Diagnostic evaluation of the infertile male: a committee opinion

Practice Committee of the American Society for Reproductive Medicine

American Society for Reproductive Medicine, Birmingham, Alabama

The purpose of this ASRM Practice Committee report is to provide clinicians with principles and strategies for the evaluation of couples with male infertility problems. This revised document replaces the document of the same name, last published in 2012 (Fertil Steril 2012;98:294–301). (Fertil Steril® 2015;103:e18–e25. ©2015 by American Society for Reproductive Medicine.) **Earn online CME credit related to this document at www.asrm.org/elearn**

Discuss: You can discuss this article with its authors and with other ASRM members at http://fertstertforum.com/asrmpraccom-diagnostic-evaluation-infertile-male/

Use your smartphone to scan this QR code and connect to the discussion forum for this article now.*

* Download a free QR code scanner by searching for "QR scanner" in your smartphone's app store or app marketplace.

Approximately 8%–15% of couples are unable to conceive after 1 year of unprotected intercourse (1). A male factor is solely responsible in ~20% of infertile couples and contributes in another 30%–40% of couples (2). A male infertility factor is often defined by abnormal semen parameters but may be present even when the semen analysis is normal. The purpose of this document is to provide clinicians with principles and strategies for the evaluation of couples with male infertility problems.

GOALS OF EVALUATION

Male infertility can be due to a variety of conditions, many, but not all, of which can be identified and treated. When the cause of abnormal semen parameters cannot be identified, as is true in many patients, the condition is termed idiopathic. Rarely, patients with normal semen quality may have sperm that either are incapable of oocyte fertilization or harbor genetic abnormalities that prevent normal fetal development.

Ideally, the identification and treatment of correctable conditions will improve the male partner's fertility and allow conception to be achieved naturally. Detection of certain genetic causes of male infertility provides the opportunity to inform affected couples about the risk of transmitting genetic abnormalities that may affect the health of offspring, may affect the chance for successful treatment, and can help to guide treatment options. Evaluation of the infertile man also is aimed at identifying any underlying medical conditions that may present as infertility. Some, such as testicular cancer and pituitary tumors, can have serious health consequences if not properly diagnosed and treated (3).

INDICATIONS FOR EVALUATION

Evaluation for infertility is indicated for couples who fail to achieve a successful pregnancy after ≥12 months of regular unprotected intercourse. Earlier evaluation and treatment may be justified, based on medical history and physical findings and is warranted after 6 months for couples in which the female partner is >35 years old (4). Men

having concerns about their future fertility also merit evaluation.

At a minimum, the initial screening evaluation of the male partner of an infertile couple should include a reproductive history and analysis of at least one semen sample. If the initial evaluation is abnormal, then referral to someone experienced in male reproduction is recommended.

Reproductive History

The reproductive history should include: 1) coital frequency and timing; 2) duration of infertility and previous fertility; 3) childhood illnesses and developmental history; 4) systemic medical illnesses (such as diabetes mellitus and upper respiratory diseases); 5) previous surgery; 6) medications and allergies; 7) sexual history (including sexually transmitted infections); and 8) exposures to gonadotoxins (including environmental and chemical toxins and heat). Previous fertility does not exclude the possibility of a newly acquired, secondary, male infertility factor. Evaluation is the same for men with primary infertility (never having fathered a pregnancy) and secondary infertility (having previously fathered a pregnancy).

Semen Analysis

Semen analysis is the cornerstone of the laboratory evaluation of the

infertile man and helps to define the severity of the male factor. Physicians should provide patients with standardized instructions for semen collection, including a defined pre-test abstinence interval of 2–5 days. Although a standard duration of abstinence is important for evaluation of semen parameters, some men with severe oligozoospermia can have equal or better sperm concentration with a short (hours) period of abstinence, supporting the potential use of multiple semen analyses during assisted reproductive technology treatment cycles (5–7). Semen can be collected by means of masturbation into a specimen cup or by intercourse with the use of special semen collection condoms that do not contain substances toxic to sperm. Ideally, the specimen should be collected at the laboratory. If collected at home, the specimen should be kept at room or body temperature during transport and examined in the laboratory within 1 hour of collection. To ensure accurate results, the laboratory should have a quality control program for semen analysis that conforms to the standards outlined in the Clinical Laboratory Improvement Amendments (CLIA); additional information including proficiency testing can be found on the CLIA website (8).

