Treatment of the Hypogonadal Infertile Male—A Review

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ABSTRACT

Introduction. Testosterone treatment for hypogonadism is detrimental for men in reproductive age as it impairs spermatogenesis, and therefore affects fertility. It is, therefore, not indicated in men with hypogonadism and infertility.

Aim. The aim of this review is to analyze current data regarding options of treatment for men with hypogonadism and infertility.

Main Outcomes Measures. A comprehensive review of the current literature on management of infertility among hypogonadal men.

Methods. A literature search using PubMed from 1980 to 2012 was done on articles published in the English language. The following medical subject heading terms were used: "infertility," "infertile," "hypogonadism;" "testosterone deficiency" and "men" or "male;" and "treatment" or "management."

Results. The options for hypogonadal testicular failure are limited. Hormonal treatment is by and large ineffective. For secondary hypogonadism (hypogonadotropic/normogonadotropic hypogonadism), the options include gonadotropin-releasing hormone, human chorionic gonadotropin (hCG), human menopausal gonadotropin (hMG), follicle-stimulating hormone (FSH), and anti-estrogens and aromatase inhibitors. Dopamine antagonist is indicated for prolactinoma. Artificial reproductive technique is indicated for primary testicular failure and also when medical therapy fails.

Conclusion. The most suitable option with the current data available is hCG with or without hMG/FSH. Testosterone supplementation should be avoided, but if they are already on it, it is still possible for a return of normal sperm production within 1 year after discontinuing testosterone. **Ho CCK and Tan HM. Treatment of the hypogonadal infertile male—A review. Sex Med Rev 2013;1:42–49.**

Key Words. Hypogonadism; Infertility; Men; Treatment; Hormonal

Introduction

Hypogonadism can either be primary (hypergonadotropic hypogonadism) or secondary (hypogonadotropic/normogonadotropic hypogonadism). In hypergonadotropic hypogonadism, there is primary testicular failure resulting in low *testosterone. As a consequence of this, the negative feedback to the hypothalamus and pituitary is reduced, therefore causing increased gonadotropin-releasing hormone (GnRH) and gonadotropins secretion. On the other hand, in hypogonadotropic hypogonadism, the defect is in the hypothalamus or pituitary causing reduced gonadotropin release* [1]. *In normogonadotropic hypogonadism, the gonadotropin levels are normal. The common factor in both* hyper- and hypo- or normogonadotropic hypogonadism is the low serum testosterone level.

Hypogonadism may occur during fetal development, puberty, and adulthood. If it occurs during fetal development, it may cause ambiguous genitalia. At puberty, it may cause gynecomastia and arrested secondary sexual development. In adulthood, erectile dysfunction and infertility may prevail.

Testosterone replacement therapy has often been used in patients with hypogonadism. Testosterone can induce the development of adolescence, and normalize the height and secondary sex characteristics. However, it cannot induce

testicular maturation and spermatogenesis [2]. Testosterone is known to inhibit GnRH and gonadotropin secretion. When exogenous synthetic testosterone is administered, this results in negative feedback on the hypothalamic–pituitary axis. GnRH as well as gonadotropin is thus inhibited, and this causes a decrease in intratesticular testosterone and overall testosterone production [3].

Intratesticular testosterone levels are usually 50–100 times that of serum levels. When intratesticular testosterone levels drop to less than 20 ng/mL as a result of suppression by exogenous synthetic testosterone, spermatogenesis can be drastically affected [4]. Intratesticular testosterone is important for normal spermatogenesis. In fact, complete inhibition of intratesticular testosterone can result in azoospermia [5,6]. This has resulted in intramuscular testosterone being investigated as a male contraceptive agent [7].

Therefore, testosterone therapy is not advocated for hypogonadal men with paternity in mind. A more appropriate approach in these patients would be to increase their own endogenous testosterone. This review aims to analyze the current data on treatment for hypogonadal infertile men.

Methods

We conducted a literature search using PubMed from 1980 to 2012. The following medical subject heading terms were used: "infertility," "infertile," "hypogonadism;" "testosterone deficiency" and "men" or "male;" and "treatment" or "management." Inclusion criteria for article selection were the following: articles in English, studies (of any design) on infertility and hypogonadism in men, and publication in a peer-reviewed journal. The abstracts and full text of the articles, identified from the initial search, were reviewed by two authors independently, who subsequently reached a consensus on adding each included article. The reference lists of identified articles were reviewed manually for additional relevant articles. Additional studies, recommended by expert peer reviewers, were examined and added.

