Optimal Endocrine Evaluation and Treatment of Male Infertility

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KEYWORDS

• Male • Infertility • Endocrine • Hypogonadism • Anabolic steroid • Testosterone • Genetic testing

KEY POINTS

- Endocrinopathies that affect male fertility are rare, but important to consider as causes of male factor infertility and should be screened for in the initial history and physical examination.
- Classification of hormonal abnormalities by their effect on the hypothalamic-pituitary-testicular axis and the potential for reversibility guides evaluation and treatment.
- The endpoint for treatment is stimulation of spermatogenesis, usually through hormonal pharmacology to raise the intratesticular concentration of testosterone.
- Precision medicine and genetic testing will likely become standard for infertility evaluation in the future, as more candidate genes for infertility are identified.

Endocrinopathies are uncommon etiologies of male factor infertility. The incidence of primary hormonal disorders as the cause of male infertility ranges from less than 1% to 3%.[1–3] Nonetheless, endocrine disorders are important to consider in the infertility evaluation, as up to 70% of men with infertility have concurrent endocrine dysfunction.[4] Metabolic syndrome, which is characterized by insulin resistance with hyperinsulinemia and obesity, has deleterious effects on fertility. Furthermore, couples in which the male partner has diabetes mellitus have a significantly longer time to pregnancy.[5,6] Depending on the endocrinopathy, infertility can be reversible or potentially indicative of significant medical pathology.[1,7]

Endocrine regulation of spermatogenesis and testicular function is dependent on an intact hypothalamic-pituitary-testicular axis (**Fig. 1**). The hypothalamus produces and secretes gonadotropin-releasing hormone (GnRH), which is carried through the portal circulation to the pituitary gland. In response to GnRH, the gonadotropic cells of the anterior pituitary secrete luteinizing hormone (LH) and follicle-stimulating hormone (FSH). These hormones circulate systemically and bind to membrane receptors on target organs. LH stimulates the production of sex steroids in the Leydig cells of the testicle. FSH supports the function of the Sertoli cells in the seminiferous tubules, which are critical for sperm cell maturation. The Leydig cells mainly generate testosterone, which is secreted in a pulsatile manner and binds to serum proteins like albumin and sex hormone–binding globulin (SHBG). Leydig cells also produce smaller amounts of estradiol and dihydrotestosterone. However, the main source of estradiol in the body is the peripheral conversion of testosterone via aromatase in adipose tissues. Dihydrotestosterone is also produced in other organs like the

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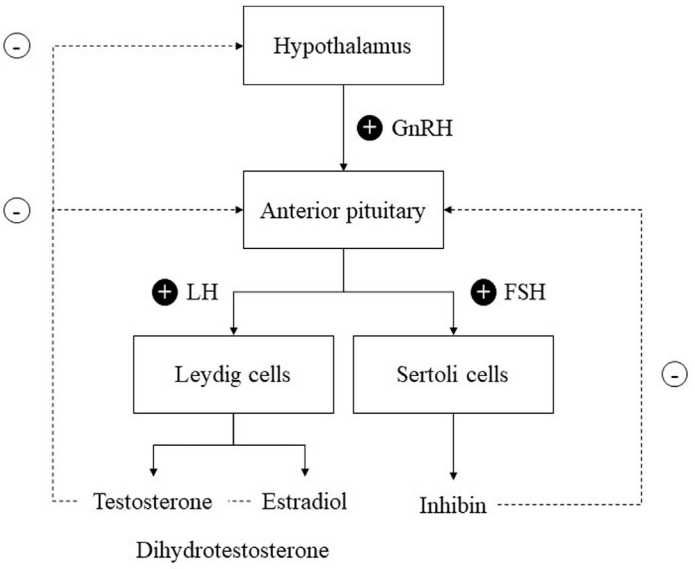

Fig. 1. The hypothalamic-pituitary-testicular axis with end products that regulate feedback inhibition.

prostate and epididymis, which contain 5-alpha-reductase for the conversion of testosterone. Regulation of gonadotropic cell products LH and FSH is maintained by feedback inhibition from the production of testosterone, estradiol, and inhibin, a regulatory hormone produced and released by the Sertoli cells.

