NYU Langone Health

Department of Urology
Case of the Month

Managing Fertility in Men with Hypogonadotropic Hypogonadism

CASE PRESENTATION

A man in his thirties presented with a history of panhypopituitarism secondary to childhood craniopharyngioma. He is married to a woman, and he and his wife, who is also in her thirties, are interested in starting a family.

PAST MEDICAL HISTORY

The patient was diagnosed with and treated for craniopharyngioma when he was 3 years old. The resection of his craniopharyngioma resulted in panhypopituitarism, and he has been on levothyroxine, hydrocortisone, somatropin, and testosterone for at least 20 years. His history also includes a unilateral testicular torsion at the age of 10, for which he underwent a bilateral orchiopexy.

The rest of the patient's medical and surgical history was unremarkable. The only medications he takes are for his panhypopituitarism. He has been using topical testosterone gel for 5 years. He was previously taking short-acting testosterone intramuscular injections. He denied smoking or using illicit drugs and has no relevant family history. He works in the finance industry and denied genital trauma or exposure to toxic or radioactive agents. His wife is healthy and has never been pregnant.

EVALUATION AND MANAGEMENT AT NYU LANGONE HEALTH

The patient had a normal masculine hair distribution. His BMI was 23.7. No gynecomastia was present. Testes bilaterally were soft and about 8 cc (normal volume, ≥18 cc). No varicocele was present.

A semen analysis was performed, which was fructose positive with normal volume, normal pH, and no sperm seen after centrifugation (see Table 1). Serum total testosterone at baseline was normal at 606 ng/dL (normal, 300-1080 ng/dL) and estradiol was 17 pg/mL (normal, 7.6-42.6 pg/mL). Pituitary hormones were consistent with panhypopituitarism and use of exogenous testosterone, as both luteinizing hormone (LH) and follicle stimulating hormone (FSH) were undetectable.

Table 1. Laboratory and Semen Analysis Values over Time

Event	Date	Total Testosterone (ng/dL)	17-OH Progesterone	Semen Volume (mL)	Sperm Concentration (M/mL)	Motility (%)
On testosterone gel	2/2020	606	<10	1.5	0	
Started HCG	5/2020	1021				
Stopped testosterone	7/2020	366	77			
	9/2020	564				
	11/2020					
Started rFSH	1/2021			2.5	0	
	4/2021			3	5.5	79
	7/2021	705		3.5	10	62

The patient was counseled to cease his exogenous testosterone therapy; however, he was concerned that hypogonadal symptoms might have an impact on his work performance. He therefore decided to start intramuscular human chorionic gonadotropin (HCG) therapy while tapering off his testosterone gel. Two months later, his total testosterone had increased to 1021 ng/dL (normal, 300-1080 ng/dL), at which point he stopped taking testosterone gel and remained on HCG.

After ceasing exogenous testosterone, the patient's serum total testosterone decreased to the lower range of normal at 366 ng/dL and slowly increased to 564 ng/dL after being on HCG for 6 months. Having achieved normal serum total testosterone levels, he underwent a repeat semen analysis, which showed persistent azoospermia. He started taking subcutaneous recombinant FSH (rFSH) to induce spermatogenesis.

Three months after starting rFSH, the patient underwent another semen analysis, which demonstrated a total motile sperm count of 13 million (normal, >20 million). Three months later, another semen analysis showed 21.7 million moving sperm. At this point, the couple decided to proceed with in vitro fertilization (IVF) to better plan the timing of birth. Following successful IVF, the patient's wife delivered a healthy infant weighing 7 pounds 6 ounces.

DISCUSSION

The management of fertility in men with hypogonadotropic hypogonadism requires a strong understanding of the male hypothalamic-pituitary-gonadal (HPG) axis (Figure 1). Hypogonadotropic hypogonadism, or secondary hypogonadism, can result from a variety of congenital abnormalities, such as Kallmann syndrome, or acquired diseases, such as in this patient. This patient's resection of a craniopharyngioma resulted in panhypopituitarism prior to puberty. In order to initiate puberty, the patient was started on testosterone in his mid-teens. As a result, he had been on exogenous testosterone for 2 decades before seeking fertility care. Given the history of testicular torsion, the patient was also concerned that fertility might not be possible. In hypogonadotropic hypogonadism, induction of spermatogenesis requires correction of the inability to produce pituitary LH and FSH.