Results

The workup for someone with hypogonadism is shown in Figure 1. It is important to know that other causes of high levels of prolactin, besides prolactinoma, include renal failure, antipsychotic drugs, hypothyroidism, estrogen exposure, and stress usually (acute or chronic).

The management of hypogonadism is outlined below.

Hypergonadotropic Hypogonadism (Primary Testicular Failure)

There are various causes of primary testicular failure, and these include gonadotoxins (e.g., alcohol, nicotine, anabolic steroids, cocaine, marijuana, chemotherapy, radiation, pesticides), genetic abnormalities (e.g., Klinefelter syndrome, Noonan syndrome), and absent testes and nonfunctioning testes (cryptorchidism, atrophy, torsion).

Currently, there is no endocrine therapy available for the treatment of infertility in men with primary testicular failure. The options are limited—that is, artificial insemination with donor semen adoption, in vitro fertilization (IVF), or intracytoplasmic sperm injection (ICSI) [8,9]. Primary testicular failure, as well as those with normal hormones but oligospermia, may benefit from recombinant follicle-stimulating hormone (FSH) therapy prior to IVF/ICSI [10].

Eleven percent of azoospermic men are diagnosed with Klinefelter syndrome. The abnormality is an extra X chromosome (47 chromosomes, XXY), which can arise from chromosomal nondisjunction in either parent. These patients have gynecomastia, elevated serum estradiol levels, and sclerosis of the seminiferous tubules, which typically results in azoospermia and small testicles. Nevertheless, testis biopsy may yield sperm with normal karyotype. These sperms can be procured for ICSI.

A study by Schiff et al. showed that for patients with serum testosterone levels less than 15.6 nmol/L who were treated with an aromatase inhibitor, the sperm retrieval rate was 72% per testicular sperm extraction (TESE) attempt, and 69% had adequate sperm found for ICSI. Thirty-three IVF cycles yielded embryos for transfer in the 39 (85%) cycles with sperm retrieved. It resulted in 46% live births, and all children had normal karyotypes [8].

There is also evidence that men with abnormal testosterone : estradiol ratios can be treated with aromatase inhibitors, with some improvement in spermatogenesis [11,12]. There is also the option of using antioxidants. A few studies have investigated the usage of antioxidants like vitamins C and E, and had positive findings, but these studies are not robust and valid conclusions cannot be made

