Controversies in the management of nonobstructive azoospermia

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The fertility potential of patients with nonobstructive azoospermia (NOA) depends on sperm extraction from the tissue sample and then in vitro fertilization with intracytoplasmic sperm injection (IVF/ICSI). Unfortunately, there is no consensus regarding predictors that can identify nonobstructive azoospermic men with a potentially high yield at the time of sperm extraction. This article analyzes two competing approaches to these patients: noninvasive and invasive. The noninvasive approach, based on clinical, laboratory, and ultrasonographic investigations, excludes from IVF/ICSI a significant number of patients owing to errors in predicting the presence of sufficient intratesticular spermatozoa. The invasive approach, with available percutaneous or surgical testicular biopsy techniques followed by morphologic examination and or sperm recovery, permits many patients with NOA to receive a favorable prognosis and therapeutic trial. However, the available testicular biopsy techniques are so variable that their performance parameters cannot be adequately compared. As a result, any progress in optimizing these techniques must involve delineation of specific selection criteria for each NOA patient. (Fertil Steril® 2009;91:963–70. ©2009 by American Society for Reproductive Medicine.)

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The diagnosis of nonobstructive azoospermia (NOA) includes idiopathic as well as identifiable etiologies (1). Among the identified causes, there are different congenital and acquired diseases or abnormalities (1). Regardless of the underlying etiology, management of patients with NOA usually relies upon restoring fertility by the recovery of spermatozoa with a testicular biopsy/sperm extraction procedure and a successful in vitro fertilization with intracytoplasmic sperm injection (IVF/ ICSI) (2). However, the recovery of sperm cells is successful in only about 50% of cases (1, 3, 4), and the subsequent pregnancy rate after IVF/ICSI is even lower (5). The importance of a successful pregnancy is an incentive to systematically attempt sperm retrieval in almost all men with NOA (1, 3, 5, 6). Because of the significant probability of eventual failure, which includes the 30%–60% of men without sperm plus the 50%–91% of the IVF/ICSI couples who do not obtain a pregnancy (7–9), a different, possibly more efficient, approach is needed. Simply put, this would be to select men with a reasonable probability of successful sperm retrieval before the procedure (10, 11). Unfortunately, no consensus on this patient selection process or the timing of the procedure exists (10, 11).

If an algorithmic approach is to be crafted, both the physician and the patient must consider the safety, invasiveness, cost, and potential results of the proposed evaluations before undertaking them. This process can vary from a clinical examination and a few laboratory tests to bilateral testicular surgery with attendant complication risks. In the present review, we examine the controversial aspects of this topic and focus on two principal, competing types of clinical approach: noninvasive and invasive.

NONINVASIVE APPROACH

Physicians and patients naturally prefer noninvasive medical evaluations, which are inherently safer, even if less accurate, over invasive procedures, which carry relatively greater risk, even if more accurate.

The performance characteristics of the principal tests that can predict sperm retrieval success with testicular biopsy are discussed below and summarized in Table 1.

Clinical and Hormonal Data

Serum FSH concentration reflects testicular volume and germ cell content of the testis. Men with an FSH level of $\geq$7.6 mIU/mL or a testicular long axis of $\leq$4.6 cm may be

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TABLE 1

Accuracy values of noninvasive tests or techniques proposed for predicting sperm retrieval after testicular biopsy in nonobstructive azoospermia.

