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Management of nonobstructive azoospermia: a committee opinion

The Practice Committee of the American Society for Reproductive Medicine

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The management of nonobstructive azoospermia in the context of fertility treatment is discussed. This document replaces the ASRM document titled "Evaluation of azoospermia," last published in 2008. (Fertil Steril® 2018;110:1239–45. ©2018 by American Society for Reproductive Medicine.)

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Approximately 5%–10% of men evaluated for infertility are azoospermic (1, 2). Survey data from the United States suggests that there are approximately 600,000 azoospermic reproductive-aged U.S. men at any time, most of whom have nonobstructive azoospermia (NOA) (3). Nonobstructive azoospermia results from severe deficits in spermatogenesis that most commonly result from primary testicular dysfunction, but that may also result from impairment of the hypothalamus or pituitary. The development and widespread adoption of intracytoplasmic sperm injection (ICSI) has revolutionized treatment for NOA and enabled biological paternity in many men using surgically retrieved spermatozoa.

Practice patterns for the management of azoospermic men are variable within the United States. In some centers, procedures for sperm retrieval are coordinated with oocyte retrieval so that fresh sperm are used for ICSI. In contrast, other centers offer sperm retrieval with cryopreservation with the intention of using thawed sperm at a later date. Finally, the methods used for sperm retrieval in men with NOA are variable.

GOALS OF MANAGEMENT FOR MEN WITH NOA

Men with NOA are entitled to a diagnostic evaluation that targets identification of treatable, genetically transmissible, prognostic, and/or health-relevant conditions. This evaluation should include a comprehensive clinical history, physical examination, serum testing of total testosterone and follicle-stimulating hormone (FSH) levels, and further diagnostic testing in some cases based on results of the initial diagnostic evaluation (4). Each azoospermic man's female partner should also undergo a systematic, cost-effective evaluation in preparation for assisted reproduction using ICSI, which is required for reproduction in the vast majority of NOA cases. Evaluation of the female partner should include clinical assessment of ovulatory function and the structure and patency of the female reproductive tract (5).

Men with NOA are also entitled to counseling regarding therapeutic alternatives to immediate sperm retrieval when appropriate, counseling about the advantages and disadvantages of available sperm-retrieval procedures and protocols, and treatment of

health-relevant conditions that are discovered during their diagnostic evaluation. These management objectives are best met with a multidisciplinary clinical team that includes a reproductive urologist or other specialist in male reproductive medicine (6).

DIAGNOSIS OF GENETIC ABNORMALITIES IN MEN WITH NOA

The majority of patients with NOA have primary testicular failure. Genetic testing is indicated to evaluate for transmissible and health-relevant genetic lesions that are critical to consider when counseling and treating affected couples (7). Cytogenetic evaluation by karyotyping will identify cytogenetic abnormalities in approximately 5% of men with NOA (8); nonmosaic Klinefelter syndrome (47,XXY) is the most commonly detected cytogenetic anomaly (9). The diagnosis of Klinefelter syndrome informs treatment decisions about sperm retrieval and has important relevance to the health of affected men, who are at increased risk for testosterone deficiency (TD), osteoporosis, metabolic syndrome, type 2 diabetes, breast cancer, and extragonadal germ-cell tumors (10). Other cytogenetic abnormalities detected in azoospermic men include Robertsonian translocations, reciprocal translocations, and chromosomal inversions.

Some of these genetic lesions predispose to sperm and embryo aneuploidy that can affect the genetic health of offspring conceived with assisted reproductive technology (ART) (11–13).

Men with NOA associated with primary testicular failure should also undergo Y chromosome microdeletion testing. Testing for Y chromosome microdeletions is essential for counseling affected men about the risk of infertility in potential male offspring, and to avoid unnecessary surgery in patients with a very poor prognosis for sperm retrieval. Approximately 4% of American men with NOA carry transmissible azoospermia factor (AZF) C deletions that will be inherited by any sons conceived with ART, and approximately 6% of men with NOA carry more severe Y-chromosome microdeletions involving the complete AZFa and AZFb regions that confer a very poor prognosis for sperm retrieval (14).