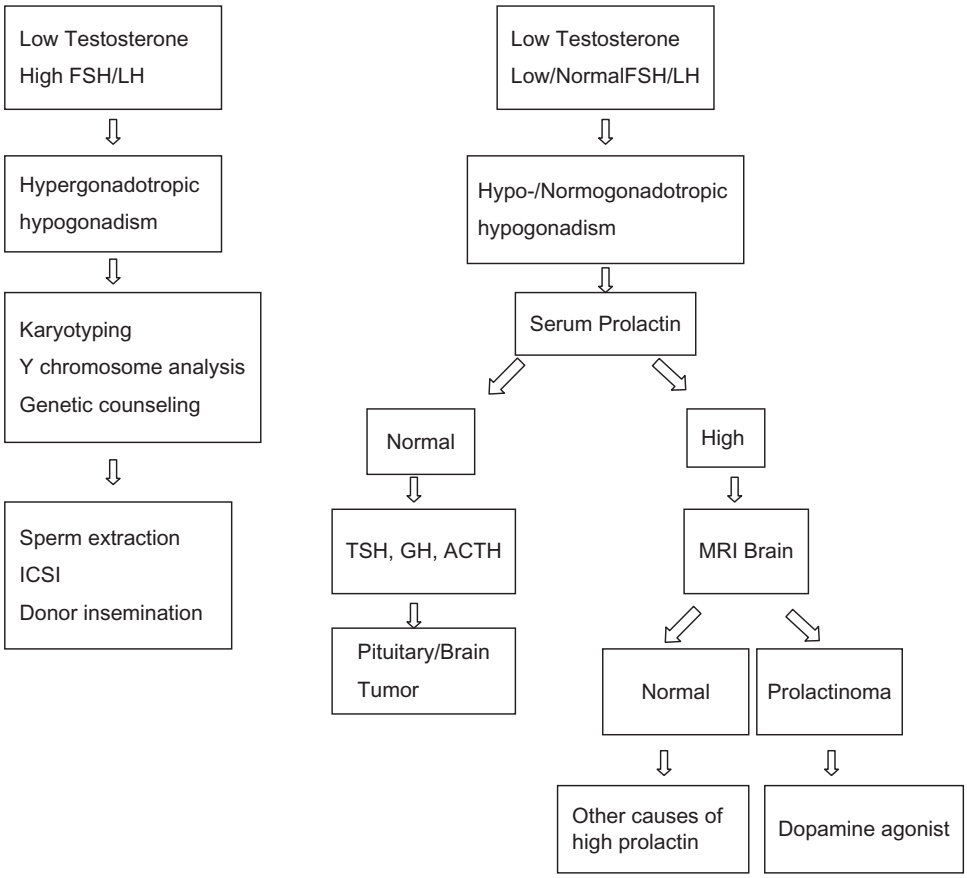

Figure 1 Workup for hypogonadism.

[13–15]. More randomized controlled trials are needed to confirm the efficacy and safety of antioxidant supplementation in the medical treatment of spermatogenic failure besides the need to determine the ideal dose of each compound to improve semen parameters, fertilization rates, and pregnancy outcomes [16].

Secondary Hypogonadism (Hypogonadotropic/ Normogonadotropic Hypogonadism)

Unlike primary testicular failure, hypogonadotropic hypogonadism is amenable to medical treatments, which are described in detail below.

GnRH

GnRH is one option if the patient has a hypothalamic cause for hypogonadism. It is usually not successful if given solely for those with pituitary cause of hypogonadism as these patients inevitably require gonadotropins to stimulate the testes.

GnRH administration requires pulsatile doses given via a portable pump and a butterfly needle placed in the abdominal wall, which needs to be changed every 2 days. The subcutaneous administration of GnRH is given at 90- to 120-minute intervals to mimic the luteinizing hormone (LH) and FSH pulse frequency observed in normal men. The dose needed varies. It could be 5–25 ng/kg, which are individualized to maintain serum LH concentrations in the mid-normal range, or in other cases ranges from 5 mg to 20 mg over 120 minutes, or 100–400 ng/kg over 120 minutes. After at least 6 months of treatment, it has been shown that serum testosterone concentrations and testicular volume are within normal levels. However, serum LH, FSH, and serum inhibin B concentrations are significantly lower than those in normal men [17–19].

The success of spermatogenesis is demonstrated by finding sperm in the ejaculate. In patients who have partial or complete pubertal development after 12 months of therapy, mature sperms have been proven to be present in the ejaculate [18,20]. However, the sperm counts were below the normal range ($1.2–15.3 \times 10^6$/mL). Despite this setback, pregnancy can be achieved. The average duration

until conception is about 6–7 months [21–23]. There are a few factors that give a better prognosis for achieving an adult testicular size, which in turn will optimize spermatogenesis. These factors include previous medical history of sexual maturation, a baseline inhibin B of more than 60 ng/L, and absence of cryptorchidism [18]. Causes of pulsatile GnRH treatment failure include mutation of the GnRH receptor gene as well as anti-GnRH antibodies, which are formed during intravenous administration [24,25].

Although there is some evidence that testicular growth is faster with GnRH therapy as compared with gonadotropins, it has been shown that there is no advantage of GnRH over gonadotropin therapy in achieving final testicular volume, onset of spermatogenesis, sperm counts, or pregnancy rates [21,23,26]. GnRH therapy is not favored in many centers because of the cumbersome nature of the treatment where the patient has to wear a continuous infusion pump, the high cost of the therapy, as well as the inconvenience of having to rotate the infusion site to prevent potential infection [27].

However, recently, there was a case report of a successful usage of low-dose (15 μg) buserelin nasal spray, administrated in each nostril three times a day (total: 90 mg/day), which improved semen parameters and serum gonadotropin and testosterone levels. After approximately 1 year, semen analysis showed normozoospermia, and pregnancy was successful with the ICSI [28].