The semen analysis provides information on semen volume as well as sperm concentration, motility, and morphology (Table 1) (9). Methods for semen analysis are discussed in many textbooks, and detailed laboratory protocols have been published by the World Health Organization (WHO) (10). The diagnosis of azoospermia can be established only after the specimen is centrifuged (preferably at 3,000g) for 15 minutes and the pellet is examined. The current WHO criteria for evaluating sperm morphology (10) are similar to the "strict criteria" described by Kruger (Tygerberg) (11, 12), in that relatively few sperm are classified as having normal morphology, even in semen obtained from fertile men. Strict sperm morphology has been used to identify couples at risk for poor or failed fertilization with the use of standard in vitro fertilization (IVF) techniques (11) and thus to identify those who may be candidates for intracytoplasmic sperm injection (ICSI) (13). However, the value and necessity for ICSI in those having isolated abnormalities in strict morphology has been questioned (14).

Clinical reference ranges have been established for sperm concentration, motility, and morphology to help classify men as fertile or subfertile (15). The semen parameters of men with documented fertility have been compared with those of infertile men among couples participating in a clinical trial of superovulation and intrauterine insemination (IUI). Sperm parameters that predicted male fertility were sperm concentration >48 million/mL, sperm motility >63%, and sperm morphology >12% normal (strict criteria). Parameters that predicted male subfertility were sperm concentration <13.5 million sperm/mL, sperm motility <32%, and sperm morphology <9% normal. Values between the fertile and subfertile thresholds were considered to be "indeterminate" (16). Although each sperm parameter could predict fertility and subfertility, none was a powerful discriminator. It is important to emphasize that normal reference values for semen parameters do not reflect normal sperm concentration in the general population, nor do they equate with the minimum values required for conception; men with semen variables outside the reference ranges may be fertile, and conversely, men having values within the reference range still may be infertile.

COMPONENTS OF A COMPLETE EVALUATION FOR MALE INFERTILITY

When the initial screening evaluation reveals an abnormal male reproductive history or demonstrates abnormal semen parameters, a thorough evaluation by a urologist or other specialist in male reproduction is indicated. More detailed evaluation of the male partner should be considered also in couples with unexplained infertility and those who remain infertile after successful treatment of identified female infertility factors.

The more thorough evaluation for male infertility should expand on the screening evaluation by including a complete medical history and physical examination performed by a urologist or other specialist in male reproduction. Based on the results obtained, additional tests and procedures may be recommended, including serial semen analyses, endocrine evaluation, post-ejaculatory urinalysis, ultrasonography, specialized tests on semen and sperm, and genetic screening.

Medical History

The patient's medical history can identify risk factors and behaviors or lifestyles that could have significant impact on male infertility. In addition to all of the elements of the reproductive history described above, the medical history should be expanded to include: 1) a complete review of systems; 2) family reproductive history; and 3) a detailed social history, including any past or current use of anabolic steroids, recreational drugs, tobacco, and alcohol.

Physical Examination

A general physical examination is an integral part of the evaluation of infertile men. Particular attention should be directed to the genitalia, including: 1) examination of the penis, noting the location of the urethral meatus; 2) palpation and

---

TABLE 1

Lower limits of the accepted reference values for semen analysis.

Parameter	Reference value
On at least two occasions	
Ejaculate volume	1.5 mL
pH	7.2
Sperm concentration	15×10^6 spermatozoa/mL
Total sperm number	39×10^6 spermatozoa/ejaculate
Percentage motility	40%
Forward progression	32%
Normal morphology	4% normal
And	
Sperm agglutination	Absent
Viscosity	≤2 cm thread after liquefaction

Note: Data from World Health Organization, 2010 (10).