The design of the hypothalamic-pituitary-testicular axis is elegant but can result in aberrant hormone signaling when there is a defect at any point along the pathway. Furthermore, exogenous administration of end products can result in dysfunction in an otherwise intact endocrine system. For example, exogenous testosterone does not directly affect the intratesticular concentration of testosterone because of the tight junctions in the blood-testicular barrier. However, the serum level of testosterone rises with supplementation and inhibits the production of LH and FSH, resulting in a paradoxic decrease in intratesticular testosterone production.[8] The endocrinopathies that disrupt male fertility can be grouped into categories, such as hypothalamic disease, pituitary disease, primary and secondary hypogonadism, and other pre-testicular causes[9–12] (**Table 1**).

EVALUATION

Due to the wide range of endocrinopathies, health care practitioners must have a systematic approach. Before considering endocrine etiologies for male factor infertility, an initial evaluation must be completed. This is typically performed in the outpatient setting and begins with a complete history, with careful attention to the reproductive and sexual history. This consists of the following:

- Coital frequency, timing, and use of lubricants
- Prior history of pregnancies for either the male or female partner
- Erectile and ejaculatory function
- Duration of infertility and prior fertility
- Childhood illnesses and development
- History of urologic trauma or disease (eg, epididymitis, orchitis, sexually transmitted infection)
- Past medical and surgical history
- Medications and supplements
- Family history of infertility
- History of traumatic brain injury
- Exposure to wet heat, chemicals, toxins, drugs, or radiation

When reviewing medications, physicians must also specifically ask about prior or present testosterone and/or anabolic steroid use. Careful evaluation of dietary and nutritional supplement usage is critical, as their ingredients are not regulated by the Food and Drug Administration (FDA). Studies have demonstrated that more than 20% of legally sold supplements contain anabolic steroids not listed on nutritional labels.[13–15]

The initial evaluation also includes a comprehensive physical examination and 2 semen analyses. Urologists should perform a thorough genitourinary examination in addition to noting body habitus, development of age-appropriate male secondary sex characteristics, and presence of any signs that could suggest an underlying

Table 1
Table of endocrine-related disorders that can result in male factor infertility

Hypothalamic	Testicular
Tumors, for example, craniopharyngioma, secondary metastasis	Anorchia, for example, viral orchitis, testicular torsion
Infiltrative disease, for example, tuberculosis, sarcoidosis	Other causes
Cranial radiation	Klinefelter syndrome
Pituitary	Diabetes mellitus
Tumors, for example, prolactinoma	Obesity
Acromegaly	Thyroid disease
Cushing disease	Congenital adrenal hyperplasia
Hyperprolactinemia	Androgen resistance
Kallmann syndrome	Exogenous androgen administration
Empty sella syndrome	Illicit drugs, for example, anabolic steroids, cannabis
Pituitary stalk interruption syndrome	Eating disorders
Pituitary stalk transection, for example, trauma	Medications

endocrinopathy (eg, gynecomastia, striae, thyroid enlargement). Multiple international guidelines recommend 2 semen analyses separated by at least 1 month if possible.[1,16–19] Although a single semen sample cannot be relied on to exclude abnormal spermatogenesis, the presence of multiple severe semen parameter abnormalities may obviate the need for a second semen analysis, as it would not significantly alter management and would otherwise delay treatment.[20]

Absolute indications for endocrine evaluation include an abnormal semen analysis, impaired sexual function, or clinical findings in the history or physical examination suggestive of a specific endocrinopathy.[21] There is ongoing debate as to whether all men presenting for fertility evaluation should undergo an endocrine evaluation. Studies that support evaluation of hormone levels during the initial evaluation associate low total serum testosterone with abnormal sperm morphology and lower live birth rates.[22,23] Patel and colleagues[24] also found low total serum testosterone in men with idiopathic infertility and normal sperm concentrations, which would have been missed had a hormonal evaluation not been performed. On the other hand, endocrine causes of male factor infertility are uncommon. Although the individual cost of a blood draw and serum hormone analysis is relatively affordable, the annual cost to the medical system is greater and may be as high as $70,000.[2] The American Society for Reproductive Medicine acknowledges that there is no consensus, but it is the opinion of this expert that hormonal evaluation should be performed at the initial evaluation of the infertile male.

