Chapter 10
Hypogonadism and Infertility

Geoffrey S. Gaunay, Seth D. Cohen, Peter J. Stahl, and Doron S. Stember

Introduction

The Practice Committee of the American Society has defined infertility for Reproductive Medicine (ASRM) as a failure to conceive after 12 or more months of regular unprotected intercourse [1]. Studies have related 20 % of cases of infertility to purely male factor etiology, while an additional 30–40 % involve both male and female factor pathology [2]. Newer studies have shown little change in this distribution with more than 50 % attributable to male factor, despite advances in the diagnosis and management of infertility [3, 4]. Men with impaired fertility commonly also manifest serum low testosterone (T), or hypogonadism (HG).

Current recommendations by the Practice Committees of the American Urological Association (AUA) and ASRM recommend a couple undergo an infertility evaluation before 1 year if (1) male infertility risk factors (e.g., history of bilateral cryptorchidism) are known to be present, (2) female infertility risk factors including advanced female age (i.e., older than 35 years) are suspected, or (3) the couple questions the male partner's fertility potential [5]. A thorough history and physical exam is the primary initial step in the diagnosis and treatment of male infertility. In most cases, the etiology of subfertility or the need for adjunctive diagnostic testing can be readily ascertained from the history, physical examination, and semen analysis [6]. The basic evaluation for male infertility also requires serum follicle-stimulating hormone (FSH) and T levels.

The term HG describes a diminished T level and, by definition, one or more symptoms from a constellation that includes decreased libido, energy, overall sense of well-being, and erectile function. HG may be secondary to disruption of the hypothalamic-pituitary axis or primary testicular failure. Testicular failure is, in

D.S. Stember (✉)
Department of Urology, Beth Israel Medical Center, Mount Sinai Health System,
10 Union Square East, Suite 3A, New York, NY 10002, USA
e-mail: dstember@chpnet.org

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turn, characterized by impairment of either, or both, the endocrine production of T or exocrine production of sperm.

We herein review the relationship of HG with male factor infertility and review therapeutic management options that address both conditions.

The Male Reproductive-Hormonal Axis

An intact hypothalamic-pituitary-gonadal axis is critically important for normal sperm production. The hypothalamus secretes gonadotropin-releasing hormone (GnRH), also known as luteinizing hormone-releasing hormone (LHRH), in a pulsatile fashion. GnRH stimulates the release of the gonadotropin FSH and luteinizing hormone (LH) from the anterior pituitary gland [6].

Testicular function is dependent upon both FSH and LH. Whereas LH stimulates Leydig cells in the testicular interstitium to synthesize and secrete T (approximately 5–10 mg per day), spermatogenesis is maintained by the action of FSH on testicular Sertoli cells [6, 7]. T is then secreted both into systemic circulation and diffuses into the seminiferous tubules that surround the Leydig cells. This latter paracrine distribution of T results in highly concentrated levels that are needed to support spermatogenesis in the germinal epithelium and sperm maturation in the epididymis. Concentrations within the testes are 50–100 times higher than serum [8, 9].

T exerts negative feedback effects on LH secretion both directly and indirectly (via conversion to estradiol (E2) in the brain) [10]. T is converted to E2 in peripheral adipose tissue by the enzyme aromatase. When serum T/E2 ratios are low, usually <10, feedback central inhibition may negatively impact spermatogenesis. When sperm production is impaired, feedback inhibition of FSH release is diminished and serum FSH levels are usually elevated (>8 IU/L) [6].

It is extremely important for clinicians to understand these physiologic effects. The message is that men who are interested in fertility should not be treated with T replacement therapy (TRT), particularly for the diagnosis of infertility. TRT will produce a robust serum T level but will also cause intratesticular T concentration to sharply decline, for the reasons stated above, with results deleterious to spermatogenesis.