Practice Committee. Evaluation of the infertile male. Fertil Steril 2015.

---

measurement of the testes; 3) the presence and consistency of both vasa and epididymides; 4) the presence or absence of a varicocele; 5) secondary sex characteristics, including body habitus, hair distribution, and breast development; and 6) digital rectal examination where indicated. The diagnosis of congenital bilateral absence of the vasa deferentia (CBAVD) is established by physical examination; scrotal exploration is unnecessary.

OTHER PROCEDURES AND TESTS FOR ASSESSING MALE INFERTILITY
Endocrine Evaluation

Hormonal abnormalities of the hypothalamic-pituitary-testicular axis are well recognized, but uncommon, causes of male infertility. Endocrine disorders are extremely uncommon in men with normal semen parameters.

An endocrine evaluation is indicated for men having: 1) abnormal semen parameters, particularly when the sperm concentration is <10 million/mL; 2) impaired sexual function; or 3) other clinical findings that suggest a specific endocrinopathy. Some experts think that all infertile men merit an endocrine evaluation, but there is no established consensus of opinion. The minimum initial hormonal evaluation should include measurement of serum FSH and total testosterone (T) concentrations. When the total T level is low (<300 ng/mL), more extensive evaluation is indicated and should include a second early morning measurement of total T and measurements of serum free testosterone (T), LH, and prolactin (PRL). Although serum gonadotropin concentrations vary because they are secreted in a pulsatile manner, a single measurement usually is sufficient to determine the clinical endocrine status. The relationships among serum T, LH, follicle-stimulating hormone (FSH), and PRL concentrations help to provide an understanding of the source of abnormal total T levels (Table 2). Whereas many men with abnormal spermatogenesis have a normal serum FSH level, a markedly elevated serum FSH concentration clearly indicates an abnormality in spermatogenesis. In individuals with an FSH level in the upper normal range, there may be impaired spermatogenesis as well. Measurement of the thyroid-stimulating hormone (TSH) concentration also should be obtained in men who require a more thorough endocrine evaluation.

Serum inhibin B concentration has been proposed as a marker for spermatogenesis. Inhibin B levels are significantly lower in infertile men than in fertile men and correlate better than FSH levels with sperm parameters (17). Given the significantly greater cost of measuring inhibin B, FSH currently remains the preferred test for screening purposes.

Post-ejaculatory Urinalysis

A low-volume or absent antegrade ejaculate suggests incomplete semen collection, retrograde ejaculation, lack of emission, ejaculatory duct obstruction, hypogonadism, or CBAVD. To exclude retrograde ejaculation, a post-ejaculatory urinalysis should be performed in men having an ejaculate volume <1.0 mL, except in those diagnosed with hypogonadism or CBAVD. It is important also to determine whether an improper or incomplete collection or a very short abstinence interval (<1 day) might be the cause.

The post-ejaculatory urinalysis is performed by centrifuging the urine specimen for 10 minutes at 300g, followed by microscopic examination of the pellet at ×400 magnification. In men with azoospermia or aspermia, the presence of any sperm in the post-ejaculatory urinalysis suggests retrograde ejaculation. In men with low ejaculate volume and oligozoospermia, "significant numbers" of sperm must be observed to support the diagnosis of retrograde ejaculation; there is no consensus of expert opinion on the minimum number required (18).

Ultrasonography

Because nearly the entire male genital tract can be imaged easily and accurately, ultrasonography is a useful tool for detecting abnormalities of the male genital tract that may adversely affect fertility. However, ultrasonography is indicated for only a minority of infertile male patients.

Transrectal ultrasonography. Normal seminal vesicles are usually <1.5 cm in anteroposterior diameter (19). Transrectal ultrasonography (TRUS) revealing dilated seminal vesicles or ejaculatory ducts and/or midline cystic prostatic structures suggests, but does not by itself establish, the diagnosis of complete or partial ejaculatory duct obstruction (20). Affected men typically produce a low-volume acidic ejaculate containing no sperm or fructose. Men with CBAVD may exhibit similar findings because they often have absent or atrophic seminal vesicles. Men with partial ejaculatory duct obstruction often, but not always, exhibit low semen volume, oligoasthenospermia, and poor progressive motility. Some experts recommend routine TRUS for oligospermic men having low-volume ejaculates, palpable vasa, and normal

---

TABLE 2

Basal hormone levels in various clinical states.

