

REVIEW ARTICLE



Diagnosis and treatment of hypogonadism in men seeking to preserve fertility – what are the options?

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Male hypogonadism is a clinical syndrome that results in low testosterone levels and frequently leads to infertility. The syndrome occurs due to disruption at one or more levels of the hypothalamic-pituitary-gonadal axis. Testosterone replacement therapy (TRT) is the most common treatment utilised for male hypogonadism. However, long-acting forms of TRT leads to infertility and so is inappropriate for patients wishing to conceive. For patients who wish to remain fertile, nasal TRT, clomiphene citrate, exogenous gonadotropins, gonadotropin releasing hormone and aromatase inhibitors have been used as alternative treatment options with different degrees of success. A review of the literature was performed to identify the safety and efficacy of alternative treatment options. Gonadotropin releasing hormone can successfully induce spermatogenesis but is impractical to administer. Likewise, aromatase inhibitors have limited use due to inducing osteopenia. Nasal TRT may be a good treatment option for these patients, but its efficacy has so far only been demonstrated in small sample sizes. However, clomiphene citrate and exogenous gonadotropins are safe, offer good symptom control and can successfully induce fertility in hypogonadism patients.

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INTRODUCTION

Male hypogonadism is a clinical syndrome associated with decreased function of the testes resulting in reduced testosterone production and impaired spermatogenesis [1]. It accounts for approximately 10% of male infertility [1].

Primarily, hypogonadism is categorised according to the point within the hypothalamic-pituitary-gonadal axis (HPGA) that is not functioning. Primary hypogonadism, also referred to as hypergonadotropic hypogonadism, is due to testicular failure. The pituitary attempts to compensate for testicular failure by increasing the levels of LH and FSH secreted. Secondary or hypogonadotropic hypogonadism is due to a fault with either the hypothalamus or anterior pituitary. As the hypothalamus and anterior pituitary maintain LH and FSH levels they as well as testosterone are reduced in secondary hypogonadism (Table 1). Mixed hypogonadism is a defect in the testes, as well as the anterior pituitary and/or the hypothalamus. The gonadotropin levels vary, dependent on whether primary or secondary failure is dominant [2]. Therefore, in clinical practice, mixed hypogonadism is often classified as either primary or secondary hypogonadism based upon its endocrine profile. Finally, subclinical hypogonadism has been identified more recently [3]. The condition is also termed compensated hypogonadism as normal testosterone levels are maintained by elevated LH levels. More recently classification systems have been proposed which also consider the age of onset and the type of testicular cells primarily affected [4].

Primary hypogonadism can be divided further into congenital and acquired forms. Klinefelter syndrome is an inherited form of primary hypogonadism associated with the karyotype 47, XXY [5]. The prevalence of the syndrome is approximately one in every six-

hundred and fifty births but over two-thirds of cases are not diagnosed [6]. This makes it the most prevalent cause of primary hypogonadism [7]. Clinically Klinefelter syndrome is associated with small, firm testes, tall stature and gynecomastia [5]. Other congenital causes of hypogonadism include Down syndrome and Y chromosome microdeletions, both of which are less common [8]. Acquired primary hypogonadism occurs with injury to the testes. This includes testicular trauma, infection such as mumps orchitis, medications such as Ketoconazole, or exposure to radiation or chemotherapy [8, 9].

Secondary hypogonadism can also be subdivided into acquired and congenital forms. There is around one case of congenital secondary hypogonadism for every ten thousand births [10]. Kallmann syndrome makes up half of these cases [11]. Patients with Kallmann syndrome have decreased GnRH levels and anosmia [12, 13]. Kallmann syndrome is associated with congenital malformations such as renal agenesis, a cleft palate or lip, hearing loss and bimanual synkinesis [14]. The syndrome has been linked to several gene mutations, the first of which to be identified was *KAL-1* [15]. While the specific gene mutation can subtly alter the pathophysiology, all the mutations target the neurons responsible for GnRH secretion. These neurons also play a key role in olfactory bulb development and is why the patients report anosmia. Cases of congenital secondary hypogonadism without anosmia are classified as idiopathic congenital hypogonadism [16]. Over thirty gene mutations have been isolated as causative [16]. Acquired secondary hypogonadism is more common than the congenital form [2, 12]. It is the result of either disease of the pituitary or hypothalamus, sometimes termed organic, or induced functionally by medication, malnutrition, or chronic disease [8, 12]. Organic

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Table 1. Subcategories of hypogonadism with typical gonadotrophin levels.

