

Medical management of non-obstructive azoospermia

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Non-obstructive azoospermia is diagnosed in approximately 10% of infertile men. It represents a failure of spermatogenesis within the testis and, from a management standpoint, is due to either a lack of appropriate stimulation by gonadotropins or an intrinsic testicular impairment. The former category of patients has hypogonadotropic hypogonadism and benefits from specific hormonal therapy. These men show a remarkable recovery of spermatogenic function with exogenously administered gonadotropins or gonadotropin-releasing hormone. This category of patients also includes some individuals whose spermatogenic potential has been suppressed by excess androgens or steroids, and they also benefit from medical management. The other, larger category of non-obstructive azoospermia consists of men with an intrinsic testicular impairment where empirical medical therapy yields little benefit. The primary role of medical management in these men is to improve the quantity and quality of sperm retrieved from their testis for in vitro fertilization. Gonadotropins and aromatase inhibitors show promise in achieving this end point.

KEYWORDS: Infertility; Drug Therapy; Gonadotropins; Hypogonadism; Aromatase Inhibitors.

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INTRODUCTION

Non-obstructive azoospermia (NOA) is generally considered a non-medically manageable cause of male infertility. These patients, who constitute up to 10% of all infertile men, have abnormal spermatogenesis as the cause of their azoospermia. The establishment of in vitro fertilization using intracytoplasmic sperm injection (ICSI) as a standard treatment modality has resulted in a number of these men successfully fathering a child through surgically retrieved sperm from the testis. The challenge, however, is to improve their spermatogenic function to enable the appearance of sperm in their ejaculate or to improve the chances of a successful retrieval from the testis for ICSI.

The initial evaluation aims at resolving the following issues: (1) confirming azoospermia, (2) differentiating obstructive from non-obstructive etiology, (3) assessing for the presence of reversible factors and (4) evaluating for the presence of genetic abnormalities. An elevated follicle-stimulating hormone (FSH) level or an absence of normal spermatogenesis by testicular histology in the presence of azoospermia is generally considered sufficient evidence of a non-obstructive etiology. The most common reversible factors that need to be ruled out include recent exogenous

hormone administration, severe febrile illnesses, chemotherapy/radiation or prolonged antibiotic use.

Hormone analysis forms the cornerstone of the further evaluation and management of NOA and serves two important functions. The first function is to identify a distinct subset of men who have hypogonadotropism (low FSH), in which azoospermia results from an inadequate stimulation of the testis by gonadotropins. The inherent spermatogenic potential of the testis may be partially recoverable, and the management and prognosis of infertility in these men differ from all other subsets. The second function is to predict the success of medical therapy and of surgical sperm retrieval. Based on these initial hormone studies, the two broad categories are hypogonadotropic hypogonadism and hypergonadotropic hypogonadism or eugonadism (Table 1). There is considerable overlap in the hormone statuses of men who do not have hypogonadotropism, with similar etiologies producing a spectrum of hormonal changes. The American Urological Association recommends an estimation of serum FSH and testosterone as the initial hormonal assessment (1). However, endocrine abnormalities are a rare cause of male infertility and account for less than 3% of all cases. Additional hormone analysis, including luteinizing hormone (LH), estradiol and prolactin evaluations, is performed based on the likelihood of their abnormality and potential impact on management.

HYPOGONADOTROPIC HYPOGONADISM

Hypogonadotropic hypogonadism (HH) is a condition of low serum testosterone due to a decrease in the secretion of FSH and LH from the pituitary gland. HH may be congenital, acquired or idiopathic. The congenital forms

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Table 1 - Non-obstructive azoospermia classification

Hypogonadotropic hypogonadism
● Low FSH, Low LH, Low testosterone ● Congenital: Kallmann syndrome (hypothalamic GnRH deficiency) ● Acquired: Pituitary tumors
Hypergonadotropic hypogonadism/eugonadism
● High/normal FSH, Normal/high LH, Normal/low testosterone ● Congenital: Genetic abnormalities (Chromosomal) ● Acquired: ● Varicocele ● Orchitis ● Gonadotoxins (chemotherapy/radiation) ● Trauma/torsion ● Idiopathic

are classically syndromic, such as Kallmann syndrome, Prader-Willi syndrome and Laurence-Moon syndrome. Acquired HH usually results from the destruction of normal pituitary function following radiotherapy, trauma or a pituitary tumor. Another form of acquired HH is due to excess exogenous steroids or androgens. Hyperprolactinemia may also cause infertility by inhibiting the hypothalamic secretion of gonadotropin-releasing hormone (GnRH) and also through a direct inhibition of the binding of LH to the Leydig cells in the testis.