Clinical condition	FSH	LH	T	PRL
Normal spermatogenesis	Normal	Normal	Normal	Normal
Hypogonadotropic hypogonadism	Low	Low	Low	Normal
Abnormal spermatogenesis[a]	High/normal	Normal	Normal	Normal
Complete testicular failure/hypergonadotropic hypogonadism	High	High	Normal/low	Normal
PRL-secreting pituitary tumor	Normal/low	Normal/low	Low	High

[a] Many men with abnormal spermatogenesis have a normal serum FSH, but a marked elevation of serum FSH is clearly indicative of an abnormality in spermatogenesis.

Practice Committee. Evaluation of the infertile male. Fertil Steril 2015.

testicular size with normal serum T, although there is no consensus on this.

Scrotal ultrasonography. Careful physical examination can identify most scrotal pathology, including varicoceles, spermatoceles, absent vasa, epididymal induration, and testicular masses. Scrotal ultrasonography can identify occult varicoceles that are not palpable, but such lesions have no demonstrated clinical significance (21). Scrotal ultrasonography can be helpful for better defining vague or ambiguous physical examination findings or abnormalities (including apparent masses) and can be performed in men having testes located in the upper scrotum, a small scrotal sac, or other anatomy that hinders physical examination. Scrotal ultrasonography should also be considered for men presenting with infertility and risk factors for testicular cancer, such as cryptorchidism or a previous testicular neoplasm, but not as a routine screening procedure.

Specialized Clinical Tests on Semen and Sperm

In some cases, semen analyses have failed to predict fertility accurately, spurring a search for other methods that might improve the diagnostic evaluation of the infertile man. Generally, such specialized clinical tests should be reserved for circumstances where results would clearly help to direct treatment.

Quantification of Leukocytes in Semen

Increased numbers of white blood cells in semen have been associated with deficiencies in sperm function and motility. Under wet-mount microscopy, leukocytes and immature germ cells appear quite similar and are properly called "round cells." Unfortunately, many laboratories improperly report all round cells as "white blood cells," and in men with such findings, the clinician must ensure that the two types of cells are differentiated. A number of methods are available to distinguish leukocytes from immature germ cells, including traditional cytologic staining and immunohistochemical techniques (22). Men with true pyospermia (>1 million leukocytes/mL) should be specifically evaluated to exclude genital tract infection or inflammation.

Tests for Antisperm Antibodies

Antisperm antibodies (ASA) are a rare cause of male subfertility that do not require routine testing and are typically managed with the use of ICSI. Testing for ASA has historically been done when the semen analysis reveals isolated asthenospermia (with normal sperm concentration) or sperm agglutination. ASAs can be found in the serum, in the seminal plasma, or bound directly to sperm. ASAs can form when there is a breach in the blood-testis barrier and the immune system is exposed to large quantities of sperm antigens or after vasectomy. Risk factors for ASA formation include trauma, torsion, biopsy, orchitis, testicular cancer, and vasectomy. Whereas indirect antibody agglutination assays are used to detect ASA in serum or seminal plasma, a direct immunobead test is used to detect ASA (IgG and IgA) bound to the sperm head or tail. Sperm-bound antibodies are thought to be clinically important because they can decrease motility,

block penetration of the cervical mucus, and prevent fertilization, thereby decreasing the likelihood for conception (23). Although some have suggested ASA testing for couples with unexplained infertility, the clinical utility of the test in such couples is uncertain, and ASA testing is unnecessary if ICSI is planned (24). One recent study has suggested that detection of serum ASA correlates with the presence of spermatogenesis in men with azoospermia and can obviate the need for diagnostic testicular biopsy to help determine whether obstruction is present (25). Men with azoospermia and ASA are likely to have reproductive tract obstruction. Otherwise, routine testing for ASA is not indicated.