Condition	Testosterone	LH	FSH
Primary hypogonadism	Decreased	Increased	Increased/Normal
Secondary hypogonadism	Decreased	Decreased	Decreased
Sub-clinical hypogonadism	Normal	Increased	Increased/Normal

diseases include a tumour of the pituitary or hypothalamus (including prolactinoma) or infiltrative disease [17].

It is normal for men's free testosterone levels to reduce by 1.3–3% per year after 30 [18, 19]. The reduction in testosterone is not usually great enough to reduce total testosterone below normal limits or produce symptoms [8]. Late onset hypogonadism (LOH) is used to describe a mixed, primary and secondary hypogonadism, that occurs in later life [20]. The incidence of testosterone deficiency is very high, 17% of 40–70-year-old men's total testosterone is <11 mmol/L [21]. However, for a diagnosis of LOH low testosterone must be accompanied by symptoms [22]. Based on this definition the prevalence of LOH is found to be 0.1% in 40–49-year-olds increasing up to 5.1% in 70- to 79-year-olds [21]. Free testosterone is also a useful parameter. The European Association of Urology recommend its use in cases where total testosterone is between 8–12 mmol/L [1]. More recent studies have shown it to be more closely correlated to symptoms than total testosterone and advocated for its routine use [23]. The likelihood of LOH increases with obesity, type two diabetes, and other chronic illness [19]. The relationship between obesity and testosterone levels is complex. Obesity increases the risk of hypogonadism through increased cytokine levels which inhibit GnRH release and through greater testosterone to oestradiol conversion [24]. Conversely, low testosterone increases levels of body fat [25]. As such it can be difficult to know whether obesity has led to hypogonadism or vice versa.

This paper is a review of the literature on treatments available for hypogonadism in those wishing to maintain fertility. A literature review was conducted, and papers were screened for relevance based on their title and then abstract. The references of the papers included were also screened. No formal inclusion and exclusion criteria were used, and papers were included at the discretion of the authors. This is a potential source of bias.

TESTOSTERONE REPLACEMENT THERAPY

Testosterone replacement therapy (TRT) is the most common treatment for hypogonadism. TRT has been shown to induce the development of secondary sexual characteristics, improve sexual function, and improve body composition [26–31]. There are side effects (Table 2), these include gynaecomastia, polycythaemia, and an increase in PSA [29, 31–33]. Despite increasing PSA, the recent TRAVERSE study has demonstrated TRT does not increase the incidence of either urinary symptoms or prostate cancer [33]. However, TRT is contraindicated in those with metastatic or locally advanced prostate cancer and also in those with breast cancer and polycythaemia (haematocrit $\geq 54\%$) [1]. Previously, TRT was believed to increase the risk of cardiac event in patients with underlying cardiovascular disease [1]. The TRAVERSE study has proven this not to be the case [34]. Traditionally TRT has been in long-acting forms such as intra-muscular injections. These formulations are not an appropriate option for those who wish to maintain fertility [35]. Testosterone negatively feedbacks on the HPGA, suppressing both LH and FSH production. The resulting low levels of FSH leads to impaired spermatogenesis which results in

reduced fertility. Over time testicular atrophy may also occur [36]. More recent, short acting nasal formulations of TRT have been shown to not impair spermatogenesis [37, 38]. Moreover, patients with azoospermia on long acting TRT resumed spermatogenesis when switched to 4.5% nasal testosterone gel (Natesto, produced by Acerus Biopharma Incorporation in the USA) [38]. While this data is promising these studies are limited by small population sizes, 60 and 27 men respectively, as well as short follow up periods (six and three months). Further studies are required to ascertain the efficacy and safety of nasal testosterone. For patients wishing to conceive over the next year long-acting TRT is not an appropriate treatment option. Nasal formulations may provide a valid alternative, but more research is required.