Genetic testing should also be considered in NOA associated with congenital forms of hypogonadotropic hypogonadism (HH), to inform patients about the risks of HH in their offspring. Mutations in a number of genes have been described, including but not limited to the Kallman syndrome (KAL) family of genes that is implicated in anosmic congenital hypogoandism. Overall, genetic lesions with variable inheritance patterns are detectable in one third of cases. Testing affords clinicians the opportunity to counsel patients about the risks of HH in their offspring, and empowers clinicians to screen for unaffected embryos using preimplantation genetic testing for aneuploidy (PGT-A) (15).

MANAGEMENT OF DETECTED GENETIC ABNORMALITIES IN MEN WITH NOA

Detection of any genetic abnormality during the diagnostic evaluation of NOA should prompt genetic counseling by an appropriately trained health-care provider before treatment. Counseling should focus on the impact of the specifically detected genetic lesion on the patient's health and his prognosis for sperm retrieval, and on the risks posed by the detected genetic lesion to the health and fertility of any potential offspring conceived using surgically retrieved sperm. Detection of cytogenetic abnormalities seen on peripheral blood karyotyping should trigger consideration of PGT-A during in vitro fertilization (IVF). Men discovered to harbor complete AZFa or AZFb deletions upon Y chromosome microdeletion testing should be counseled to consider use of donor sperm or adoption, given that sperm identification is rare. Physicians treating men with AZFc Y-chromosome microdeletions should inform those men that any sons conceived with their surgically retrieved sperm will be at high risk for NOA when they reach adulthood. In rare cases, atypical Y-chromosome microdeletions will be detected. Treatment of these men should be individualized based on published reports describing the sequelae of their specific rare Y-chromosome microdeletion (if available).

HORMONAL OPTIMIZATION THERAPY IN MEN WITH PRIMARY TESTICULAR FAILURE

Low levels of intratesticular testosterone and abnormalities in the ratio of testosterone to estrogen may be implicated in the pathophysiology of NOA (16). It is therefore rational that therapy directed at improving the hormonal environment for spermatogenesis might be beneficial. Ejaculated sperm have been reported in men with NOA after treatment with the aromatase inhibitor letrozole (17–19). One small nonrandomized study reported successful sperm retrieval after human chorionic gonadotropin (hCG) therapy in 6 of 28 men who had previously undergone failed sperm-retrieval attempts, compared with 0 of 20 men ($P < .05$) in whom a second sperm retrieval was attempted without any hormonal therapy (20). In a larger nonrandomized multicenter study of 442 men with NOA who underwent sperm retrieval, sperm-retrieval rates were superior in the hormonal-optimization group (57%) to the group that underwent immediate sperm-retrieval surgery without hormonal therapy (34%). In this study, hormonal-optimization therapy was administered using a stepwise protocol starting with clomiphene citrate and titrated to biochemical response using hCG and human menopausal gonadotropin in nonresponders (21). Despite these signals from the literature that hormonal-optimization therapy may be beneficial in men with NOA, the quantity and quality of the availability of evidence is insufficient to recommend hormonal-optimization therapy as standard clinical practice.

MEDICAL THERAPY FOR NOA ASSOCIATED WITH HYPOGONADOTROPIC HYPOGONADISM

Hypogonadotropic hypogonadism is an uncommon cause of male infertility, affecting approximately 1%–2% of infertile men. HH is characterized by hypothalamic or pituitary dysfunction, low/suppressed serum gonadotropins, and decreased testicular function that manifests clinically as testosterone deficiency, oligospermia/azoospermia and/or decreased testicular volume. Failure of spermatogenesis results from lack of gonadotropin stimulation. HH may be congenital, acquired, or idiopathic. Common notable etiologies of HH are Kallman syndrome, which results from deficient gonadotropin-releasing hormone (GnRH) secretion from the hypothalamus, and anabolic steroid−induced hypogonadism (ASIH), which results from prolonged suppression of the hypothalamic−pituitary−gonadal axis from exogenous androgen excess. Other acquired forms of HH are related to trauma, radiation, chronic opioid use, and cerebral tumors. Management strategies are tailored to the age of presentation and underlying etiology.