An endocrine evaluation for infertility should at minimum consist of serum testosterone and FSH levels.[21] Most infertility experts additionally measure serum levels of free testosterone, sex hormone–binding globulin, prolactin, and LH. Although serum inhibin B is superior to FSH as a marker of spermatogenesis, FSH remains the preferred screening test in practice because of the high cost of serum inhibin B analysis.[25] Physicians also should consider estradiol and thyroid function studies, as alterations in these hormones can have a negative effect on sexual function and fertility.[12] Imaging also may be warranted as part of the endocrine evaluation if there are abnormal laboratory results (eg, brain MRI for elevated prolactin).

TREATMENT

The goal of treatment is to correct any reversible hormonal pathology and restore fertility. If restoration of fertility is not possible, then it is important for urologists to counsel the couple on prognosis, as this can provide relief and an opportunity to recommend other methods of parenthood (eg, adoption). The remainder of this section addresses the current research and standards of care for endocrinopathies that impact function of the hypothalamic-pituitary-testicular axis.

HYPERGONADOTROPIC HYPOGONADISM

Primary hypogonadism, also known as hypergonadotropic hypogonadism or primary testicular failure, is diagnosed via the presence of low testosterone despite high levels of GnRH, LH, and FSH. The pathology underlying this hypergonadotropic state can be congenital or acquired.

Klinefelter syndrome is the most common congenital etiology of hypergonadotropic hypogonadism, as well as the most common sex

chromosome disorder overall, affecting approximately 1 in 500 male individuals.[26] It is characterized by aneuploidy of the sex chromosomes, with most cases displaying a 47, XXY genotype. Clinical findings include above-average height, eunuchoid body habitus, gynecomastia, and small testes. However, these symptoms can be subtle and the initial presentation for these men can occur during adulthood as difficulty with conception. Diagnosis is established by karyotyping, although a normal karyotype can be present in up to 20% of men with mosaic Klinefelter syndrome.[27] Although men with Klinefelter syndrome were previously thought to be irreversibly sterile, use of conventional testicular sperm extraction (TESE) or microsurgical TESE (microTESE) with intracytoplasmic sperm injection has allowed some to achieve pregnancy with their partners. Literature suggests that urologists should discuss family planning with these men early, as extraction of viable sperm is less successful with older age.[28] Some experts also have called for studies examining the success of TESE in adolescents with Klinefelter syndrome, as significantly more sperm may be retrieved for cryopreservation before the initiation of hormone therapy for secondary sexual characteristics.[29]

Variants in the genes associated with the beta subunit of gonadotropins and their associated receptors also have been linked to primary testicular failure.[30–34] Acquired etiologies of hypergonadotropic hypogonadism are typically caused by direct testicular insult and include anorchia, testicular torsion or trauma, viral orchitis, chemotherapeutic toxins, and radiation. These conditions are generally irreversible, and options for future fertility are limited to surgical retrieval of sperm or donor insemination.

HYPOGONADOTROPIC HYPOGONADISM

Secondary hypogonadism is characterized by low testosterone in the presence of low GnRH, LH, and FSH levels. This clinical presentation is also referred to in the literature as hypogonadotropic hypogonadism or secondary testicular failure. In patients with acquired secondary hypogonadism, evaluation with thyroid and adrenal function studies, serum prolactin, and cranial MRI should be performed to rule out structural abnormalities of the pituitary (eg, prolactinoma).

Current literature has suggested that anabolic steroid–induced hypogonadism is now the most common cause of hypogonadism among men.[35] Anabolic steroid use is a growing public health concern, as these substances are increasingly used by younger men of reproductive age, with a lifetime prevalence use of 3% to 4%.[36,37] The mechanism by which anabolic steroids result in hypogonadotropic hypogonadism is via inhibition of GnRH release through a negative feedback loop, ultimately decreasing signaling for intratesticular production of testosterone. Although these drugs may have the desired effect of increased muscle mass, their androgenic component commonly produces side effects of gynecomastia, testicular atrophy, sexual dysfunction, and infertility secondary to decreased spermatogenesis, among others.[37] All patients should be counseled to discontinue anabolic steroid use in the interest of fertility and overall health.[9,38] After suspending use, the literature suggests that average time to recovery of spermatogenesis (>5 million sperm per milliliter) ranges from 4 to 12 months.[39,40] If spermatogenesis does not return after 4 months, then it is possible these patients had underlying, undiagnosed infertility and urologists should consider alternate diagnostic evaluations.[41]

