

Gonadotropin Therapy for Infertile Men With Hypogonadotropic Hypogonadism

Androlog Summary

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Note: Postings to *Androlog* have been lightly edited before publication.

Over the years, clinicians have proposed various therapeutic agents to treat male infertility. These agents are intended to improve male reproductive impairment either by addressing a specific detectable pathology or by empirically globally improving male reproductive function. Hypogonadotropic hypogonadism is a rare but a well-known cause of male infertility. This condition is thought to account for approximately 1%–2% of cases of male factor infertility, but the exact incidence is unclear and may be substantially greater than historically reported. The diagnosis is established when low serum gonadotropin levels coincide with low serum testosterone and when azoospermia or oligospermia is noted on semen analysis (Whitten et al, 2006). Hypogonadotropic hypogonadism may be congenital or a result of acquired alteration in the hypothalamic-pituitary-gonadal axis. Depending on the underlying problem, different management options are available to the clinician.

Recently, Phillip G. Wise posed the following patient case scenario for discussion on *Androlog*:

A 40-year-old African American male with primary infertility of 6 years was referred to me in April 2007. His wife is 39, G0, without any risk factors. His evaluation and treatment by his wife's reproductive endocrinologist started 3 years ago, in October 2003, with 2 semen analyses. The first showed severe oligospermia with 2–3 nonmotile sperm per spun specimen; the second was azoospermic (azo) on spun specimen. The volumes have all been normal (from 2–3 ml) and the pH has been normal (7.9–8.1). His gonadotropins were FSH <0.6 (1.4–18.1 mIU/ml), LH 2.5 (1.4–18.1), and his total testosterone was 143 (241–827 ng/ml); the Prolactin was

7.5 (2.1–17.1 ng/ml). The repeat testosterone was 171. An MRI of the pituitary was ordered and no pituitary tumor was discovered. A cystic fibrosis screening was negative. His karyotype was interpreted as chromosomally normal male with an increased amount of centromeric heterochromatin, considered a rare variant within the population. There is no mention of a physical examination in the notes.

Although he was asymptomatic from his hypoandrogenism, he was started on Novarel 5000 units Monday, Wednesday and Friday; a repeat testosterone level was 518 ng/dl three months later. Though it is not clear from the notes, it appears that he was started on FSH 150 IU Monday, Wednesday, and Friday about 3 months after he started the Novarel. A repeat semen analysis in September of 2004 showed 8 nonmotile sperm after centrifugation.

I am not sure what happened to him between September 2004 and June of 2006. In June of 2006 he had an FSH of 1.35, an LH of 2.9, testosterone of 268 and azoospermia on spun specimen. He was either restarted or continued on his gonadotropin injections. Repeat semen analyses in November of 2006 and again in March of 2007 were azo.

I first saw him in April of 2007. He is working toward his masters' degree in computer sciences. He has no environmental risk factors; neither he nor his wife have been involved in any prior pregnancies. In addition to the gonadotropin therapy, he takes InnoPran, a beta-blocker, for central tremors. He denies any groin surgery or infections that may have caused any blockage.

The physical examination: he is moderately obese (6'00" tall and 258 lbs), no groin scars, normal phallus, both testicles are descended, normal size and consistency, the vasa are palpable, but the spermatic cords have lipoma. The epididymides are difficult to palpate; indeed I thought the right was absent and the left was rudimentary, but they could be hiding in the lipoma.

The biopsy showed normal testicular architecture, and there were numerous whole spermatozoa on the touch prep. We have scheduled them for a TESE, IVF ICSI cycle as soon as possible, out of concern for his wife's age (39). My question now is what to do about the gonadotropin injections if the cycle is unsuccessful.

Paul Turek responded with the following suggestion to investigate a pathologic basis for the hypogonadotropic hypogonadism and with a suggestion for a simpler, oral form of treatment:

Consider an evaluation for sickle cell anemia/trait. Also consider treatment with clomiphene citrate rather than gonadotropins.

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Keith Jarvi requested further clarification regarding evaluating the state of spermatogenesis:

Could you clarify a few things: was he on gonadotropins at the time of the biopsy, and did the biopsy show normal spermatogenesis?

Darius A. Paduch responded with several points regarding gonadotropin therapy:

This patient falls into a subcategory of idiopathic hypogonadotropic hypogonadism with isolated LH deficiency and normal FSH—this is known as fertile eunuch syndrome. In this group of patients stimulation with hCG often stimulates adequate maturation of Leydig cells, and the patients' requirements for hCG may be much lower. FSH is sometimes added in those men if FSH is low although it seems in this patient it is not really indicated because he had normal FSH. I assume that his TSH, cortisol, and iron studies are normal and his MRI is negative—craniopharyngioma and microadenoma.

The fact that he had sperm on testicular biopsy and azoospermia in ejaculated semen indicates obstructive azoospermia. Based on wife's age, IVF with testicular sperm is an adequate choice.