Irrespective of HH etiology, it is one of the most medically treatable causes of NOA. GnRH therapy is as effective as gonadotropin therapy in achieving spermatogenesis and pregnancy in patients with hypothalamic disorders who have intact pituitary function (22). Pulsatile administration of 5–20 μg every 2 hours via an infusion pump (worn on the body) is used more commonly than intravenous or intranasal GnRH for convenience and improved adherence. Using this regimen over 12–24 months has resulted in the presence of spermatogenesis in 77% (n = 24/31) of initially azoospermic men (23). Recovery occurred within 6 months for men who had signs of puberty when GnRH therapy was initiated. Pretreatment with recombinant FSH prior to GnRH therapy

optimizes fertility outcomes and may be considered as an alternative to GnRH monotherapy (24). In current practice, pulsatile GnRH is likely to be less used than gonadotropin therapy due to its cumbersome nature and its ineffectiveness in men with panhypopituitarism.

Gonadotropin treatment with hCG, with or without FSH (recombinant, menopausal, or purified), can lead to sperm production usually within 3–6 months (25). Human chorionic gonadotropin is dosed at 1,000–3,000 IU two to three times weekly and may be titrated to achieve a eugonadal state. If spermatogenesis is not achieved by 6 months, recombinant or highly purified FSH is initiated at 75 IU two to three times weekly and titrated up an additional 75 IU per dose after several months if spermatogenesis induction is inadequate. This dosing regimen can be extended beyond 6 months if sperm does not return to the ejaculate (26). FSH administration is required to complete spermatogenesis in some men with congenital or acquired HH (i.e., after cerebral trauma or radiation) who may lack pituitary function.

Clomiphene citrate may also be effective for men with idiopathic HH (27). Clomiphene therapy is inexpensive and requires intact pituitary function. Although only one small retrospective study has investigated clomiphene citrate in this population, and it should be considered a possible alternative to the other therapies described above.

There are no randomized controlled trials comparing gonadotropin treatment regimens; all studies are observational. A recent meta-analysis of men with HH and azoospermia investigated time to sperm production and predictors of response to both gonadotropin and GnRH therapy (28). A response to medical therapy resulting in at least one spermatozoon in the ejaculate as a result of gonadotropin and GnRH therapy occurred in 75% (69–81) and 75% (60–85) of patients, respectively. Factors predicting an improved response to gonadotropin therapy included postpubertal onset of HH and combined FSH/hCG therapy over hCG monotherapy. Site of HH (pituitary vs. hypothalamic), previous history of testosterone replacement therapy (TRT), and type of FSH administered were not predictive of response. Combined pregnancy rate for the gonadotropin and GnRH study groups were 30% and 50%, respectively, with a minority of the pregnancies requiring ART.

For men with HH who do not respond sufficiently to medical therapy to achieve pregnancy via unassisted conception, ART should be recommended (29). Some men may be candidates for intrauterine insemination, whereas others may require IVF/ICSI using ejaculated sperm. Sperm-retrieval procedures should be considered if ejaculated sperm remain undetectable. Although data are lacking, a period of at least 6 months of therapy, associated with increased testicular volumes and normalization of hormones, may be considered as treatment endpoints prior to retrieval.

For men with ASIH, discontinuation of exogenous androgens/steroids and prevention of further use is recommended. Time to recovery of spermatogenesis in suppressed individuals is variable (30). For men with HH from anabolic steroid abuse, administration of intramuscular injections of hCG at doses of 3,000 units 2 to 3 times per week for 3 or more months can expedite recovery of spermatogenesis (31–33). Because higher doses of hCG can suppress FSH, adding clomiphene citrate to preserve pituitary function may be beneficial. Monotherapy with clomiphene citrate can also be considered, but hypogonadal symptoms may affect adherence (34).

