

Effects of Testosterone and Gonadotropin Therapy in Men with Hypogonadotropic Hypogonadism

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Limited data is available on the treatment of male infertility in patients with hypogonadotropic hypogonadism (HH). The aim of this study was to evaluate the impact of therapy with testosterone and gonadotropins on the development of sexual characteristics and fertility in men with HH. **Materials & Methods:** In this study, conducted between 1992 and 2009, 102 male patients with HH were investigated. Patients who did not have secondary sexual characteristics were treated by testosterone until normalization of pubic hair and full appearance of sexual characteristics and 41 patients, who wanted fertility received treatment with human chorionic gonadotropin (hCG), followed by human menopausal gonadotropin (hMG). Testicular volume, sperm production and fertility were assessed, before and after treatment. **Results:** Mean age at presentation was 22.7 ± 6.3 years. Means for pubic hair and genital stages were 1.8 ± 0.9 and 2.0 ± 1.3 , respectively. Testicular volume was 3.4 ± 1.9 mL and 96% had azospermia. Levels of serum testosterone of 40 ± 60 ng/dL, LH 0.5 ± 1.0 IU/l and FSH 1.0 ± 1.2 IU/l, were all in prepubertal ranges. Treatment with hMG/hCG in 32 men who completed >1 year of therapy, resulted in 24 conceptions (75%), 5 abortions and 19 pregnancies, with 18 singletons and one twin. **Conclusion:** Since treatment with gonadotropins resulted in conception in 75% and live births in 59% of the cases, it seems that in male patients with hypogonadotropic hypogonadism, this regimen is the treatment of choice.

Key Words: Hypogonadotropic hypogonadism, Testosterone, Gonadotropins

Received: 03.05.2010 **Accepted:** 02.06.2010

Introduction

Infertility is an important issue for couples and male infertility disorders play a major role in approximately 50% of the cases. In the vast majority, male infertility is treatable and medical therapies are used as an initial strategy to improve sperm production or as a preliminary therapy to boost production transiently in anticipation of a surgical sperm retrieval attempt.¹⁻³ Male hypogonadotropic hypogonadism (HH), characterized by the absence of endogenous gonadotropin secretion, may be caused by pituitary tumors, isolated gonadotropin deficiency, panhypopituitarism, or pituitary trauma. Routine evaluation of patients includes a pituitary MRI to rule out a pituitary tumor. In addition, hyperprolactinemia should be ruled out and treated before the initiation of gonadotropin replacement therapy.²⁻⁴ In males, HH testosterone therapy is sufficient for maturation and maintenance of secondary sex characteristics. However, for stimulation of spermatogenesis administration of gonadotropins is necessary.⁵ Currently available gonadotropin preparations include human chorionic gonadotropin (hCG), human menopausal gonadotropin

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(hMG), urinary FSH, highly purified urinary FSH, and human recombinant FSH.⁶ If pulsatile gonadotropin-releasing hormone (GnRH) is not indicated or desired, hCG is used as the source of luteinizing hormone (LH) activity to stimulate testosterone secretion by Leydig cells, whereas hMG is used as the source of follicle stimulating hormone (FSH).¹ More recently, recombinant gonadotropins have also been used clinically.⁵⁻⁹ Hypogonadotropic hypogonadism is a rare cause of male infertility and there is limited data on its management, even in specialized centers. Here we aimed at investigating the effects of treatment of HH in a relatively large sample of Tehranian men with HH.

Materials and Methods

Patients

Between 1992 and 2009, 102 male patients were diagnosed with HH based on their medical history, physical examinations, sperm examination and low serum concentrations of FSH, LH and total testosterone. Gonadotropin deficiency in 71 was a result of idiopathic HH and Kallmann syndrome, whereas in 31, the cause was pituitary insufficiency. Pituitary imaging by magnetic resonance imaging did not show any evidence of secondary HH.

Patients who did not have secondary sexual characteristics (n=75) were treated with testosterone enanthate 250 mg by monthly intramuscular injections until normalization of pubic and facial hair and development of the sexual male pattern; the others had been on testosterone therapy since 1 to 13 years, prior to visit and treatment was continued until they decided to have children.

For induction of spermatogenesis we used hCG 1500 IU 3 times per week and added hMG treatment 75 IU subcutaneously, three times weekly, until successful induction of spermatogenesis and attainment of conception.

Follow up

The clinical and laboratory data including pubic hair stage, genital stage, testicular volume, sexual function and sperm prod-

uction (sperm counts, sperm motility) were determined once for 102 controls and 102 patients, before and after hCG/hMG treatment. Testicular volume was measured with an ellipsoid orchidometer (Prader orchidometer, ASSI, NY) at baseline and after treatment.

Serum testosterone was determined using radioimmunoassay and serum LH and FSH were analyzed by immunofluorometric assays (Delfia, Wallace, Freiburg, Germany). The inter-assay and intracassay variance of all assays did not exceed 7.0%. Characteristics of sperm were analyzed according to WHO guidelines¹.