Sperm Viability Tests

Sperm viability can be assessed by mixing fresh semen with a supravital dye, such as eosin Y or trypan blue, or by the use of the hypoosmotic swelling (HOS) test (10). These assays determine whether nonmotile sperm are viable by identifying which sperm have intact cell membranes. In dye tests, viable sperm actively exclude the dye and remain colorless whereas nonviable sperm readily take up the stain. Unfortunately, sperm judged to be viable by means of dye tests can not be used for IVF. In the HOS test, viable nonmotile sperm, which swell when incubated in a hypoosmotic solution, can be used successfully for ICSI (26). Viable nonmotile sperm can also be identified by means of incubation in pentoxifylline. Viable sperm will develop motility after exposure to pentoxifylline (27).

Sperm Deoxyribonucleic Acid (DNA) Fragmentation Tests

DNA integrity is important for normal embryo development. Sperm DNA integrity is maintained in part by the effect of disulfide cross-links between protamines that allow for the compaction of chromatin in the nucleus. Sperm DNA damage can occur as a result of intrinsic factors, such as protamine deficiency and mutations affecting DNA compaction, or from extrinsic factors, such as heat, radiation, and gonadotoxins. The term "DNA fragmentation" refers to denatured or damaged sperm DNA that can not be repaired. A number of clinical tests have been developed to measure sperm DNA fragmentation rates. Direct methods, such as the single-cell gel electrophoresis assay (Comet) and terminal deoxynucleotide transferase–mediated dUTP nick-end labeling (TUNEL) assays, specifically analyze the number of breaks in the DNA. Indirect tests, such as the sperm chromatin structure assay (SCSA), define abnormal chromatin structure as an increased susceptibility of sperm DNA to acid-induced denaturation in situ (28). Threshold values used to define an abnormal test are $\geq$25%–27% for the SCSA (29) and $\geq$36% for TUNEL assays (30).

Sperm DNA damage is more common in infertile men and may contribute to poor reproductive performance in some couples. Sperm DNA damage is also associated with spontaneous recurrent miscarriage. However, existing data relating to the relationship between abnormal DNA integrity and reproductive outcomes are too limited to routinely

recommend any of these tests for the male partner in an infertile couple, but the effect of abnormal sperm DNA fragmentation on the value of IUI or IVF and ICSI results may be clinically informative (31). Although no treatment for abnormal DNA integrity has been proven to have clinical value, varicocele repair and antioxidant use may affect sperm DNA integrity. Sperm retrieved from the testis tend to have better sperm DNA quality in men with abnormal ejaculated sperm DNA integrity (32). Because the prognostic clinical value of DNA integrity testing may not affect the treatment of couples, the routine use of DNA integrity tests in the clinical evaluation of male-factor infertility is controversial (33).

Less Commonly Used Specialized Tests

Numerous other tests of sperm function have been used predominantly in research studies. Sperm penetration assays may detect defects in sperm fertilizing capacity and could identify patients who would benefit from application of ICSI. However, because ICSI is routinely used during IVF for male-factor infertility couples, this test is rarely of any clinical value. The acrosome reaction of human sperm can be detected with the use of specialized staining techniques. Rates of spontaneous acrosome reactions and acrosome reactions induced by agents such as calcium ionophore and progesterone have been measured. Sperm from infertile men tend to demonstrate higher acrosome levels spontaneously but lower levels in the presence of inducers (34). A number of biochemical tests of sperm function have been studied, including measurements of sperm creatine kinase (35) and reactive oxygen species (ROS). ROS appear to be generated by both seminal leukocytes and sperm cells and can interfere with sperm function by peroxidation of sperm lipid membranes and creation of toxic fatty acid peroxides (36). Other tests and procedures have been used to select sperm for ICSI and may identify gametes with better quality, including hyaluronic acid binding, membrane maturity testing, apoptotic evaluation, and magnified sperm examination (37). However, these tests have a very limited role in the evaluation of male infertility because they have limited clinical utility and typically do not affect treatment.