Evaluation of Hypogonadism and Infertility

The diagnosis of HG begins with clinical suspicion for the condition based on history and physical examination. Endocrine evaluation is indicated in men with (1) an abnormally low sperm concentration, typically defined as lower than 20 million/mL; (2) impaired sexual function; or (3) other clinical findings suggestive of endocrinopathies, such as marked reduction in testicular size or gynecomastia [5]. Although it is a rare cause of male infertility, up to 3 % of infertile men will

have an underlying endocrinopathy [8]. Initial endocrine evaluation in those with indications for testing (i.e., subfertile men with abnormal semen analysis) should include serum follicle-stimulating hormone (FSH) and morning serum T measurements [5]. Morning T specimens are preferred over afternoon blood draws, as a method of standardization, due to a normal physiologic decline in T levels that occurs throughout the day. When T levels are low, FSH levels help provide information to suggest whether the disturbance is central, hypothalamic or pituitary, or testicular. Obstructive azoospermia is usually associated with normal gonadotropin and T levels. Elevated serum gonadotropins can be indicative of hypergonadotropic hypogonadism, or primary HG, with associated testicular disturbances in spermatogenesis, although normal FSH levels do not rule out spermatogenic failure [11].

In men with low serum T, FSH, and LH levels, serum prolactin should be measured, as well as in any man with decreased libido, sexual dysfunction, gynecomastia, or galactorrhea to screen for prolactinoma. Brain magnetic resonance imaging (MRI) may be indicated to characterize a prolactinoma, if prolactin is elevated, or rule out a pituitary or hypothalamic mass, should the prolactin be within normal limits [6]. Serum E2 levels should be measured whenever gynecomastia or a testicular mass is present and can also play a role in the selection of hormonal treatment when such therapy is indicated [12].

Classification of Hypogonadism

HG is characterized by a low T level (typically below 300 or 350 ng/dL) and a wide range of associated symptoms that can be significantly bothersome and physiologically detrimental to patients. In adults, the symptoms of HG can include sexual dysfunction, cognitive impairment, decreased energy, depressed mood, increased fat mass, loss of muscle mass and strength, and reduced bone mineral density (BMD) [9]. Classification of HG is determined by the location of the primary hormonal defect.

Primary HG is characterized by organ dysfunction at the level of the testes and results in decreased serum T and impaired spermatogenesis. Increased serum GnRH and gonadotropins typically result from lack of negative feedback on the hypothalamus and anterior pituitary. Primary testicular failure may result from many clinical conditions including gonadotoxin exposure (e.g., chemotherapeutic agents, radiation, nicotine, alcohol), atrophic or undescended testes, and genetic abnormalities such as Klinefelter syndrome (KS) or Noonan syndrome. In most cases, however, a distinct etiology is not identifiable and HG is classified as idiopathic primary testicular failure.

In men with primary testicular failure of unknown etiology, a karyotype to exclude KS should be obtained, especially in men with testicular volume less than 6 mL [13]. KS is the most common chromosomal disorder in men with testicular dysgenesis syndrome (TDS) and is definitively diagnosed by

demonstration of an extra X chromosome demonstrated via karyotype (47, XXY). KS has an estimated prevalence of 0.2 % in the general population, 3 % among infertile men, and up to 11 % in men with nonobstructive azoospermia (NOA) [14].

Despite the wide variability in clinical presentation, all patients with KS suffer from absolute or relative HG, small testicular size, and impaired spermatogenesis. Sclerosis of the seminiferous tubules is typically observed on scrotal exploration [15]. The goal of TRT in adolescents with KS is to promote linear growth, increase muscle mass, preserve bone density, and allow for the development of secondary sexual characteristics [16].

Although T supplementation in KS has a beneficial effect on semen volume, exogenous T administration may also have an inadvertently detrimental impact on spermatogenesis by further suppressing testicular function overall [16]. Successful pregnancies in couples in which the male suffers from KS have been occasionally achieved using ejaculated sperm and assisted reproductive techniques. However, surgical sperm retrieval and intracytoplasmic sperm injection (ICSI) have dramatically improved the fertility potential of men with KS. This is particularly true when surgical exploration to harvest sperm is performed at a younger patient age (following puberty) since seminiferous tubules progressively lose function in a duration-dependent fashion in males with KS [17, 18]. Recent studies of men with KS, some concurrently treated with aromatase inhibitors, showed success rates of 66–72 % per testicular sperm extraction (TESE) with 69 % of men having sperm suitable for ICSI [18, 19]. Although no trials have specifically studied TRT and sperm retrieval rates, it is logical to assume TRT would lead to lower TESE yields. Studies have indicated that KS patients with higher baseline T, or those who best responded to medical therapy to correct T (as opposed to exogenous T), had more successful sperm retrieval [19].