Data were compared to those obtained from 102 age-matched normal men. Unpaired t test was used for comparison between the two groups, with paired t test being used to compare means before and after treatment.

Results

Baseline clinical and biochemical findings

The mean age of patients was 22.7±6.3y (range 15-39 y). Clinical characteristics of the entire study population are summarized in Table 1. Twenty-seven patients had been having testosterone or HCG treatment for some periods before presentation; however, all medications had been discontinued at least 3 months before evaluation.

Table 1. Baseline clinical and biochemical characteristics of the 102 patients with hypogonadotropic hypogonadism at presentation and 102 normal controls

Variable	Patients (n=102)	Controls (n=102)
Age (yr)	22.7±6.3	23.1±7.0
Pubic hair stage	1.8±0.9	4.8±0.8*
Genital stage	2.0±1.3	4.9±0.7*
Testicular volume (mL)	3.4±1.9	14.5±7.7*
Azospermia (%)	96	0*
Serum testosterone (ng/dL)	40±60	705±210*
Serum LH (IU/L)	0.5±1.0	3.0±1.8*
Serum FSH (IU/L)	1.0±1.2	3.2±1.9*

* P<0.001

Seventy-three (72%) patients were followed for at least 2 years, following initiation of testosterone treatment. All developed secondary sexual characteristics, including increase in pubic hair, muscle development and strength, erection and ejaculation. The growth of facial hair was normalized only in 89%, who continued treatment for at least 4 years, while 11% had only partial growth of facial hair, despite long term hormone therapy.

Effects of gonadotropin therapy

During 17 years of follow up, 41 patients, who wished to have children, were treated with hMG and hCG according to the prescribed protocol; of these, 9 failed to comply, while 32 patients completed gonadotropin therapy for at least 12 months (Fig. 1). Testicular size increased in all but 2 men. By six months, mean testicular volume increased from 3.3 ± 1.8 mL to 7.6 ± 1.9 mL ($p < 0.001$) and to 10.9 ± 8.1 mL after 12 months. Serum testosterone concentration increased significantly from 42 ± 34 ng/dL to 281 ± 75 ng/dL in the first month and to 507 ± 220 ng/dL in the fourth month ($p < 0.001$). Spermatozoa were detected in the ejaculate of 2, 9, 16, 20, 23, 25, 26 and 27 patients after 3, 6, 9, 12, 15, 18, 24 and 36 months of therapy respectively. Of 32 patients, who continued hMG/hCG therapy for >1 year, spermatogenesis occurred in 27 (84%), of whom 24 (75%) were able to initiate conception. Mean for number of spermatozoa at conception was 25.9 ± 17.1 million, and 6 patients had sperm counts below 20 million/mL. Of 24 pregnancies, 5 had abortions, 18 singletons and one twin were born uneventfully. Therefore, >1 yr treatment of 32 men resulted in child birth in 19 pregnancies (59%).

Five patients with azospermia had testicular biopsy, of which one had normal spermatogenesis and microinjection resulted in a twin pregnancy; 2 of 3 patients (with sperm counts of 1.2, 4.9 and 10 million), who could not conceive naturally, underwent

assistant fertility procedures and 2 conceived (Fig. 1).

There were no correlations between the initial testicular volume and maximum testicular volume after treatment, between initial testicular volume and treatment duration, between maximum sperm counts and initial testicular volume, between ages of the patients at the beginning or after hCG/hMG treatment or between their age and the time of sperm appearing in the ejaculate.

Discussion

The present study, conducted in a large number of men with HH, shows the effectiveness of testosterone therapy for development of sexual characteristics and the benefits of gonadotropin administration in induction of spermatogenesis and conception.

The hormonal deficiency in most patients with hypogonadotropic hypogonadism can be treated with administration of exogenous gonadotropins or GnRH.^{2,3,10} Gonadotropins are required for fully normal spermatogenesis. FSH is absolutely necessary to initiate spermatogenesis. FSH may stimulate early events in spermatogenesis including spermatogonial proliferation and meiosis.¹¹ In addition, the administration of FSH had a positive role in sperm cytostructural parameters. FSH in connection with LH/testosterone is also fundamental for the maintenance of quantitatively normal spermatogenesis.¹²

Several treatment regimes are available for patients who have HH and who desire fertility. Human chorionic gonadotropin (hCG) can be administered in combination with human menopausal gonadotropin (hMG); hCG monotherapy is given until normal serum testosterone levels are achieved. Months of hCG administration may be required before the addition of hMG. Spermatogenesis is observed in 80-90% of patients on this regimen.¹³