After completion of therapy for infertility, most men with HH will benefit from lifelong hormonal therapy for management of symptoms related to clinical testosterone deficiency (35). These men may continue medical therapy to maintain their reproductive potential (i.e., gonadotropin replacement therapy or clomiphene citrate), or they may switch to TRT. Testosterone replacement will result in return of the clinical infertility, but it is more cost-effective than gonadotropin replacement therapy and has been better studied when used for long durations of treatment. The risks and benefits of long-term TRT should be discussed before initiating therapy.

VARICOCELE TREATMENT IN MEN WITH NOA

Varicocele remains the most common correctable form of male-factor infertility and is found in 4.3%–13.3% of men with severely impaired spermatogenesis or azoospermia (36). The causal link between varicocele and NOA, however, is weakly established. Varicocele repair resulting in sperm production in a previously azoospermic male was first described by Tulloch in 1955 (37). A recent review of varicocele repair outcomes by ligation or embolization in men with NOA showed that detection of ejaculated sperm occurs in 44% (151/344) of treated men (38). This benefit is most pronounced in patients with histological evidence of hypospermatogenesis. Varicocele therapy may be less effective in NOA patients with maturation arrest or Sertoli cell−only syndrome. Given the prognostic potential of testicular histology, biopsy at the time of varicocele repair may provide useful information for patient counseling. Preoperative indicators such as varicocele grade, testicular volume, and preoperative FSH levels have failed to reliably predict fertility outcomes.

Azoospermia relapse has been noted in several studies at varying intervals, which raises concerns about the durability of the benefit derived from varicocele repair in this population (39–41). Thus, semen cryopreservation has been suggested. Spontaneous and assisted pregnancy outcomes using ejaculated sperm after varicocele repair in men with NOA vary and are based on retrospective data. Spontaneous pregnancy rates have been reported to be as high as 6% (14/233 patients) to 13.6% (12/88 patients) based on two recent reviews (38, 42). Pregnancy rates via ART using ejaculated sperm have been reported to range from 4% (10/233 patients) to 18.9% (58 couples) (38, 42).

There is also evidence that varicocele repair may improve sperm-retrieval rates in men with NOA in whom sperm do not become detectable in the ejaculate after varicocele treatment. A recent meta-analysis suggests that the likelihood of sperm retrieval is 2.65-fold higher in men with varicocele-associated NOA if the varicocele is treated before attempted sperm retrieval (38). The optimal timing of sperm retrieval after varicocelectomy has not been investigated; however, an interval of at least 3 months between varicocele repair and sperm retrieval is recommended. Ultimately, evidence supports consideration of varicocele repair in men with NOA.

METHOD OF SPERM RETRIEVAL

The method of sperm retrieval may also be critical in the management of NOA. Because testicular sperm production, when present, is randomly and heterogeneously distributed throughout one or both testes, surgical methods for sperm retrieval have been developed to achieve wide sampling of the testicular parenchyma. Percutaneous, incisional, and microsurgically assisted techniques have been described. Percutaneous methods such as testicular sperm aspiration (TESA) involve aspiration of testicular tissue using small- or large-bore needles. The needle is typically attached to a syringe that is used to create suction while the needle tip is moved around within each testis to achieve wide sampling of the seminiferous tubular tissue. Incisional methods are generally referred to as conventional testicular sperm extraction (cTESE) or microdissection testicular sperm extraction (mTESE). In cTESE, seminiferous tubular tissue is extracted through one or more testicular incisions. Microdissection TESE is performed by making a large testicular incision and then selectively sampling the largest-diameter seminiferous tubules using optical magnification provided by an operating microscope.