Gonadotropins

Gonadotropins are used mainly in cases of pituitary cause of hypogonadism and GnRH receptor gene defects. They are also an option in hypothalamic cause of hypogonadism. Gonadotropins that have been used include human chorionic gonadotropin (hCG), human menopausal gonadotropin (hMG), FSH, and recombinant FSH.

hCG. hCG is used to substitute LH. They are structurally very similar and act on the same receptor on Leydig cells. These in turn will produce testosterone. When used on its own, hCG can initiate and maintain spermatogenesis, but in terms of testicular growth and normalization of serum testosterone, the effect is rather poor [29–31]. hCG should be administered at a dosage of 1,500–2,000 IU two to three times per week for 18–24 weeks until normal serum testosterone levels are achieved, and there is no further increase in testicular growth or improvement in sperm production [32]. Spermatogenesis can be maintained for 16 months if hCG is used after gonadotropins or GnRH replacement therapy. However, without initial induction by gonadotropins or GnRH, sperm concentration will decrease gradually after 12 months. Serum FSH and LH levels as well will drop to the borderline of normal value [33]. hCG, as a substitute of LH, is always given before FSH due to the following:

- Stimulation of Leydig cells to secrete testosterone, which causes intratesticular testosterone concentration to rise up to 100 times that in the peripheral circulation, which is essential for induction of spermatogenesis.
- Stimulation of spermatogenesis may be achieved with hCG alone, which is not possible with FSH alone.
- hCG is much cheaper than FSH [34,35].

hMG/hCG. hMG, which contains FSH, stimulates spermatogenesis, but only after intratesticular testosterone is brought into the normal range with hCG stimulation. Therefore, hMG needs to be given only after hCG administration [32]. The dose is 75 IU two to three times weekly until pregnancy is achieved. HMG treatment is usually continued until pregnancy has been achieved, and maintained for 3 months. After that, it can be withdrawn, and spermatogenesis can be maintained by continued administration of hCG [36]. Besides spermatogenesis, the combination of hCG/hMG therapy can induce pubertal development, increase physical strength, double the testicular volume, and normalize testosterone level [21,29,37]. When treated with hCG plus hMG, 64.9–89.2% of patients had spermatozoa in the ejaculate with an average treatment duration of 9.2–10.5 months [2,38,39].

hCG and FSH. Purified urinary FSH has more specific activity in comparison to hMG (10,000 IU:mg of protein vs. 150 IU:mg of protein for hMG). The routine dosage is 1.5 IU/kg FSH weekly, and 500 IU hCG per 2 weeks to 4,000 IU hCG per week [40].

In one study, 25 out of 28 men with hypogonadotropic hypogonadism who were given hCG 2,000 IU twice weekly for 3–6 months, followed by 18 months of additional subcutaneous administration of highly purified urinary FSH, achieved spermatogenesis, with 18 of them having a sperm density of more than 1.5×10^6/mL. The median time to initiation of spermatogenesis was 9 months. Mean testicular volume also increased

threefold [41]. Other studies have also shown that combination of hCG and FSH therapy for 6–24 months results in testicular growth in almost all and spermatogenesis in 80–95% of patients without undescended testes [26,40,42,43].

Prepubertal-onset hypogonadism men are also more likely to require addition of FSH besides hCG as compared with those with post-pubertal onset of hypogonadism [44].

hCG and Recombinant Human Follicle-Stimulating Hormone (rhFSH). The rhFSH was initially developed for use in ovulation induction to avoid the small amount of LH present in hMG preparations. It has advantages over urinary preparations of FSH in terms of purity, specific activity, consistent composition, and constant supply [1]. Its efficacy is comparable to urinary FSH in restoring normal fertility in men with gonadotropin deficiency [45]. The dosage is 450 IU (3×150 IU or 2×225 IU) r-FSH weekly combined with hCG for about 48 weeks. The sperm concentration could reach more than 1×10^6/mL after treatment [46]. Other studies have also shown similar results [42,47–50].

So far, there is no head-to-head trial comparing the rhFSH and urinary hMG, but their efficacy when added to hCG in stimulating spermatogenesis in men with hypogonadotropic hypogonadism seems similar. Since the improved purity of the rhFSH is not necessary in men, the increased cost that comes with the rhFSH makes it not a favorable choice.

hCG and Testosterone. In a study by Avila et al., 10 men were given short-acting testosterone preparations in addition to low doses of hCG, and the result was that based on semen analysis, spermatogenesis was essentially maintained. There was minimal decline in sperm density, but none developed azoospermia. In other words, hCG administered with testosterone can maintain intratesticular testosterone levels and spermatogenesis [51].

Anti-Estrogens

Clomiphene citrate is an estrogen receptor modulator with predominant antagonist activity that blocks negative feedback exerted by estrogen at the hypothalamus and anterior pituitary. The result is increased secretion of GnRH from the hypothalamus, which stimulates pituitary gonadotropin production that could stimulate both testicular production of testosterone and spermatogenesis [16]. Based on this, treating hypogonadotropic hypogonadism men with clomiphene might be expected to have the same biological effect compared with gonadotropins. With the advantage of its low price, clomiphene may be a good choice for the treatment of hypothalamic hypogonadotropic hypogonadism. There are reports of successful treatment with clomiphene which resulted in normalization of gonadotropins, testosterone, and semen parameters [52,53].