Hypogonadotropic hypogonadism (HH) is a condition caused by insufficient or absent production of gonadotropin-releasing hormone (GnRH). In the absence of GnRH serum, FSH and LH will be low in addition to T. There are numerous identified causes of HH. HH in the presence of midline defects, such as anosmia, is defined as Kallmann's syndrome. Genetic causes like Prader-Willi syndrome (PWS) and Laurence-Moon-Bardet-Biedl syndrome may include a constellation of abnormalities, such as the mental retardation and physical defects associated with PWS. HH may result from a prolactin-secreting pituitary adenoma or iatrogenic causes, such as radiation or neurosurgical procedures, administration of opioids, anabolic steroids, or exogenous T. Regardless of the underlying cause, both T levels (due to low T) and sperm production (due to low T and FSH) are negatively affected [20]. Careful history is essential in ruling out iatrogenic causes, and adverse oral agents should be immediately discontinued.

Fertility potential can frequently be restored, with appropriate hormonal stimulation, in patients with HH. Men with primary testicular failure, on the other hand, cannot usually be successfully treated with medication alone. Fertility options for men in this group are limited to the use of donor sperm, adoption, or, in some patients, TESE to harvest sperm to be used with in vitro fertilization (IVF) and ICSI [18, 21].

Varicocele

The presence of varicocele, or dilated pampiniform plexus of the spermatic cord, can be identified in 15 % of the general population and in 35–40 % of subfertile men [22, 23]. Palpable varicoceles have been associated with decreased fertility and surgical varicocelectomy has been demonstrated to improve semen quality and pregnancy rates [22, 24, 25]. More recent studies have shown that varicoceles are also associated with HG and may be an independent risk factor for androgen deficiency [25]. The pathogenesis for this effect is not well understood but it has been speculated that increased intratesticular temperature in the presence of a varicocele may impair the enzyme 17 α-hydroxyprogesterone aldolase, which plays an important role in T production [27]. Surgical repair of varicoceles in men with low T has recently been shown to provide significant subsequent T level increases in the majority of study patients [26, 28]. The concept of varicocele as a risk factor for HG is covered in more detail in Chap. 11.

Effect of Exogenous T on Male Fertility

Therapeutic options to treat symptomatic HG are available in multiple forms. These include T replacement by intramuscular injections, patches, topically applied gels, and subcutaneous T pellet administration [13]. All of these options, however, have the effect of impairing spermatogenesis even while normalizing serum T levels. Iatrogenic androgens inhibit spermatogenesis due to direct feedback inhibition of gonadotropin secretion at the level of the hypothalamus and pituitary. This ultimately results in low intratesticular levels of T that are inadequate for maintenance of spermatogenesis. In fact, the effect on sperm production is so significant that there is a growing body of research exploring TRT as a potential male contraceptive medication [29].

Anabolic steroid users represent a distinct subpopulation of men with subfertility. As opposed to organically hypogonadal men who become subfertile due to TRT, steroid users typically have normal or high T levels initially. After one or more cycles of steroid use, native T production by Leydig cells declines and produces similar effects to those seen in men who undergo TRT. Studies of semen quality in athletes using high doses of anabolic steroids revealed severe impairment of sperm concentration, motility, and morphology [30]. Although cessation of use allowed normalization of seminal parameters in an average of 4 months, cases of persistent azoospermia have been reported occurring more than 1 year later [29].

Medical Treatment of Men with Hypogonadism and Infertility

As noted previously, patients with HH or primary testicular failure often require ARTs, such as IVF/ICSI, in order to achieve conception. This procedure may be performed using either ejaculated sperm or sperm obtained by percutaneous (TESA) or open testis biopsy (TESE) [17, 18]. Some potential benefit may be derived with use of recombinant FSH before IVF/ICSI in patients with testis failure, but this has not been conclusively established [31].

More medical options are available to men with HH who desire fertility. These therapies may be combined with assisted reproductive technologies such as IVF with ICSI, which may allow pregnancy to occur with very low numbers of sperm [32]. The medications are outlined below and summarized in Table 10.1.

