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REVIEW

Systemic review of hormone replacement therapy in the infertile man

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KEYWORDS

Gonadotrophins;
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Infertility;
Systematic review;
Testosterone therapy

ABBREVIATIONS

CC, clomiphene citrate;
E2, oestradiol;
hCG, human chorionic gonadotrophin;
hMG, human menopausal gonadotrophin;
HPG, hypothalamic–pituitary–gonadal;

Abstract ***Objectives:*** To highlight alternative treatment options other than exogenous testosterone administration for hypogonadal men with concomitant infertility or who wish to preserve their fertility potential, as testosterone replacement therapy (TRT) inhibits spermatogenesis, representing a problem for hypogonadal men of reproductive age.

Materials and methods: We performed a comprehensive literature review for the years 1978–2017 via PubMed. Also abstracts from major urological/surgical conferences were reviewed. Review was consistent with the Preferred Reporting Items for Systemic Reviews and Meta-Analyses (PRISMA) criteria. We used Medical Subject Heading terms for the search including 'testosterone replacement therapy' or 'TRT' and 'male infertility'.

Results: In all, 91 manuscripts were screened and the final number used for the review was 56. All studies included were performed in adults, were written in English and had an abstract available.

Conclusions: Exogenous testosterone inhibits spermatogenesis. Hypogonadal men wanting to preserve their fertility and at the same time benefiting from TRT effects can be prescribed selective oestrogen receptor modulators or testosterone plus low-dose human chorionic gonadotrophin (hCG). Patients treated for infertility with

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PRISMA, Preferred Reporting Items for Systemic Reviews and Meta-Analyses;
SERM, selective oestrogen receptor modulator;
SHBG, sex hormone-binding globulin;
TRT, testosterone replacement therapy

hypogonadotrophic hypogonadism can be prescribed hCG alone at first followed by or in combination from the start with follicle-stimulating hormone preparations.

Introduction

Male hypogonadism is characterised by low serum testosterone and associated with symptoms such as fatigue, decreased libido, erectile dysfunction, concentration difficulty, sleep disturbance, and loss of lean body mass or weight gain [1].

The prevalence of male hypogonadism is reported to be 37% in the USA and a higher prevalence is seen with increasing age [2–4]. Another large population-based study in the USA showed the prevalence of symptomatic hypogonadism to be 5.6% in men aged 30–79 years [5].

The impact of testosterone deficiency on the overall health of men was recently examined in a meta-analysis. Hypogonadism was found to be linked to cardiovascular mortality, metabolic syndrome, osteoporosis, frailty, non-insulin dependent diabetes, and depression [6]. Treatment for hypogonadism typically includes testosterone replacement therapy (TRT), which results in satisfactory amelioration of symptoms and normalisation of serum testosterone. However, treatment with exogenous testosterone decreases serum gonadotrophins, impairs normal spermatogenesis and suppresses intra-testicular testosterone. Azoospermia develops in up to 40% of patients on TRT and, as a result, treatment of hypogonadal men desiring to reproduce whilst on TRT remains a challenge [7].

Testosterone deficiency may result in some clinical manifestations as shown in Table 1, which may affect sexual health, reproductive health, and overall quality of life. These clinical symptoms and signs improve dramatically with TRT [8].

Infertility is defined as the inability of sexually active non-contracepting couples to achieve clinical pregnancy within 1 year. It affects 10–15% of all couples who are seeking conception within the first year and seek medical treatment for infertility [9].

Amongst all infertile couples, male factor represents 40–50% of all causes of infertility. Several causes have been attributed to reduced male fertility including; congenital and acquired urogenital abnormalities, genital tract infections, genetic and chromosomal anomalies, varicocele immunological factors, exposure to gonadotoxins, and endocrine disturbances. No causal factor is found in 30–40% of cases and thus known as idiopathic male infertility [10].

Physiology of hypothalamic–pituitary–gonadal (HPG) axis

The hypothalamus, the pituitary, and the testes form the HPG axis, which acts in harmony and synchronisation to achieve adequate secretion of androgens and normal spermatogenesis. Under the influence of neuropeptides (i.e. kisspeptin, noradrenaline and leptin with stimulatory effects, and prolactin, dopamine, serotonin, γ-aminobutyric acid (GABA) and interleukin 1 being inhibitory), the arcuate nucleus and preoptic area in the hypothalamus secrete GnRH in a pulsatile manner that in turn stimulates the gonadotrophs in the anterior pituitary gland to release the gonadotrophins; FSH and LH [11].

Table 1 Symptoms, signs, and conditions indicative of testosterone deficiency.

Vasomotor and nervous symptoms:
• Hot flushes (similar to those of menopause in women)
• Episodes of sweating
• Insomnia and disturbed sleep rhythm
• Nervousness
Mood disorders and cognitive functions:
• Irritability and lethargy
• Decreased sense of well-being
• Lack of motivation
• Difficulties with short-term memory
• Depressive symptoms
Masculinity/virility:
• Decreased vigour and physical energy
• Diminished muscle mass (sarcopenia) and strength (sarcoasthenia)
• Loss of sexual body hair
• Abdominal obesity
• Gynaecomastia
Sexuality:
• Decreased interest or desire for sex
• Reduction of sexual activity
• Poor erectile function
• Limited quality of orgasm (unpleasurable orgasm)
• Weakness or reduction of ejaculation