The most important outcome when assessing sperm extraction is sperm-retrieval rate. No randomized controlled trials have been performed to compare techniques of sperm extraction. Two recent systematic reviews have been performed examining surgical sperm-extraction techniques in men with NOA; both identified the same seven studies comparing mTESE to cTESE. The authors report successful sperm retrieval in 35% of cTESE cases (range: 17%–45%) and 52% of mTESE cases (range: 45%–63%), estimating that the performance of a mTESE was 1.5 times more likely to retrieve sperm (95% confidence interval [CI] 1.4–1.6) (43, 44). Using a combination of prospective and retrospective data, the authors of both reviews concluded that mTESE was superior to cTESE for surgical sperm extraction in men with NOA. It was noted that the greatest advantage seemed to be in men with limited sperm production such as Sertoli cell−only pattern. In addition, seven studies were also pooled to provide a comparison in sperm-retrieval rates between TESA (28%, range: 7%–42%) and cTESE (56%, range: 43%–64%), concluding the superiority of cTESE vs. TESA (relative risk [RR] 2.0, 95% CI 1.8–2.2). Although sperm-retrieval rates were different for cTESE in each of the comparison groups, the conclusions suggest the superiority of mTESE over cTESE and of cTESE over TESA. When a repeat procedure is necessary, data suggest that allowing at least 6 months to pass increases the retrieval rate (80% vs. 25%, $P=.02$ [calculated]) (45).

A diagnostic biopsy (either open or percutaneous) has also been advocated. Although it may allow men to avoid a more extensive procedure to identify sperm, a diagnostic biopsy obligates men to undergo a second procedure to obtain sperm for reproduction. Data suggest that a diagnostic biopsy may provide information about the likelihood of sperm retrieval at the time of sperm extraction. Men in whom biopsy results demonstrate hypospermatogenesis (79%–98%), matu-ration arrest (47%–94%), and Sertoli cell−only (5%–24%) have different sperm-retrieval rates (46–48).

In addition to the sperm-retrieval rate, safety and complication rates are also important considerations. Overall, complications from all sperm-retrieval techniques are uncommon and minor (49). Percutaneous approaches are thought to have the lowest rate, with many studies reporting no complications (50, 51). However, a study of 267 procedures reported a 3% complication rate including hematoma and syncope during the procedure (52). Complications of TESE have been reported as hematoma, hypogonadism, and wound infection. Few studies have been reported that compare complications rates between TESE groups. However, higher postoperative intratesticular hematoma formation with cTESE compared to mTESE as assessed by scrotal ultrasonography has been suggested by several studies (53–55). The use of the microsurgical technique may allow decreased testicular parenchyma harvest and reduced sequelae including hypogonadism. Serum testosterone levels do fall acutely after TESE but return to 95% of baseline after healing is complete (55, 56).

TIMING OF SPERM RETRIEVAL

Another important consideration in the management of NOA is the timing of sperm retrieval. Surgical sperm retrieval can be performed during an IVF cycle to coincide with oocyte retrieval with the intent of using fresh sperm, if identified, for ICSI. Alternatively, sperm retrieval can be performed before ovarian stimulation with the plan for cryopreservation if sperm are identified for use in future IVF cycles. There are theoretical advantages of each strategy. The use of freshly extracted sperm allows sperm to avoid the stress of cryopreservation. Freezing the extracted sperm for later use separates timing of the IVF from sperm extraction so that if sperm is not found, the female partner can potentially avoid an unnecessary ovarian stimulation. In addition, both members of the couple will be undergoing gamete retrieval on separate days, allowing each to help the other rather than involving a third party for transportation/assistance. Moreover, due to the inherent work flows of coordinating an operating room, scheduling a sperm extraction for a precise day or time can be challenging when the exact timing is known only a few days prior. Establishing the efficacy of frozen sperm can also allow men to undergo a single sperm extraction rather than a separate procedure for each cycle.