Gonadotropin-Releasing Hormone (GnRH)

In patients with hypothalamic dysfunction underlying HH, the treatment goal is to increase GnRH or its downstream effectors. Although it may seem intuitive to simply administer GnRH, in practice, it is largely impractical and logistically difficult. GnRH is administered subcutaneously through the abdominal wall over 90–120 min intervals, thus mimicking gonadotropin pulsatility. GnRH has been shown to improve testis volume and serum T, but gonadotropin levels typically remain low, making it a poor choice for those with pituitary causes of HG [33–35].

Multiple studies have shown non-superiority of GnRH versus gonadotropin therapy for the induction of spermatogenesis or rate of pregnancies [36–38]. In addition to the high financial cost and impractical nature of this treatment, there also exists potential for infusion site infection [39]. Given these drawbacks, GnRH is usually utilized only after all other treatment options have failed to induce spermatogenesis.

Estrogen Receptor Modulators

Perhaps the most commonly used agents for hypothalamic hypogonadotropic HG are the antiestrogen agents clomiphene, tamoxifen, and enclomiphene. These estrogen receptor modulators raise T indirectly by blocking the coupling of estradiol with its receptors. The subsequent lack of negative feedback results in upregulation of LH and T [40]. Typical starting doses are 25–50 mg of clomiphene citrate taken every other day and are extremely well tolerated.

Increasing testicular T production has the benefit of normalizing serum T levels via an increase in intratesticular T production. Increasing T concentration within

Table 10.1 Medical therapies for men with hypogonadism and impaired fertility

Category	Formulation	Standard dosage	Benefits	Disadvantages
Gonadotropin therapy	Human chorionic gonadotropin (hCG)	1,000–2,000 International Units (IU) 2–3 times per week	– Financially inexpensive—may restore spermatogenesis in men with HH as a single agent	Requires intramuscular (IM) injection
Gonadotropin therapy	Human menopausal gonadotropin (HMG)	25–75 IU, 3 times per week	– May induce spermatogenesis when added to hCG – May be discontinued after spermatogenesis induced (patient can be maintained on hCG alone)	Requires IM injection
Gonadotropin therapy	Follicle-stimulating hormone (FSH)	– 1.5 IU/kg weekly × 18 months (urinary FSH) – 450 IU weekly × 12 months (recombinant FSH)	– May induce spermatogenesis when added to hCG	– Limited availability – Financially expensive – Requires IM injection
Physiological gonadotropin-releasing hormone (GnRH) replacement	GnRH	100–600 ng/kg per pulse, pulses given at approximately 2-h intervals, pumps worn for up to a year	– May be effective even if all other modalities have failed	– Financially expensive – Requires subcutaneous administration via portable abdominal wall infusion pumps for weeks or months – May result in pump site infections
Estrogen receptor modulator	Clomiphene citrate	25–50 mg daily or 25–50 mg every other day	– Easily tolerated – Oral convenience	– Potential side effects include breast tenderness, gynecomastia, and headache – 25 mg dose is not commercially available; 50 mg pills must be split in

(continued)

Table 10.1 (continued)

Category	Formulation	Standard dosage	Benefits	Disadvantages
				half to achieve that dose
Aromatase inhibitor	Anastrozole	1 mg daily	– Easily tolerated – Oral convenience	– Potential side effects include gastrointestinal distress, muscle aches, headache, and hypertension
Aromatase inhibitor	Testolactone	100–200 mg daily, taken orally	– Easily tolerated – Oral convenience	– Not available in the United States – Potential side effects include gastrointestinal distress, hypertension, edema, and paresthesias

the testes facilitates seminiferous tubule sperm production, which is in direct contradistinction to the decreased local testicular environment that results from exogenous T administration. Since antiestrogens work by raising LH levels, the candidates most likely to respond are patients with low to normal starting LH levels.

Supporting studies have shown normalized T levels and improved semen analyses in patients treated with clomiphene [41, 42]. However, a Cochrane meta-analysis of 738 men combining ten randomized controlled studies of the effects of short-term clomiphene and tamoxifen on men with oligoasthenozoospermia failed to show significant difference improvements in pregnancy rates when compared with controls [43]. Similar randomized controlled trials using tamoxifen therapy have not conclusively supported efficacy in either improved semen parameters or pregnancy rates [44].

