Review Article

Endocrine management of male subfertility

Belinda George, Ganapathi Bantwal

Department of Endocrinology, St. Johns Medical College Hospital, Bangalore, Karnataka, India

ABSTRACT

Infertility in a couple is defined as failure to conceive after 12 months of regular unprotected intercourses. Male infertility due to impaired spermatogenesis may result from hypothalamic, pituitary or testicular disorders. Medical management of infertility associated with gonadotropin deficiencies have high success rate, but for primary testicular failure assisted reproduction techniques (ART) with adjunctive endocrine manipulation remains the best therapeutic option. This article discusses various therapeutic options and regimes using gonadotropins, anti-estrgens, aromatase inhibitors in management of male subfertiltiy.

Key words: Hypogonadotropic hypogonadism, male subfertiltiy, oligo-azoospermia

Introduction

Infertility in a couple is defined as failure to conceive after 12 months of regular unprotected intercourses. Subfertility is often used interchangeably with infertility; however, the term refers to any individual with compromised or reduced fertility potential. Typically this includes patients with known endocrine diseases that could interfere with spermatogenesis and testicular function or those with abnormalities on semen analysis. A subgroup of patients with unexplained abnormalities on semen analysis including oligo--astheno--teratozoospermia with normal gonadotropin profile have also been categorized as subfertile. Impaired spermatogenesis may result from hypothalamic, pituitary, or testicular disorders. Medical management of infertility associated with gonadotropin deficiencies have high success rate, but the same cannot be said about primary testicular failure. The primary mode of intervention remains assisted reproduction techniques (ART), with endocrine manipulation serving as an adjunctive therapy.[1] Lastly, a subset of patients who may have compromised gonadal function in the future, as a result of treatment or illness, may be counseled regarding fertility preserving strategies and options.

Endocrine treatment for male infertility has been disappointing and the interest in the same has waned over the past few decades. The most important aspect for success of medical management of male infertility depends on the presence of a specific underlying etiology. For example men who have been diagnosed with hypogonadotropic hypogonadism can be successfully treated with gonadotropin replacement therapy. This is in contrast to the poor pregnancy rate achieved with empirical hormonal therapy in cases of unexplained male subfertility, where the only abnormality is oligo-asthenozoospermia with normal hormonal profile.

Gonadotropin Therapy

In patients with hypogonadotropic hypogonadism, correction of underlying pathology, if possible may lead to restoration of spermatogenesis, and fertility. If not, gonadotropin replacement and gonadotropin releasing hormone (GnRH) pulsatile therapy are effective treatment options in these patients. Conventionally, treatment is started with human chorionic gonadotropin (HCG) with doses ranging from 1000 IU to 2500 IU thrice weekly given subcutaneously alone or in combination with follicle stimulating hormone (FSH). Usually, luteinizing

Access this article online	
Quick Response Code:	Website: www.ijem.in
	DOI: 10.4103/2230-8210.119500

Corresponding Author: Dr. Belinda George, Department of Endocrinology, St. Johns Medical College, Bangalore - 560 034, Karnataka, India. E-mail: george.belinda@gmail.com

hormone (LH) deficiency is corrected first until testosterone normalizes followed by addition of FSH to aid in spermatogenesis. HCG therapy is continued until the nadir testosterone levels (checked 48 hours after the testosterone injection) reach the mid normal range. After 6 months of therapy with HCG alone, if no sperm are detected on semen analysis, FSH is added to the treatment regime. This regime may take up to 1 to 2 years for its maximum efficacy on spermatogenesis. FSH may be given in the form of human menopausal gonadotropin (HMG) or recombinant FSH (rFSH) subcutaneously two to three times weekly. The usual dose of FSH for hypogonadotropic hypogonadism is around 75 IU of HMG or 100 to 150 IU of rFSH.

The best predictors of response to gonadotropin therapy are testicular volume and time of onset of gonadotropin deficiency (prepubertal vs. postpubertal). A testicular volume of 8 ml at the time of initiating treatment and postpubertal onset of gonadotropin deficiency is more likely to respond to gonadotropin therapy compared with prepubertal onset of disease and a testicular volume of 4 ml. Patients with cryptorchidism who have undergone orchidopexy had a poorer prognosis with negative outcome for restoring spermatogenesis.[2] Pulsatile GnRH therapy may be used for those patients with hypothalamic dysfunction, provided there is no primary pituitary pathology. It is typically started at an initial dose of 25 ng per kg per pulse delivered subcutaneously through a portable infusion pump every 2 hours. The dose of pulse is adjusted to maintain the testosterone levels in the mid normal range. Given the cumbersome nature of pulsatile GnRH therapy and need of portable infusion pump, the most preferred regime in cases of secondary testicular failure remains gonadotropin replacement therapy.