Exogenous testosterone administration can result in infertility due to a paradoxic decrease in intratesticular testosterone levels via the same mechanism by which anabolic steroids inhibit testosterone production. Although prescribing of testosterone is decreasing nationally (eg, 40% decline within the Veterans Administration system), testosterone prescriptions in America surged from 1.2 million in 2010 to 2.2 million in 2013.[42–44] A survey of American Urologic Association urologists found that approximately 25% have prescribed testosterone for infertility associated with low testosterone.[45] Outcomes are generally favorable after discontinuation of testosterone, but risk factors for prolonged infertility include increased duration of exogenous testosterone use and older age, independent of puberty.[34,40]

If patients with prior anabolic steroid or testosterone use are persistently hypogonadal after discontinuation, then pharmacologic management can be considered. Some experts suggest implementing medical therapy early, for example, when anabolic steroids are discontinued.[46] Clomiphene citrate, a selective estrogen receptor modulator (SERM) that prevents the inhibitory effects of estrogen on LH and FSH, is often used initially, as it is relatively inexpensive, available in an oral formulation, and has been demonstrated as safe and efficacious for long-term use.[47] In this expert's experience, the combined use of clomiphene citrate and human chorionic gonadotropin (HCG) provides a rapid return to spermatogenesis. The adjunct use of FSH in addition to the preceding pharmacologic therapies can be considered in men who are refractory to clomiphene and HCG. Notably, the use of clomiphene may be limited by estrogenic effects, limiting its benefit.[48]

In select patients with testosterone-to-estradiol ratios of less than 10:1, aromatase inhibitors can be used to decrease estrogen production.[49] This class of medications achieves the same effect as SERMs by decreasing estrogen feedback to the pituitary, resulting in increased testosterone production and spermatogenesis. However, long-term use of aromatase inhibitors is associated with osteoporosis in women, although the long-term effects in men are uncertain.

HCG mimics LH function with a structurally similar beta subunit. HCG is the only FDA-approved treatment for secondary hypogonadism, although studies on its safety with long-term use are lacking. Even with concurrent testosterone therapy, HCG can maintain spermatogenesis relatively well and can be prescribed as concurrent therapy with testosterone.[50,51] All medications other than testosterone that are currently used for the treatment of hypogonadotropic hypogonadism are considered off-label, and patients should be appropriately counseled on potential risks. HCG-based therapy in combination with SERMs, aromatase inhibitors, or recombinant FSH is a promising treatment for testosterone-related infertility, with an improvement in spermatogenesis observed in approximately 96% of participants.[51] However, a limitation of this study, as with most of the literature on this topic, is the lack of a control group to mitigate temporal treatment bias. Superiority of medication to discontinuation alone has not yet been demonstrated in the literature and requires further investigation.

Other acquired forms of secondary hypogonadism include hypothalamic and pituitary disorders. Pituitary adenomas are the most common pituitary pathology.[52] Of these, functioning tumors such as prolactinomas occur more often in young adults of reproductive age. Excess prolactin can result in galactorrhea and bitemporal hemianopsia. Medical management with dopamine agonists is sufficient for most patients with prolactinomas, as these tumors rarely require surgery or radiation. Gonadotropin deficiency also can result from head trauma through damage to the pituitary (eg, transection of the pituitary stalk). Patients with history of traumatic brain injury should be monitored for the development of gonadotropin deficiency, as a prospective study demonstrated the prevalence of hypogonadism to be 7.7% at 12-month follow-up.[53] Insults to the hypothalamus also can result in secondary hypogonadism. Although not as well studied in men as compared with women, eating disorders in men appear to have similar suppression of the hypothalamus that can result in decreased GnRH release.[11] Conversely, diabetes mellitus and obesity result in an excess estrogen state that suppresses the release of gonadotropins and can result in infertility. Infiltrative diseases like sarcoidosis also can present with hypothalamic-pituitary disease that results in clinically significant hypogonadism.[54]