Parameter or exam	Reference	Sensitivity, %	Specificity, %	Overall predictive value, %
Testicular volume	15	7.6–50	6.7–71	
FSH	15	9–71	40–90	
Inhibin B	23	44.6	63.4	
FSH, total T, inhibin B	10	71	71.4	
Testicular volume + hormones	11			80.8
Doppler ultrasound imaging	31	47.3	89	

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considered to have NOA and counseled accordingly (12). These men are best treated with therapeutic testicular biopsy and sperm extraction, with processing and cryopreservation for usage in IVF/ICSI if they accept advanced reproductive treatment (12). Several reports have reviewed the sperm retrieval success rate as a function of testicular volume and serum FSH values with an upper limit as high as 20 IU/mL (13–15). Various upper limits of serum FSH up to 20 IU/mL were evaluated. For FSH levels, sensitivity varied from 9% to 71% and specificity from 40% to 90%. For the different cut-off values of testicular volume ranging as low as 5 mL, sensitivity varied from 7.6% to 50% and specificity from 6.7% to 71%. Within the range of normal FSH levels, the sensitivity of FSH in predicting successful testicular sperm extraction (TESE) is low. With elevated FSH levels, sensitivity increases and specificity decreases (10). Furthermore, many patients with maturation arrest have a normal FSH level and testicular volume (10, 16). Other reports showed that spermatozoa or mature spermatids were retrieved from, or described in testicular biopsies of, patients with an elevated FSH level and small testicle (e.g., 26 mIU/mL and 5 mL, respectively) (10, 17, 18). More recently, 42 men with Klinefelter syndrome and mean FSH levels of 33.2 IU/L showed a sperm retrieval rate of 72% per TESE attempt (19). There was no lower limit of testicular volume that excluded the presence of spermatozoa; therefore, this clinical marker cannot preclude a trial of sperm retrieval (10).

Serum inhibin B levels also have been proposed as a marker of spermatogenesis (20), and some reports have suggested its use in predicting successful sperm retrieval by testicular biopsy (21, 22). A large series that compared serum inhibin B levels with sperm retrieval results after TESE found that the best discriminating concentration, 13.7 pg/mL, had a sensitivity of 44.6% and a specificity of 63.4% (23).

Therefore, they are inadequate to determine whether or not a patient should undergo a TESE solely on the basis of a serum inhibin B concentration (23).

In a different series of 100 patients with idiopathic NOA who underwent microdissection TESE (mTESE; see below), nine parameters (age, testicular volume, LH, FSH, total T, free T, E_2, PRL, and inhibin B) correlated well with sperm retrieval outcome using a multivariate logistic regression model (10). Of the nine parameters, FSH, total T, and inhibin B were most predictive of successful sperm retrieval, with a sensitivity and specificity of 71% and 71.4%, respectively (10). A different analysis was performed based on eight similar variables in predicting successful TESE in 303 NOA patients (11). The LH lvel and testicular volume were the only parameters significantly lower in the sperm negative than in the sperm positive group. In this study, mathematical modeling using an artificial neural network was used for predicting the outcome of TESE (11). The results were compared with those obtained by the analysis of the same data using a standard logistic regression model. The neural network analysis correctly predicted the outcome in 80.8% of the patients, whereas the logistic regression model did so only in 65.7% of the same cases (11). Thus, clinical and hormone data elaborated by artificial intelligence–based models can yield an accurate prediction of sperm retrieval after TESE in NOA patients. At present, this method as well as the use of other biomarkers, such as activins and antimullerian hormone, have limited utility owing to their novelty (11, 24, 25).

Nonhormone and Ultrasonographic Data

It is controversial whether the detection of spermatids in the ejaculate can predict the probability of sperm retrieval (26, 27). It has been suggested that NOA patients with Y chromosomal AZF region microdeletions have a poor prognosis of sperm retrieval with TESE (1, 28). Moreover, among the different AZF microdeletions of the Y chromosome, the isolated AZFc deletion seems to be associated with a good probability of sperm detection after testicular biopsy or TESE (29). Furthermore, the importance of a karyotypic abnormality is reduced based on the recent finding of a high sperm retrieval rate with TESE in patients with Klinefelter syndrome (19).

Recently, Doppler ultrasound imaging has been proposed to identify regions of the testis in which spermatozoa are most likely to be retrieved by TESE (30, 31). In a study of 24 men with NOA having 107 regions biopsied, sensitivity and specificity of this Doppler ultrasound technique in