Various forms of gonadotropin treatment have been tried in idiopathic subfertility including HCG, HMG, and FSH alone or in different combinations. A meta-analysis of four randomized controlled studies using gonadotropin therapy in normogonadotropic male subfertility found significant increase in pregnancy rates within 3 months of initiating treatment. Most studies using FSH which showed positive response in terms of spermatogenesis and pregnancy rates with or without adjunctive ART had used higher doses of FSH compared to the conventional dose of 150 IU thrice a week.[3] Hence, the dose of FSH needed in these groups of males with idiopathic subfertility may be higher. GnRH and luteinizing hormone releasing hormone (LHRH) has no role in empiric management of idiopathic subfertility.

Antiestrogen Therapy

Clomiphene citrate and tamoxifen citrate are two estrogen receptor modulators with predominant antagonist activity. They block estrogen activity at the level of hypothalamus and anterior pituitary thereby abolishing the negative feedback exerted by estrogen. This results in increased gonadotropin secretion which could theoretically increase testosterone synthesis and enhance spermatogenesis. In view of their low cost, safety, and ease of oral administration, they were popular in the pre-ART era in the management of normogonadotropic male subfertility.

Several small observational and uncontrolled studies using clomiphene or tamoxifen in the management of idiopathic male subfertility have yielded mixed results with some showing improvement in spermatogenesis and pregnancy rates and others failing to prove any benefit. A meta-analysis studied 738 subfertile men with oligoastheno-zoospermia who received short-term treatment protocols with anti-estrogens. The pregnancy rate was 15.4% in the patient group versus 12.5% in the control group (odds ratio: 1.56; 95% CI: 0.99–2.19). The authors concluded that there were not enough data to support or disprove the utility of antiestrogens in the management of idiopathic male subfertility. It is possible that these agents in combination with other therapeutic modalities could be useful in the management of idiopathic male subfertility.

Aromatase Inhibitors

Aromatase inhibitors reduce the conversion of androgens (testosterone and androstenedione) to estrogens (estradiol and estrone), thereby reducing the negative feedback on hypothalamus and pituitary. This leads to increase in gonadotropin secretion and increased androgen synthesis and secretion. Administration of aromatase inhibitors also restores the ratio of testosterone to estradiol (T: E2) to normal and has been thought to improve sperm concentration and motility. The T: E2 ratio has been shown to be significantly lesser in infertile men compared to normal controls (14.5 in fertile men versus 6.9 in men with nonobstructive azoospermia versus 4.4 in Klinefelters syndrome). Candidates for aromatase inhibition have usually been identified as men with serum T: E2 ratio less than 10. Aromatase inhibitors are available as steroidal (testolactone) and nonsteroidal (anastrozole) oral preparations. Both these drugs have been shown to improve the T: E2 ratio in several studies, however it's translation into clinical benefit is not conclusively proven.[4] Improvement in semen parameters have been noticed in few studies. Improvement in pregnancy rates have not been studied adequately.

Endocrine Management in Cryptorchidism

Both unilateral and bilateral cryptorchidism have been associated with subfertility and reduced germ cell count in histopathology even after early orchidopexy. This has been attributed to the attenuated gonadotropin surge seen during mini puberty thereby explaining the reduced germ cell count seen in the contra lateral descended testes as well.

The GnRH analogues buserelin and naferelin have been tried in cryptorchid patients who have undergone orchidopexy. Preliminary results are promising with improvement seen in germ cell count and semen parameters.[5] Additional controlled studies are required.

References

1. Bhasin S. Approach to the infertile man. J Clin Endocrinol Metab 2007;92:1995-2004.
2. Pitteloud N, Hayes FJ, Dwyer A, Boepple PA, Lee H, Crowley WF Jr. Predictors of outcome of long-term GnRH therapy in men with idiopathic hypogonadotropic hypogonadism. J Clin Endocrinol Metab 2002;87:4128-36.
3. Foresta C, Bettella A, Garolla A, Ambrosini G, Ferlin A. Treatment of male idiopathic infertility with recombinant human follicle-stimulating hormone: A prospective, controlled, randomized clinical study. Fertil Steril 2005;84:654-61.
4. Vandekerckhove P, Lilford R, Vail A, Hughes E. Clomiphene or tamoxifen for idiopathic oligo/asthenospermia. Cochrane Database Syst Rev 2000;2:CD000151.
5. Ramasamy R, Stahl PJ, Schlegel PN. Medical therapy for spermatogenic failure. Asian J Androl 2012;14:57-60.

Cite this article as: George B, Bantwal G. Endocrine management of male subfertility. Indian J Endocr Metab 2013;17:S32-4.

Source of Support: Nil, **Conflict of Interest:** None declared.