Outcomes for the use of fresh vs. frozen sperm for ART in men with NOA have been compared. A meta-analysis compiled data from 11 studies reporting on 574 ICSI cycles (275 fresh and 299 frozen) that involved injection of 4,177 oocytes (57). No difference between fresh and frozen sperm was identified in clinical pregnancy rate (RR 1.00, 95% CI 0.75–1.33) or fertilization rate (RR 0.97, 95% CI 0.92–1.02). Three additional studies involving 401 cycles also failed to identify a difference in outcomes using fresh vs. frozen sperm in men with NOA (58–60). Identification of sperm after cryopreservation was not reported by all studies, but five groups report identification ranging from 79% to 100% (61–65). Three studies reported post-thaw identification

rates of 100% with an overall weighted average of 87% for all studies. Laboratory comfort and experience with cryopreservation of testicular tissue in men with spermatogenic failure are crucial to success.

DIAGNOSIS AND MANAGEMENT OF HEALTH-RELEVANT DISORDERS IN MEN WITH NOA

Comprehensive management of men with NOA includes the diagnosis and treatment of associated health-relevant conditions. NOA can be the presenting sign of pretesticular diseases, such as prolactin-secreting pituitary tumors, and testicular diseases, such as germ-cell tumors. Some of the same genetic defects in cell-cycle control and DNA repair pathways that drive tumorigenesis have been identified in men with NOA, and NOA has been reported to be the presenting sign of benign and malignant Sertoli cell, Leydig cell, and germ-cell tumors (66–70). Men with NOA also appear to be at an approximately 3-fold increased risk for being diagnosed with a future cancer compared with other infertile men (71).

Spermatogenic failure in NOA is often accompanied by Leydig-cell dysfunction, which can result in the clinical syndrome of testosterone deficiency (TD). The prevalence of TD in men with NOA is 29%–32% (72, 73) and increases after sperm-retrieval surgery (55, 72, 74). Testosterone deficiency is a health- and quality-of-life—impairing disease state in which circulating androgen levels are inadequate to support androgen-dependent physiological processes. Signs and symptoms of TD include sexual dysfunction, visceral adiposity, loss of bone mineral density, depressed mood, and lethargy. Affected men are at increased risk for metabolic syndrome, cardiovascular disease, type 2 diabetes, and osteoporosis (72).

SUMMARY

- Detection of genetic abnormalities in men with NOA may affect prognosis for sperm retrieval and should trigger genetic counseling.
- The quality of currently available evidence is insufficient to recommend hormonal-optimization therapy in men with NOA associated with primary testicular failure.
- Endocrine therapy is an effective first-line therapy for men with NOA associated with hypogonadotropic hypogonadism and allows natural conception in many cases.
- Hypogonadotropic hypogonadism associated with exogenous steroids or androgens is associated with a variable time to sperm recovery and may be assisted with clomiphene citrate and/or hCG.
- Reported sperm-retrieval rates in men with NOA are highest using microdissection testicular sperm extraction.
- Reproductive outcomes using frozen-thawed testicular sperm from men with NOA appear to be similar to outcomes using freshly retrieved sperm, but sperm recovery after cryopreservation is not 100%.
- Comprehensive management of men with NOA includes the diagnosis and treatment of associated health-relevant conditions such as TD.

CONCLUSIONS

- Optimal care for men with NOA requires a multidisciplinary clinical team that includes a reproductive urologist or other specialist in male reproductive medicine.
- Preimplantation genetic testing may be helpful to minimize the risks to offspring of affected men.
- Men who harbor complete AZFa or AZFb Y-chromosome microdeletions should be counseled to consider donor sperm or adoption in conjunction with psychosocial counseling, given that sperm identification is rare.
- Varicocelectomy should be considered in men with varicocele-associated NOA prior to sperm retrieval.
- Patients with NOA should be counseled about the advantages and disadvantages of available sperm-retrieval techniques.
- Other options, including donor insemination and adoption, should be discussed with the patient.

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