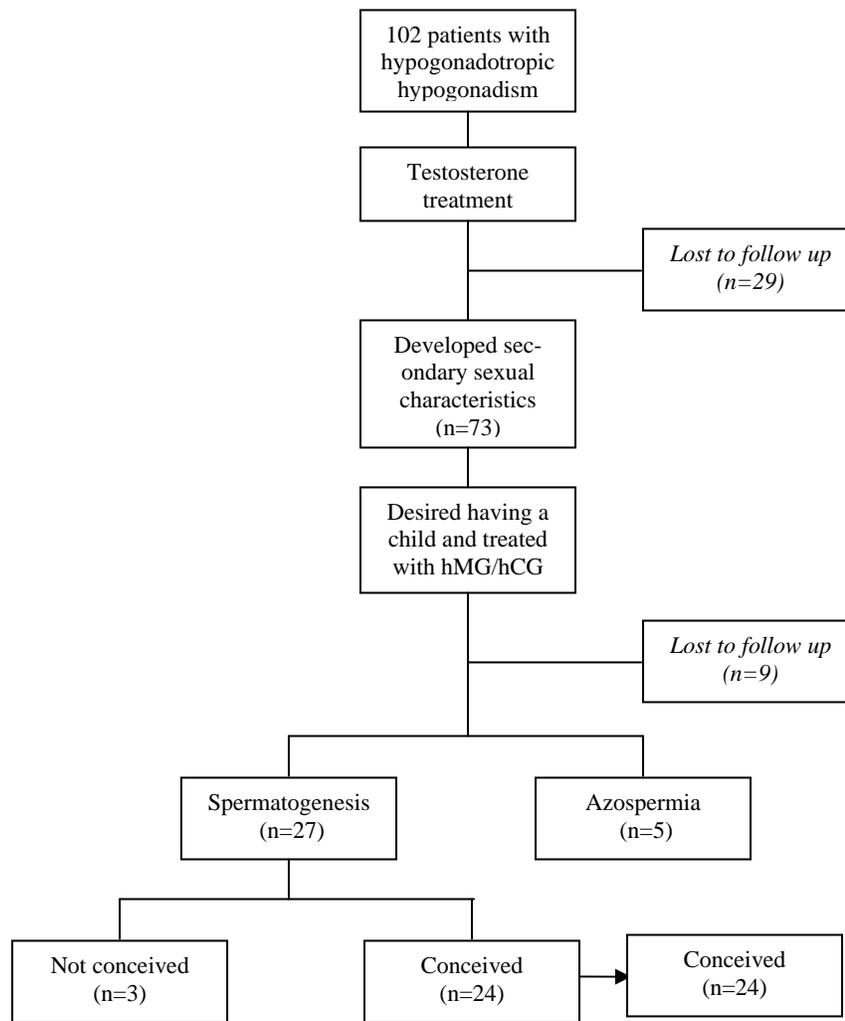


Fig 1. Follow up of 102 patients with hypogonadotropic hypogonadism and the effect of gonadotropin administration

Vicari, in 1992, demonstrated that spermatogenesis can even be induced with hCG per se in HH patients, but the addition of hMG improved the sperm output in some patients.¹⁴ Alternative regimens include the use of intermittent injections or pulsatile infusion of GnRH (in men who have intact pituitary function) and highly purified FSH or recombinant FSH (rFSH). Those who do not respond to one regimen may benefit from another;^{1,6,15-20} although it takes 6 to 9 months on average

before sperm appear in the ejaculate, therapy may be needed for 1 to 3 years, and some patients may not respond at all.¹

In the present study, patients were treated by testosterone enanthate until normalization of pubic hair growth and appearance of secondary sexual characteristics. Thirty-two patients also received hCG in combination with hMG treatment for more than one year and spermatogenesis occurred in 84% of patients.

Comparison of GnRH therapy with gonadotropin therapy has not shown a difference significant enough to justify the increased expense and inconvenience of GnRH as first-line therapy. GnRH infusion pump therapy is reserved for patients who fail to respond adequately to gonadotropin therapy.^{21,22}

Mean testicular volume significantly increased after hMG/hCG treatment in all of our patients except for 2, and there was no significant correlation between duration of the treatment and maximum testicular volume. There was no remarkable correlation between maximum sperm counts and initial testicular volume or the age of patients at the beginning of treatment, although, it has been reported that initial testicular volume values may predict sperm output in response to hCG/hMG therapy.¹⁹

Larger baseline testicular volume, prior gonadotropin therapy, postpubertal status, or the absence of bilateral mal descended testes may positively correlate to the patient's response and hasten the time of sperm detection in the ejaculate.^{1, 23, 24}

Although spermatogenesis was induced in 84% of patients and treatment resulted in

75% pregnancies, sperm counts did not reach normal levels in all patients and 6 pregnancies occurred with sperm concentrations below 20 million/mL.

Oligospermia with counts below 10 million sperm/mL is common in these patients; however, sperm motility and morphology are usually good. Many patients treated for hypogonadotropic hypogonadism can initiate a pregnancy despite low sperm densities.²⁵

This study has a few limitations. It is a retrospective study and a few patients were lost to follow up. The ability of patients' wives for ovulation and conception was not studied. The strength of study is that it is one of the largest studies in a general endocrine practice setting.

We conclude that testosterone therapy in HH can normalize growth of pubic hair, genitalia growth and secondary sexual characteristics and treatment with gonadotropins are necessary for spermatogenesis and pregnancy induction and should be used for infertile patients with HH.

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