Traditionally, the focus of endocrine physiology in the male reproductive system has centered on the hypothalamic-pituitary-gonadal (HPG) axis, which

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constitutes the backbone of current understanding of the male reproductive system. The interplay of various hormone systems with the HPG axis may also play a role in its regulation and effects. However, as understanding of the depth and limitations of assessment of the HPG axis has evolved, so too has rudimentary understanding of the so-called neohormones that may also aid in the treatment of male infertility.

HPG Axis

Intratesticular testosterone levels are vital to the growth and maturation of sperm. High testicular concentrations of testosterone are required to maintain spermatogenesis,[4] and intratesticular testosterone levels are approximately 40 to 100 times higher than serum levels.[5] Thus, small variations in serum testosterone levels may represent massive fluctuations in the intratesticular environment. Testosterone is produced primarily by Leydig cells in the interstitium of the testis. Luteinizing hormone (LH) produced from the pituitary gland is chiefly responsible for steroidogenesis by Leydig cells. LH binds to its receptor, which initiates a cyclic adenosine monophosphate (cAMP)-mediated pathway leading to testosterone production and release via mitochondrial and smooth endoplasmic reticulum membranes.[1] These androgens then diffuse out of the Leydig cell structure into capillaries and adjacent tissue within the interstitium and surrounding germinal epithelium.

Once in the capillaries, testosterone is quickly bound by proteins in circulation, mainly sex-hormone binding globulin (SHBG) and to a lesser extent albumin.[1,6] Some testosterone is further metabolized by aromatase and 5α-reductase to estrogen and dihydrotestosterone, respectively.[1] Serum testosterone is the primary source of hypothalamic feedback inhibition, whereas estrogens modulate gonatotropin secretion in response to gonadotropin-releasing hormone (GnRH)[1,7] in the pituitary.

The hypothalamus produces GnRH in a pulsatile manner[1] in response to input from other parts of the brain, various neurotransmitters and neuropeptides, and serum testosterone levels (**Fig. 1**). This pulsatile GnRH then acts on the pituitary gonadotropes to produce LH and follicle-stimulating hormone (FSH). In addition to the influence of testosterone and estrogen on LH production, FSH is further regulated by 2 proteins secreted by Sertoli cells in the seminiferous tubules. Inhibin, or more accurately inhibin B, selectively suppresses FSH production by the gonadotropes, whereas activins stimulate production of FSH.[1,8] Follistatin, which is produced by Sertoli cells and, to a lesser extent, germ cells, plays a role in local inhibition of activin secretion within the testis and regulates germ cell growth and division.[9,10] FSH stimulates Sertoli cells to chaperone germ cells throughout spermatogenesis. FSH is not strictly required for spermatogenesis in humans, but it does augment Sertoli cell function and, through feedback with Sertoli cells, is a core component of optimal testicular function (see **Fig. 1**).[11]

Nongonadotrope Hormones

Regulation of androgens is more complex than previously believed. The role of prolactin and growth hormone (GH), and several other hormones that have been implicated in spermatogenic function, is discussed in this section.

In men, prolactin is a peptide hormone produced by pituitary lactotropes and in the prostate.[12] The

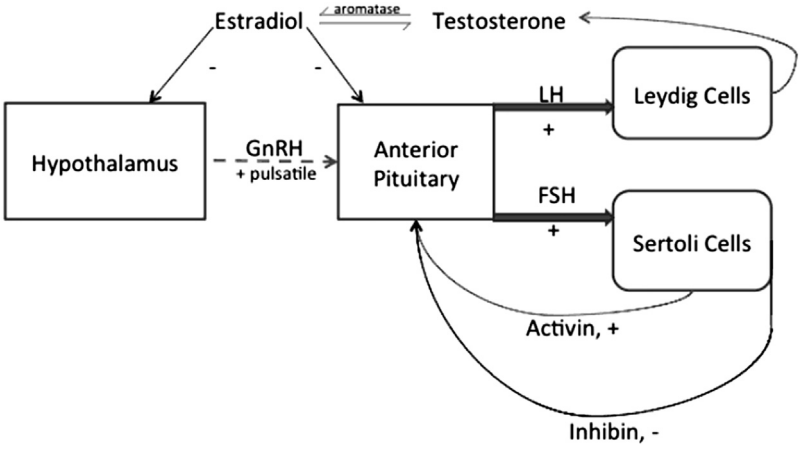

Fig. 1. HPG axis and effects.