One could consider holding off on hCG and FSH and repeating them together with testosterone in 6 weeks. If his LH and FSH are normal and testosterone within normal limit for an age-adjusted group, no further treatment is needed. An interesting aspect of fertile eunuch syndrome is the presence of sperm despite low circulating testosterone. This is most likely related to an adequate concentration of testosterone within testis to maintain qualitative spermatogenesis but not enough production for normal peripheral testosterone. Those men produce small amounts of LH (often too low to measure using current assays); otherwise they would not go through puberty.

Of note, 5000 units of hCG is a dose used for diagnostic stimulation and not typically used for treatment anymore. Recent literature supports using much lower doses of hCG, even 500 units subcutaneously every other day. The main concern comes from studies in animals that showed that excess of hCG may create a chronic inflammatory-like response in the interstitium.

Ibrahim Fahmy shared a historical perspective:

Regarding the case of deficiency of FSH and testosterone: it has been reported that some azoospermic patients with symptomatic hypogonadotropic hypogonadism may respond to hCG treatment alone. In such cases, the low FSH is sufficient to stimulate spermatogenesis (Vicari et al, 1992). In this particular case, because testicular biopsy showed normal spermatogenesis, there is no need for FSH replacement therapy. Concerning the low testosterone, I suggest repeating testosterone by other methods because some chemiluminescent assays may give false low results.

The clinical picture of a rare condition known as a fertile eunuch includes eunuchoid habitus, large testes, and small-volume ejaculate that may or may not contain

a few sperm (Faiman et al, 1968). The levels of FSH are usually normal, and serum testosterone and LH levels are low. The hallmark of this condition is isolated LH deficiency. However, there appears to be an adequate amount of intratesticular testosterone to sustain some spermatogenesis. The Leydig cell function appears to be preserved in these patients, because they seem to respond to hCG therapy with a rise in serum testosterone (Makler et al, 1977). However, as with all initial historical observations, refinement is necessary. It is likely that a fertile eunuch lies on one end of a much larger spectrum of hypogonadotropic hypogonadism, with independent alterations in both LH and FSH.

Acquired and congenital forms of hypogonadotropic hypogonadism have variable clinical presentations and call for different treatment strategies. The patient scenario described in this month's *Androlog* column may represent a subset of patients who present with relatively subtle hypogonadotropic hypogonadism after puberty. In these individuals pharmacologic manipulation of the entire hypothalamic-pituitary axis with clomiphene citrate may be a feasible and inexpensive approach. Whitten and coauthors (2006) stratified patients based on the cause of hypogonadal hypogonadism and showed that a subset with the adult onset idiopathic form may benefit from treatment with this oral medication.

Pharmacologic agents for empiric treatment of idiopathic infertility have been available for decades. Their use and effectiveness have been debated greatly with often controversial or inconclusive results (Paulson and Wacksman, 1976; Sigman and Vance, 1987). Clomiphene citrate is a commonly used agent to empirically treat idiopathic oligospermia by increasing LH and, thus, intratesticular testosterone. Multiple investigators reported improvement in the semen analysis in patients treated with clomiphene citrate. Hussein and coinvestigators (2005) treated 42 patients with nonobstructive azoospermia and reported a 64.3% rate of sperm in the ejaculate subsequent to treatment in azoospermic men and a change in the spermatogenic pattern on biopsy to favor an increased likelihood of sperm extraction.

An intriguing question posed by Dr Wise remains unanswered: how should the clinician proceed with gonadotropin therapy in the case of an unsuccessful cycle? Of particular interest in this case is the patient's low testosterone level. Should the patient continue with any of the agents suggested to manipulate his hormonal axis or, if fertility is no longer an issue, should exogenous testosterone be administered?

Incidences of hypoandrogenism in specific diagnostic populations of infertile men have not been fully investigated. At the University of Illinois in Chicago, we recorded the incidence of hypoandrogenism in

diagnostic categories of patients presenting to an infertility clinic by retrospectively reviewing charts of 120 consecutive patients presenting to our infertility clinic. Inclusion criteria were diagnoses of nonobstructive azoospermia, obstructive azoospermia, oligospermia defined by World Health Organization (1999) criteria, and men with normal semen analyses. Serum testosterone was measured by electrochemiluminescent immunoassay or turbulent flow liquid chromatography tandem mass spectrometry, and hypoandrogenism was defined per Food and Drug Administration criteria as a morning serum testosterone less than 300 ng/dL. Interestingly and surprisingly, the incidence of hypogonadism in men with nonobstructive azoospermia was 45.0%; in men with oligospermia, 42.9%; in men with normal semen analyses, 35.3%; and in obstructive azoospermia, 16.7%. In this set of men, those with obstructive azoospermia may be considered a negative control, and that the incidence of hypogonadism in this group parallels that of the general population serves to validate the observations of this study. That infertile men had an incidence of one third to nearly one half argues that hypogonadotropic hypogonadism may be considerably more prevalent in the infertile male population than previously believed.

This lively and informative *Androlog* thread reveals that hypogonadotropic hypogonadism manifesting as male infertility may be more common than previously

thought, and we note that a simple, oral medication may serve to treat the condition. Clinicians treating reproductive dysfunction may want to consider screening for testosterone in the men who present for care.

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