Congenital hypogonadotropic hypogonadism typically occurs in association with anosmia and is known as Kallmann syndrome. It has varying genetic modes of transmission, including via both sex chromosomal (X-linked) and autosomal abnormalities. Hypogonadism results in abnormal secondary sexual characteristics, including gynecomastia, cryptorchidism and micropenis. The primary abnormality is decreased GnRH secretion from the hypothalamus with consequent low levels of gonadotropins (FSH and LH) from the pituitary.

Hypogonadotropic hypogonadism is one of the few causes of NOA that have shown a consistent response to medical management (2,3). Gonadotropin therapy is begun at the time the patient wishes to father a child, and three to six months of treatment are usually sufficient to induce spermatogenesis (4,5). Therapy is initiated with human chorionic gonadotropin (hCG) at 2,000 IU subcutaneously three times per week or 2,500 IU twice a week and supplemented with FSH (menopausal, purified or recombinant) at 37.5-150 IU three times a week after three to six months. hCG is sufficient to initiate spermatogenesis, but FSH is required to complete the spermiogenesis, particularly in patients with congenital abnormalities. In one of the largest reported series, Burgues et al. (6) evaluated self-administered highly purified follicle-stimulating hormone in 60 men with hypogonadotropic hypogonadism who showed an adequate response to an initial hCG therapy. Subjects self-administered 150 IU of FSH three times per week and 2,500 IU of hCG twice a week for at least six months, with non-responders continuing treatment for a further period. By the end of the treatment, 80% of these azoospermic/aspermic men had sperm in their ejaculate, with a median time to sperm presence of five months. Similar data reported from other studies support the specific role of hormone replacement therapy in these men (7,8).

An alternative method for treating hypogonadotropic hypogonadism is with a pulsatile injection of GnRH in

patients with intact pituitary glands. GnRH can be administered subcutaneously, intravenously or intranasally, but the 2-hour dosing regimen makes the intravenous and intranasal routes impractical. The standard method is 5-20 micrograms administered every 2 hours subcutaneously. In a large cohort of men with idiopathic hypogonadotropic hypogonadism (IHH), a bihourly pulsatile administration of GnRH subcutaneously through an infusion pump for 12-24 months resulted in the induction of spermatogenesis in 77% of initially azoospermic men (9). The authors reported a more rapid return of spermatogenesis in men who had achieved at least partial puberty at the time of initiating GnRH therapy, with all such subjects responding within six months. GnRH therapy reliably corrected the hypogonadism, with a reversal of azoospermia in a majority of the men, but a subset of men may exhibit pituitary resistance or atypical response (10). Other studies have also reported the successful initiation of pregnancy using GnRH therapy (11,12). Pulsatile GnRH therapy is more cumbersome and expensive than gonadotropin therapy, and this precludes its routine use. However, in men with IHH who fail to respond to gonadotropin therapy, GnRH therapy may be an option. GnRH therapy is also not possible in men who do not have functional pituitary glands.

Congenital abnormalities are likely to have been noticed early during adolescence, and a number of these men would have received testosterone therapy near the onset of puberty to induce the development of secondary sexual characteristics. This prior treatment with testosterone at the time of puberty does not interfere with the response to gonadotropins when attempting a pregnancy. A number of these men will produce sperm in their ejaculate but with total counts below the reference range. However, these men are often able to initiate a pregnancy with these low counts (13). Therapeutic interventions may be associated with a significant delay in the appearance of sperm or achieving a sufficient quantity or quality to imitate a spontaneous pregnancy, and some men may benefit from assisted reproduction techniques if an adequate response is not observed at the end of one year (14,15).

Androgen and steroid excess

Androgen excess through exogenous administration or pituitary/adrenal or testicular tumors can also lead to the suppression of spermatogenesis and NOA that is amenable to medical management. This is a form of hypogonadotropic hypogonadism, where the excess androgens produce feedback inhibition on normal pulsatile gonadotropin secretion, and suppression of excess steroids results in the recovery of spermatogenesis.