Gonadotropin Therapy

Agents used for induction of spermatogenesis in HH include human chorionic gonadotropin (hCG), human menopausal gonadotropin (hMG), and FSH.

hCG binds to the same Leydig cell receptor as LH and mimics its action, stimulating the production of T. As intratesticular levels of T rise, often up to 100 times that of serum, spermatogenesis may be stimulated [45]. hCG alone can often restore spermatogenesis in men with adult onset of HH. Treatment is usually initiated with hCG but without FSH, since hCG has the ability to stimulate and maintain spermatogenesis alone at a fraction of the cost of FSH [46, 47].

In cases where hCG alone does not prove sufficient to stimulate spermatogenesis, FSH or hMG may be added to the regimen [47]. FSH or hMG preparations, which contain FSH, are administered after a suitable course of hCG. hCG is typically given as a 1,000–2,000 IU dose two to three times weekly for 18–24 weeks and is injected intramuscularly to the deltoid. hMG may be considered once serum T normalizes and semen analysis findings plateau [12].

hMG dosing (75 IU two to three times weekly) is typically continued until through the first 3 months of pregnancy after which the patient is maintained solely with hCG [48]. Combination hCG/hMG therapy may also induce virilization in hypogonadal prepubertal males and lead to testicular growth [36, 49, 50]. Urinary purified FSH (uFSH) and recombinant FSH (rFSH) have the added benefit of greater specific activity compared with hMG. The dose is 1.5 IU/kg weekly for 18 months and 450 IU weekly for 12 months, respectively [51, 52].

Aromatase Inhibitors

It has been observed that men with NOA or oligospermia frequently have low T and elevated E2, suggesting that increased aromatase activity is responsible for excessive conversion of T and subsequently lower serum levels [53]. These patients may therefore benefit from treatment with an aromatase inhibitor to prevent the conversion of T to E2, resulting in increased T and decreased E2 levels.

Treatment is comprised of anastrozole 1 mg taken orally daily. Anastrozole is an inexpensive medication with a favorable side effect profile. Testolactone 100–200 mg oral daily has been shown to be particularly effective in men with KS but this formulation is not available in the United States [54]. The effect of aromatase inhibitors is similar to that of antiestrogens, with resultant indirect increases in gonadotropins and T level.

Aromatase inhibitors are most effective in improving spermatogenesis in patients with serum T:E2 ratios <10 as well as obese men (who have increased levels of aromatase activity) [54, 55]. These agents are particularly important for utilization in men with KS, in whom it has been shown that normalizing serum T prior to TESE increases rates of successful sperm retrieval [19]. Similar benefits have not been conclusively demonstrated in other men with HG and infertility, but clinicians may prefer to medically optimize T levels before surgical sperm retrieval in all patients.

Conclusions

HG is a prevalent and potentially treatable condition that is associated with male infertility. Scrotal varices have recently been associated with HG in addition to subfertility, and recent evidence supports the use of surgical varicocele repair for

improving T levels as well as fertility potential. Patients with primary testicular failure have impaired testicular sperm and T production. Traditional HG treatment with TRT is contraindicated in these patients since it impairs sperm production through negative feedback. There are multiple other medical options that address HG and/or sperm production and should be utilized instead of TRT. Therapies in this category include estrogen receptor modulators, aromatase inhibitors, hCG, hMG, urinary and recombinant FSH, and GnRH. The specific treatment and regimen is tailored to the individual patient and is largely based on the underlying cause of the disorder. Logistical and financial considerations are also relevant and may guide medical decision making.

Although it is desirable to correct T levels in men with HG and infertility, normalization of T levels alone is generally considered ineffective for improving or restoring spermatogenesis in patients with primary testicular failure. Men with infertility related to HH, on the other hand, are relatively responsive to a variety of therapeutic agents that help stimulate testicular sperm production as well as increase T levels. Induced spermatogenesis may be sufficient for natural conception or at least for use with ARTs.

The message that TRT should not be reflexively used to treat men with HG who desire fertility cannot be overemphasized. This concept may be counterintuitive unless the underlying physiology of the hypothalamic-pituitary axis is appreciated. Patients and physicians should be aware of medical options to restore normogonadism that may restore, improve, or, at the very least, fail to impair spermatogenesis.

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