Enclomiphene, which is the trans-stereoisomer of clomiphene citrate, similarly has the potential to increase serum testosterone levels in men with secondary hypogonadism by restoring physiological endogenous testosterone secretion while maintaining testicular volume, and potentially spermatogenesis. It has demonstrated significant efficacy in the physiological restoration of testosterone levels in males with secondary hypogonadism. It has also shown promise in the management of secondary hypogonadism associated with obesity, metabolic syndrome, and possibly infertility [54].

Aromatase Inhibitor

Estradiol inhibits gonadotropin secretion. Aromatase inhibitors function by blocking aromatase, which is a cytochrome P-450 enzyme responsible for converting testosterone to estradiol. Therefore, by reducing estradiol, aromatase inhibitors may indirectly increase serum levels of LH, FSH, and testosterone, resulting in functional effects similar to those of the anti-estrogens. Aromatase inhibitors have been used to improve male fertility and stimulate spermatogenesis. In fact, it may have greater benefit than anti-estrogens in men with lower serum testosterone to estradiol ratios (<10) and in obese patients [3]. Testolactone as well as anastrozole are two of the aromatase inhibitor preparations that have been studied and found to be equally effective in improving semen parameters in infertile men [12].

Aromatase inhibitors have been used in men with hypogonadism and also for normalization of serum testosterone levels before microscopic TESE in men with Klinefelter syndrome. There was a higher sperm retrieval rate in those who responded to treatment (total T of >250 ng/dL) than those who did not (77% vs. 55%) [55]. It has been hypothesized that aromatase activity from Leydig cell hyperplasia may be responsible for increased testosterone to estradiol conversion and impaired semen parameters [12].

Dopamine Receptor Agonist

During the workup for hypogonadism, if a prolactin-secreting pituitary macro- or microadenoma is identified, medical treatment with a dopamine receptor agonist is indicated. Bromocriptine is cheaper and effective, but cabergoline (0.125–1.0 mg twice weekly) is the preferred agent because it has the highest efficacy in normalizing prolactin levels and shrinking prolactin-secreting tumors. It has been shown that 53% of cases treated with dopamine agonist had reversal of infertility [56].

Artificial Reproductive Technique (ART)

If medical therapy fails or in cases of hypogonadism secondary to primary testicular failure, the option lies in ART. This includes testicular/epididymal sperm extraction and the ICSI [57]. In one study on azoospermic men with hypogonadotropic hypogonadism unresponsive to gonadotropin therapy where a total of 17 ICSI cycles were performed using testicular sperm retrieval, the fertilization rate was 41.7% and the cumulative pregnancy rate was 20% [58]. In another study, 11 out of 17 patients with hypogonadotropic hypogonadism had to resort to ICSI after failed medical therapy, and the pregnancy rates after ICSI were 54.5% [59]. ICSI is also recommended if, after recovery of spermatogenesis with medical therapy, pregnancy does not occur within 8 months [45].

Herbal Treatment

Two herbal medications that have undergone trials to prove their effects on infertile hypogonadal men are *Withania somnifera* and *Mucuna. W. somnifera*, or otherwise known as ashwagandha root, has been shown to increase testosterone and LH, while decreasing FSH and prolactin, among infertile men having suboptimal testosterone levels compared with controls [60–62]. It has also resulted in a significant increase in sperm count, concentration, and motility among infertile men. Similarly, treatment with *Mucuna pruriens* improved testosterone, sperm count, and motility in infertile men compared with the control group [63–66].

Conclusion

Hypogonadism affects both sexual function and fertility [67–69]. Primary testicular failure patients do not have much of a choice except to go for ART to father a child. Medical therapy generally does not work for this group of patients. On the other hand, hypogonadotropic hypogonadism patients should attempt hormonal treatment, as their chances of paternity are higher. The most suitable option, in our opinion, with the current data available is hCG with or without hMG/FSH. Testosterone supplementation should be avoided, but if they are already on it, most studies have shown that a return of normal sperm production within 1 year may occur after discontinuing testosterone. More randomized controlled trials are needed to assess the safety and efficacy of antiestrogens and aromatase inhibitors for this group of patients.

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