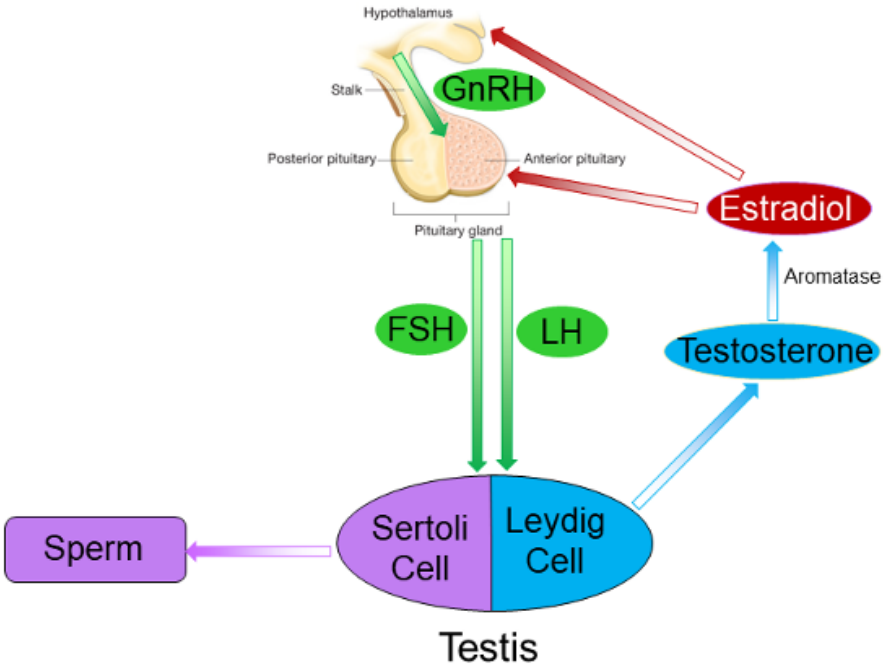

Figure 1. Normal male hypothalamic-pituitary-gonadal axis.

Induction of Intratesticular Testosterone

Although exogenous testosterone therapy resulted in normal levels of serum total testosterone, these levels are nevertheless not sufficient to support spermatogenesis. In fact, the intratesticular concentration of testosterone is normally 100 times higher than the level of testosterone measured in the serum.[1] And this high level of intratesticular testosterone is required to support spermatogenesis.[2]

We use HCG to stimulate Leydig cell production of testosterone in men who lack the ability to produce LH. Like LH, HCG is a heterodimeric protein with an α subunit identical to that of FSH, thyroid-stimulating hormone, and LH. The α subunits of these protein hormones differ; however, HCG cross-reacts with the LH receptor, allowing HCG to be used clinically to mimic LH. The goal of HCG therapy is to reach normal serum testosterone levels through endogenous testosterone production alone.

Ceasing vs. Bridging Exogenous Testosterone

Traditionally, the first step in induction of spermatogenesis in hypogonadotropic hypogonadism is cessation of exogenous testosterone and initiation of intramuscular HCG to induce intratesticular testosterone production. However, it is common for men with hypogonadotropic hypogonadism to be concerned about the potential for symptomatic hypogonadism. If exogenous testosterone is simply stopped, there can be a significant period during which serum total testosterone is low before the HCG-induced intrinsic testosterone production is sufficient to reach normal serum levels of testosterone (Figure 2). This can mean months of hypogonadal symptoms such as low energy, low libido, irritability, and poor concentration. Since the FDA considers exogenous testosterone a Schedule III controlled substance, many men have already experienced these symptoms during brief lapses in exogenous testosterone therapy due to logistical challenges in getting their treatment. The prospect of many months of these symptoms is not attractive to many men.

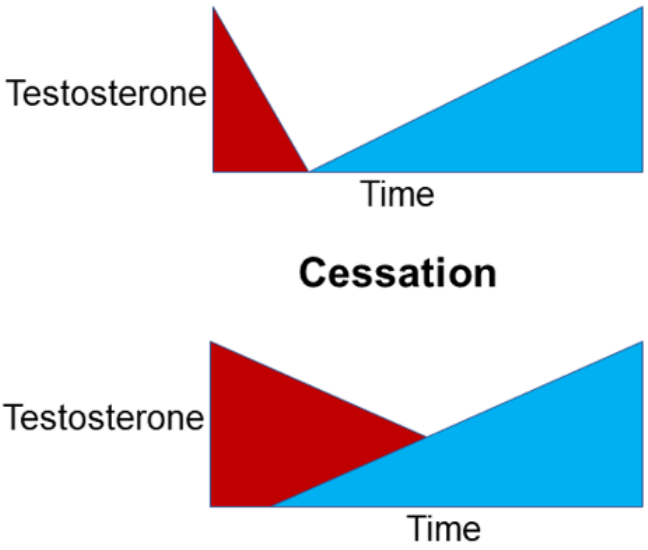

Figure 2. Approaches to managing exogenous testosterone.