ALTERNATIVE TREATMENT OPTIONS

One alternative is clomiphene citrate (CC). Originally used to induce ovulation, CC is prescribed off-label for male hypogonadism [39]. A selective oestrogen receptor modulator, CC inhibits the negative feedback effect of oestrogen on the HPGA. This increases the secretion of LH and FSH from the anterior pituitary promoting both testosterone production and spermatogenesis. By inducing spermatogenesis CC avoids the reduction in fertility caused by TRT. Paradoxically, early studies demonstrated a decrease in sperm count when CC therapy was initiated [40, 41]. Contrary to this, more recent meta-analyses, with much larger cohorts, have shown improvement in sperm parameters [42, 43]. Symptomatic control and serum testosterone levels are also comparable to TRT [39, 42, 44]. Studies have demonstrated CC to be safe with minimal side effects (Table 2), which include headaches and gynaecomastia [42, 43, 45]. When determining treatment duration, the response to CC and overall fertility profile of the couple must be kept in mind. In couples where the female partner is over 35 or has low ovarian reserve then recourse to assisted contraception should be considered. For couples for whom this is not the case then CC remains effective at safely treating both the symptoms of male hypogonadism and while preserving fertility for at least eight years [45].

Exogenous gonadotropins are another option for the treatment of hypogonadotropic hypogonadism. Human chorionic gonadotropin (hCG) mimics the effects of LH, stimulating testosterone production from the Leydig cells [29, 46]. Spermatogenesis occurs in approximately three quarter of hypogonadotropic patients treated with hCG alone [11, 46, 47]. Factors decreasing the likelihood of success include patients with low testicular volume (<4 mL), low inhibin B levels or a history of cryptorchidism. These patients require concurrent FSH treatment [48–50]. This is available in different forms including recombinant urinary FSH, synthetic FSH and more recently long acting Corifollitropin alfa [29]. There is limited evidence as to which of these forms has the greatest efficacy. FSH may be given prior to hCG therapy to trigger testicular development, started concurrently, or added to hCG if it has failed to induce spermatogenesis [29]. While excellent at inducing fertility there is less evidence around symptomatic benefit seen with gonadotropins [29]. Patients may find the need for frequent injections distressing. Gonadotropins are ineffective in patients with primary hypogonadism who by definition have elevated levels of gonadotropins.

In patients with retained pituitary function gonadotropin releasing hormone can stimulate the release of LH and FSH. GnRH secretion from the hypothalamus is pulsatile and so exogenous GnRH must be given intermittently [29, 51]. This avoids the pituitary becoming desensitized. The need for pulsatile intermittent administration makes treatment of hypogonadotropic hypogonadism with GnRH logistically intensive [29, 46]. The efficacy of GnRH in inducing fertility is comparable to gonadotropin therapy with approximately three quarters of patients undergoing spermatogenesis [51]. A small study by Dwyer et al.

Table 2. A summary of the different treatment alternatives to TRT for hypogonadal men wishing to maintain fertility.