Congenital adrenal hyperplasia is a diagnosis of childhood. However, a number of these men will present as adults with infertility. Infertility is particularly common in the presence of associated testicular adrenal rest tumors (TARTs). Exogenous steroid administration results in suppression of adrenocorticotrophic hormone (ACTH) with a consequent decrease in the size of the TARTs and the possible return of fertility (16,17). Devoto et al. (18) reported a 29-year-old male with azoospermia and congenital adrenal hyperplasia with a 21-hydroxylase deficiency who had normal serum hormones but a testicular biopsy suggesting hypogonadism. The patient was treated with exogenous corticosteroids that resulted in normal testicular development, improvement in sperm counts and spontaneous paternity



on two occasions. The authors cautioned that hormone analysis in these men might not suggest hypogonadism because the excess testosterone production from the adrenals masks the intra-testicular hypogonadism. A reversal of azoospermia may depend on the type of steroid used and its dose. Claahsen-van der Grinten (19) noted inadequate suppression with 30 mg of hydrocortisone but a significant improvement after changing to an equivalent dose of dexamethasone in a patient who had azoospermia but went on to father two children through spontaneous conception after this change. These outcomes have been supported by other reports on the reversal of azoospermia with exogenous dexamethasone treatment (20,21).

Excess androgens present in anabolic steroids or testosterone itself are potent causes for the suppression of endogenous hormone production. The initial step in the management of these men is the cessation of the use of all such hormones. It may take a year or longer for endogenous production to return to normal after the cessation of exogenous therapy. Spermatogenesis may then be spontaneously restored, or there may then be evidence of additional endocrine abnormalities that will need to be addressed.

■ HYPERGONADOTROPIC HYPOGONADISM/ EUGONADISM

Aromatase inhibitors

High intra-testicular levels of testosterone are necessary for spermatogenesis. An imbalance between the circulating testosterone and estrogen levels has been investigated as a potential therapeutic target in men with NOA. The enzyme aromatase, which is present in the adipose tissue, liver, testis and skin, is responsible for converting testosterone and other androgens to estradiol in men. Estradiol suppresses pituitary LH and FSH secretion and also directly inhibits testosterone biosynthesis. This results in an imbalance in the testosterone and estradiol (T/E) ratio, which may be reversible. Aromatase inhibitors have the potential to block the conversion of androgens to estradiol. The two types of aromatase inhibitors are steroidal (testolactone) and non-steroidal (anastrozole, letrozole). Both of these groups of agents have been studied for potential therapeutic roles in NOA.

In 2001, Pavlovich et al. reported one of the first studies on the potential role of low-dose oral testolactone in men with NOA or severe oligospermia (22), in which 63 men (NOA or sperm density below 10 million/mL) were evaluated. This study included 43 men with NOA that was documented by a testis biopsy. Data from these men were compared with those from 40 age-matched fertile controls. All men underwent a baseline hormone profile, and 45 out of 63 men had a testosterone-to-estradiol ratio below the 20th percentile of normal, as determined from the healthy controls. These 45 men included patients with Klinefelter's syndrome, chromosomal anomalies, varicoceles, etc. as the cause for NOA. Subjects received 50 to 100 mg of oral testolactone twice a day for a mean of five months. Hormone profiles were obtained at one month of therapy, and the dose of testolactone was increased from 50 to 100 mg if the ratios remained low. A semen analysis was performed after at least three months of stable drug therapy. The authors reported a decline in estradiol or an increase in testosterone with drug therapy in all patients, with

significant improvements in T/E ratios. However, while the oligospermic men demonstrated significant improvements in total sperm counts and motility, none of the 12 azoospermic men who completed three months of treatment showed any return of sperm in the ejaculate.

In a direct comparison between testolactone and anastrozole, Raman and Schlegel treated 140 men with low T/E ratios with testolactone and/or anastrozole (23). Some men received both therapies sequentially; they overlapped in the study population. Ultimately, 74 men received 50 to 100 mg of testolactone twice daily for a mean of six months, and 104 men received 1 mg of anastrozole daily for a mean of 4.7 months. The 12 azoospermic men did not exhibit any improvement. Similar to their experience with testolactone, while the T/E ratios improved in all men, none of the 14 azoospermic men experienced a return of sperm to the ejaculate.

These studies argue against the use of aromatase inhibitors in NOA men. However, there may be a potential role in improving the quality or quantity of testicular sperm, thus improving the outcomes of sperm retrieval using testicular sperm extraction (TESE) and ICSI. Schiff et al. reported their experience with pretreatment with testolactone, hCG and anastrozole in men with non-mosaic Klinefelter's syndrome prior to TESE/ICSI (24). Among their cohort of 42 men, 36 had low pre-treatment levels of testosterone. These men received either an aromatase inhibitor alone or in combination with hCG until the testosterone or T/E ratio normalized. TESE was successful in all men who received either anastrozole alone or in combination with hCG, while it succeeded in 74% of those receiving only testolactone and 54% of those receiving testolactone and hCG. The authors did not have a control group, and it is difficult to assess the contribution of the pretreatment on the successful outcomes, particularly because all six men who did not require pretreatment had successful outcomes. However, the success rates in these men were higher than historical controls. In a more recent update of their data, this group identified no significant impact of the pretreatment on a successful outcome (25). However, they did note an improved outcome if the pretreatment resulted in an improved serum testosterone level prior to performing the TESE.