Alternatively, HCG therapy can be initiated, with the intent to taper off the exogenous testosterone as the intrinsic testosterone increases (Figure 2). The goal of this approach is to minimize the length of time that a patient has lower serum testosterone levels. This approach is appealing, but it has potential logistical challenges as well. The risk with a tapering approach is that the patient will achieve supraphysiologic levels of testosterone, which may result in polycythemia. Our patient is an example of this, since his serum testosterone level reached the upper range of normal before he stopped his exogenous testosterone (Table 1). Ideally, the patient should check his serum testosterone levels monthly to ensure that he is decreasing the exogenous testosterone levels appropriately. The patient compliance required to get monthly bloodwork, and the administrative burden on the provider's office, can make this approach challenging. In addition, there can be insurance problems with covering both exogenous testosterone and HCG. The tapering approach requires a compliant, motivated patient to navigate these challenges.

The Role of 17-Hydroxyprogesterone

Whether one ceases exogenous testosterone or tapers it off, the timeline for HCG-induced improvement of intrinsic testosterone production is variable. When tapering exogenous testosterone, it can be hard to get a sense of the velocity of this improvement, because the serum testosterone level will measure both intrinsic and extrinsic testosterone. Measuring 17-hydroxyprogesterone can be helpful in this regard.[3] 17-Hydroxyprogesterone is an intermediate in the steroid synthesis pathway that produces testosterone from cholesterol. As such, it can be used as a surrogate for intratesticular levels of testosterone production.

Our patient had undetectable levels of 17-hydroxyprogesterone prior to initiating HCG therapy, which is both predictable and appropriate given the lack of Leydig cell stimulation. By 2 months after starting HCG, his 17-hydroxyprogesterone had increased to 77 ng/dL, signaling a significant increase in intratesticular testosterone production. This increase mirrored his improvement in serum testosterone, despite his simultaneously decreasing his dose of exogenous testosterone over the same period.

The strategy of monitoring 17-hydroprogesterone can also be used to monitor patients' intrinsic testosterone levels in men with primary hypogonadism (testicular dysfunction) who are transitioning from exogenous testosterone to HCG. However, it is important to be mindful of the underlying etiology. A patient with secondary hypogonadism (hypothalamic or pituitary dysfunction) will presumably have normal testicular function and should recover Leydig cell function more quickly than a patient who is on exogenous testosterone due to primary hypogonadism. The velocity of our patient's intrinsic testosterone production was quick, despite his mixed history of unilateral testicular torsion and craniopharyngioma resection.

HCG Alone vs. rFSH vs. Human Menopausal Gonadotropins

Once serum total testosterone levels are normal on HCG without exogenous testosterone, intratesticular testosterone levels are sufficient for sperm production. After these normal levels have been achieved for at least 3 months, it can be worthwhile to perform a semen analysis. Not all hypogonadotropic hypogonadism patients are the same, and there can be some intrinsic FSH activity that had previously been suppressed by the exogenous testosterone. Many patients who developed hypogonadotropic hypogonadism after puberty will have induction of spermatogenesis with HCG alone.[4] Our patient's semen analysis revealed persistent azoospermia despite normal serum total testosterone levels, which is consistent with his FSH level remaining undetectable after he was off exogenous testosterone. These findings reflect the extent of disruption of the patient's pituitary function as a result of the craniopharyngioma treatment.

In order to stimulate the Sertoli cells to support sperm production in the absence of intrinsic FSH activity, either rFSH or human menopausal gonadotropins (HMG) can be used. HMG is a combination of LH and FSH extracted and purified from the urine of postmenopausal women (who have high levels of both hormones). HMG has activity for both hormones, but it is used primarily for its FSH activity. rFSH is simply pure FSH harvested from cell lines. In practical terms, they are both effective methods to stimulate the FSH receptor and induce spermatogenesis, and one drug does not appear to be more effective than the other.[5] In our patient, we used rFSH because some data suggest a slightly quicker onset of spermatogenesis with rFSH.[6] This quicker onset can be helpful when maternal age is a factor; however, rFSH is much more expensive than HMG. In our patient, the rFSH resulted in significant improvement in motile sperm counts over the course of 3 to 6 months, enabling this couple to start their family.

CONCLUSION

The management of hypogonadotropic hypogonadism requires a thorough understanding of the male hypothalamic-pituitary-gonadal axis and reproductive physiology. While inducing endogenous testosterone production, one can minimize hypogonadal symptoms by tapering off exogenous testosterone rather than ceasing it. Monitoring 17-hydroxyprogesterone can give some indication of the onset of endogenous testosterone production. Once normal serum total testosterone levels are achieved, if spermatogenesis is not induced with HCG alone, rFSH or HMG can be used to enable these men to have children.

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