Congenital hypogonadotropic hypogonadism results from impaired migration of GnRH-producing neurons. Patients with this condition can present with impaired sense of smell, which is referred to as Kallmann syndrome, and occurs from simultaneous failure of olfactory neuron migration. Other signs of congenital hypogonadotropic hypogonadism include unilateral renal agenesis, absence of secondary sexual characteristics, and cryptorchidism, the last of which prognosticates a poor response to fertility therapy.[55] Although patients with congenital hypogonadotropic hypogonadism were previously accepted as infertile, reversal of secondary testicular failure has been demonstrated in up to 20% of them.[56,57] Treatment options directed at fertility include pump-administered pulsatile GnRH or subcutaneous gonadotropin injections. However, there is limited evidence for comparing efficacy in stimulating spermatogenesis. Most men with congenital hypogonadotropic hypogonadism rarely achieve normal sperm counts, but fertility is attainable with reports of successful pregnancies after hormonal therapy.[58,59]

FUTURE DIRECTIONS

As we better understand the genetic basis of male infertility, future male factor infertility evaluations will likely include routine genetic screening. Currently, guidelines recommend genetic screening for men with azoospermia or severe oligospermia.[16] Available technologies in clinical practice can screen for autosomal gene variants (eg, CFTR in cystic fibrosis), chromosomal abnormalities, and Y chromosome microdeletions, which are all gene factors that have been shown to impact male fertility. Use of newer methods, like microarray analysis and whole-genome sequencing, have yielded candidate genes that are related to endocrine function in infertile men, but are not in broad clinical use yet (**Table 2**).

In the context of precision medicine, genetic testing also may guide treatment selection for men with male infertility. The best example of this currently in the literature is selection of patients for pharmacologic therapy with FSH. Research has demonstrated that polymorphisms in FSH receptor genes are associated with significant difference in semen parameters after FSH treatment.[60] In addition, polymorphisms in the FSH beta subunit also may have clinical significance. Studies

Table 2
Endocrine disorder–linked genes that may result in male factor infertility

Abnormal hypothalamus development and function	Adrenal gland dysfunction
ANOS1	CYP11A1
CHD7	CYP11B1
FGFR1	CYP17A1
KISS1R	CYP19A1
PROKR2	CYP21A2
TACR3	NROB1
FGF8	HSD3B2
PLXNA1	Abnormal development of reproductive organs
PROK2	AMH
SOX2	AMHR
SOX10	AR
WDR11	NR5A1
CCDC141	SRD5A2
DCC	SRY
GHRH1	WT1
HS6ST1	MAMLD1
SEMA3A	SOX3
Pituitary gland dysfunction	GATA4
GNRHR	HSD17B3
LHB	SOX9
FSHB	RSPO1
FSHR	

Adapted from Ferlin A, Dipresa S, Delbarba A, et al. Contemporary genetics-based diagnostics of male infertility. Expert Rev Mol Diagn. 2019;19(7):623–633. doi:10.1080/14737159.2019.1633917.

by Grigorova and colleagues[61,62] examined men with variants in the −211 base pair promotor regions for the FSH beta subunit and found that these men have lower serum levels of FSH. Larger studies are warranted to determine the clinical utility of candidate genes, although approximately 1200 to 1500 genes linked to male infertility have been identified to date.

One current barrier to genetic testing is cost. On average, whole-genome sequencing costs approximately $1000. In a national survey, more than half of the respondents would not pay more than $500 for actionable sequencing and more than a third would not pay more than $200.[63] Fortunately, trends have shown that cost is decreasing with time. Future developments in technology may eventually make advanced genetic analysis techniques affordable and available to even the most socioeconomically disadvantaged patients.

SUMMARY

Endocrinopathies are rare causes of male factor infertility but should be considered in all evaluations because of their prognosis for infertility and overall health. Diagnosis of an endocrine-related infertility can potentially save couples from undergoing the stress of an expensive artificial insemination process. Optimal evaluation of endocrine disorders is systematic, and includes a thorough history, physical examination, and semen analysis. Most infertility experts would agree that serum hormone laboratories should be included in the initial infertility evaluation, as they are relatively inexpensive. Treatment is dependent on the endocrine disorder, but advances in genetic testing could further assist in determining patient responsiveness to pharmacologic therapies.

DISCLOSURE

The authors have nothing to disclose.

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