Treatment	Mechanism	Drugs	Route of administration	Dosage	Contraindications	Side effects	Licensed
Selective oestrogen receptor modulator	Inhibits the oestrogen receptors at the hypothalamus and pituitary reducing the negative feedback effect of oestrogen and so increasing GnRH, LH and FSH levels [39, 57]	Clomiphene citrate, Tamoxifen	Oral	25–50 mg/day (Clomiphene citrate), 20–30 mg/day (Tamoxifen) [39]	Tamoxifen is contraindicated if there is a personal or family history of venous thromboembolism	Headaches, Gynaecomastia [39]	Licensed for infertility treatment in female but not male patients
Exogenous gonadotropins	Stimulate the production of testosterone from the Leydig cells and spermatogenesis from the Sertoli cells	Human chorionic gonadotropin, highly purified urinary FSH, recombinant FSH	Subcutaneous/intramuscular injection	1000–2000 IU x 2–3/week (hCG),	Tumour of the hypothalamus, pituitary or testes	Gynaecomastia, Erythrocytosis [29, 50]	Not for male hypogonadism
Gonadotropin releasing hormone	Binds to the anterior pituitary leading to the production of LH and FSH	GnRH	Pulsatile subcutaneous/intramuscular injections	25–600 ng/kg every 2 h for 12–24 months [59]	None	Erythrocytosis [29]	Not for male hypogonadism
Aromatase Inhibitors	Reduces aromatisation of testosterone to oestrogen reducing the negative feedback effect of oestrogen on the HPGA [57]	Anastrozole, Letrozole	Oral	1 mg/day (Anastrozole) [60], 2.5 mg/day (Letrozole) [61]	None	Osteopenia, potential link to thromboembolic events [29, 57]	Not for male hypogonadism
Nasal Testosterone replacement	Proposed that the short acting nature of this formulation suppresses LH and FSH to a more minimal extent and so does not inhibit spermatogenesis [38]	4.5% Nasal testosterone gel (Natesto)	Intranasal	11–33 mg/Day	Prostate or breast cancer	Nasal symptoms (including rhinorrhoea and epistaxis), side effects as stated previously of other preparations of TRT	No

did find the number to be greater if FSH was given for the 4 months predating the course of GnRH [52]. GnRH is rarely used in the UK due to its expense and impracticality, but its use is more widespread in other European countries [29].

Aromatase inhibitors, originally used to treat hormone dependent breast cancer, are also utilised to treat hypogonadism [53]. Aromatase converts testosterone to oestradiol, which suppresses the secretion of GnRH and gonadotropins [54]. By reducing oestradiol, testosterone levels are increased [55–57]. Despite the increase in serum testosterone there is limited evidence to suggest aromatase inhibitors offer significant symptomatic control [58]. Aromatase inhibitors have also been shown to decrease mineral bone density [56, 59]. For these reasons the off-label use of aromatase inhibitors for hypogonadism appears to have limited merit.

As discussed above some patients may have a reversible cause of their hypogonadism. This can include obesity, medications, and chronic disease. For these patients further pharmacological intervention may be unnecessary and conservative measures should be trialled. Weight loss significantly increases testosterone levels [60, 61]. While the effect is greatest for patients classified as obese by body mass index a significant increase is still seen in those who are overweight [60]. Medications such as opioids are known to cause hypogonadism [8, 62, 63]. A medications review should therefore be undertaken, and any possibly suppressing testosterone production should be stopped if possible or given at the lowest therapeutic dose. Better management of chronic diseases may also be valuable but there is limited evidence on this topic. Type two diabetes is linked to reduced testosterone levels [64]. For these patients tighter glycaemic control may increase testosterone levels. Moreover, all hypogonadism patients should be encouraged to lead a healthy lifestyle. Weight loss, exercise and smoking cessation all increase fertility [65].

CONCLUSION

The most common treatment for male hypogonadism is TRT. While long-acting TRT is effective it can lead to infertility and so is not advised for hypogonadal men wishing to maintain their fertility. For this group of patients, different treatments are required. Two of the alternative options, GnRH and aromatase inhibitors, appear to have limited use. Aromatase inhibitors decrease bone density and GnRH is impractical to administer. Nasal formulations of TRT appear to promote spermatogenesis but this has only been demonstrated in small cohorts and with short follow up. Therefore, while nasal TRT may be a good alternative further research is required to ensure its efficacy and safety. However, CC and gonadotropin therapy are viable alternatives. Both induce spermatogenesis and appear to be safe. In addition to pharmacological intervention, the patient's general health should be optimised to maximise the chances of conception.

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AUTHOR CONTRIBUTIONS

AWCL wrote the first draft of the paper. After this AWCL amended the paper based on the contributions from the other authors. PG assisted AWCL in writing the first draft. PG reviewed the paper multiple times and recommended amendments at each stage. RM reviewed the paper and provided us with his specialist input as a fertility expert. IP reviewed the paper and gave his input. VM had the original idea for the paper and recruited the other authors. VM provided guidance throughout on how best to address the topic. He further reviewed the paper at every stage and gave his input.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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