Antiestrogens

Clomiphene citrate and tamoxifen are non-steroidal antiestrogens that have long been used as empirical options in the management of idiopathic oligospermia. Clomiphene blocks the feedback inhibition of estrogen on the pituitary, resulting in increased FSH and LH secretion and a consequent rise in testosterone. There is little scientific evidence in favor of using clomiphene empirically. However, it continues to be a popular choice and has been used in men with NOA. Hussein et al. treated 42 men with NOA and either hypospermatogenesis or maturation arrest based on a biopsy with clomiphene citrate, which was initially 50 mg every alternate day for two weeks and then increased serially until the testosterone levels reached between 600-800 ng/dL (26). Semen analysis was performed at regular intervals, and if azoospermia persisted beyond six months of treatment, a testis biopsy was performed. The results revealed that 64% of the men experienced a return of sperm in their ejaculate, with sperm density ranging from 1-16 million/mL. Among those who remained azoospermic, sperm retrieval for ICSI was successful



in all cases. Of note, the authors excluded all men with Sertoli cell-only syndrome or a low testicular volume and a mean FSH at baseline of 7.21 mIU/mL. Further, this remains the only series on the successful use of clomiphene in azoospermic men, and its results have not been replicated by other investigators.

Gonadotropins

The use of gonadotropins to induce the appearance of sperm in the ejaculate or to increase the success rates of TESE in men with NOA has been based on the rationale that high levels of exogenous gonadotropins decrease the endogenous gonadotropin secretion. This in turn allows a "resetting" of the FSH and LH receptors in the Leydig and Sertoli cells, whose functions then improve (27).

Selman et al. reported a 32-year-old man with Y chromosome microdeletions who received recombinant FSH and hCG before a successful ICSI procedure with ejaculated sperm that numbered in the few thousands (28). Similarly, Efesoy et al. reported sperm in the ejaculate of 2 of 11 azoospermic men with maturation arrest who were treated with recombinant FSH (29).

Shiraishi et al. reviewed their data on repeat TESE in men with NOA who had no sperm retrieved during the first TESE (30). Of 48 such men with no chromosomal anomalies and normal serum testosterone levels, 28 received 5,000 IU of hCG three times a week for three months. The men whose FSH declined significantly received additional recombinant FSH of 150 IU three times a week for two months, while the other men continued to receive hCG until the repeat TESE. Another 20 men in this cohort refused hormonal therapy and underwent a second TESE at a mean of 17 months after the first surgery. None of the 48 men experienced a return of sperm in their ejaculate. However, the second TESE was successful in 21% of men who received hormonal therapy, while it failed in all those who did not. By evaluating a more select group of men with normal baseline hormone profiles, testicular volumes and genetic analyses, Selman et al. treated 49 men with rFSH, which was initially at 75 IU on alternate days for two months, followed by 150 IU for two months and then an additional 2,000 IU of hCG for two months (31). All men remained azoospermic at the end of treatment; however, while none had mature sperm in the pre-treatment testis biopsy, sperm were found in the biopsies of 22% men after treatment. Similarly, Ramasamy et al. reported improved outcomes of primary TESE following gonadotropin therapy in men with NOA and Klinefelter's syndrome (25).

Antioxidants

The role of antioxidant therapy in male subfertility continues to be debated. While there is a significant amount of data documenting raised oxidative stress and low antioxidant capacity in the seminal plasma of infertile men with abnormal semen parameters, including azoospermia, there is little high-quality evidence in support of using antioxidants in the treatment of these men (32). This is primarily because such therapy has not resulted in significant improvements in pregnancy rates, although statistically significant changes in anti-oxidant capacity and improvements in measured seminal parameters have occurred. Furthermore, most of the existing literature involves men with oligo/asthenospermia and not azoospermia. One of the few studies using antioxidants on azoospermic men reported

a remarkable improvement in all subjects but was hampered by a poorly documented methodology (33).

Among men with NOA, gonadotropin therapy for hypogonadotropic hypogonadism is the only specific indication that has universally shown an improvement in semen analysis and pregnancy rates. Gonadotropins (hCG and rFSH) in combination constitute a standard therapy, with GnRH therapy reserved for non-responders. The medical management of other forms of NOA remains empirical. Drug therapy with aromatase inhibitors and gonadotropins shows potential promise in improving outcomes in men requiring surgical sperm retrieval, but there is lack of level I clinical evidence for this indication.

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