Genetic Screening

Genetic abnormalities can cause infertility by affecting sperm production or sperm transport. Men with nonobstructive azoospermia or severe oligozoospermia (<5 million/mL) are at increased risk for having a genetic abnormality compared to fertile men (38). The most common genetic abnormalities found in such men are numeric and structural chromosomal aberrations that impair testicular function and Y-chromosome microdeletions that are associated with isolated defects in spermatogenesis. In addition, most men with CBAVD can be assumed to have an abnormality of the cystic fibrosis transmembrane conductance regulator (CFTR) gene. When indicated, efforts to identify genetic causes for infertility can have a major impact on the choice and outcome of treatment.

Cystic fibrosis gene mutations. There is a strong association between CBAVD and mutations of the CFTR gene, which is located on chromosome 7 (39). Almost all men with clinical cystic fibrosis exhibit CBAVD. Additionally, as many as 80% of men with CBAVD have documented mutations of the CFTR gene. Failure to detect a CFTR abnormality in men with CBAVD does not exclude the presence of a mutation that cannot be identified with currently available methods. Therefore, most men with CBAVD should be assumed to have a CFTR gene mutation unless they have renal anomalies. To determine the risk of conceiving a child affected with cystic fibrosis, it is important to test the female partner of an affected man. Even if the female partner is negative according to currently available testing, the couple remains at some risk because some of the less common mutations may be missed unless the entire gene is sequenced.

The prevalence of CFTR mutations is also increased among men with azoospermia related to congenital bilateral obstruction of the epididymides and those with unilateral vasa agenesis. Consequently, genetic evaluation should be considered for those having either abnormality. Some men presenting with either unilateral or bilateral vasal agenesis and unilateral renal agenesis have the mesonephric duct abnormalities associated with hereditary renal adysplasia, which has an autosomal dominant form of inheritance with incomplete penetrance and variable expression. These patients do not have CFTR mutations and require genetic counseling before IVF (40, 41).

Karyotypic chromosomal abnormalities. The prevalence of chromosomal abnormalities is increased in infertile men and inversely proportional to sperm count; the prevalence is 10%–15% in azoospermic men (42), ~5% in men with severe oligozoospermia (<5 million/mL), and <1% in men with normal sperm concentrations (43). Sex chromosomal aneuploidy (Klinefelter syndrome; 47,XXY) accounts for about two thirds of all chromosomal abnormalities observed in infertile men (44). The prevalence of structural autosomal abnormalities, such as inversions and balanced translocations, also is higher in infertile men than in the general population (45). Rare azoospermic men may be found to have the 46,XX disorder of sexual development resulting from translocation of sex-determining region Y (SRY) to one of their X chromosomes. Couples in which the male partner has a gross karyotypic abnormality are at increased risk for miscarriages and for having children with chromosomal and congenital defects. Therefore, men with nonobstructive azoospermia or severe oligozoospermia should be evaluated with a high-resolution karyotype before using their sperm to perform ICSI.

Y-chromosome microdeletions. Microdeletions of clinically relevant regions of the Y chromosome have been found in 7% of infertile men with severely impaired spermatogenesis, compared with 2% of normal men. However, the percentage of men with Y-chromosome microdeletions increases to 16% in men with azoospermia or severe oligozoospermia (46). Such microdeletions are too small to be detected by standard karyotyping, but they can be identified with the use of polymerase chain reaction techniques to analyze sequence-tagged sites that have been mapped along the entire length of the Y chromosome.

Most deletions causing azoospermia or oligozoospermia occur in regions of the long arm of the Y chromosome

(Yq11) known as the azoospermia factor (AZF) regions, designated as AZFa (proximal), AZFb (central), and AZFc (distal). It appears that these regions, and possibly other regions of the Y chromosome, contain multiple genes necessary for spermatogenesis. For example, the DAZ (deleted in azoospermia) gene, which encodes a transcription factor usually present in men with normal fertility, is located in the AZFc region.

The specific location of the deletion along the Y chromosome influences its effect on spermatogenesis. Many men with a microdeletion in the AZFc region of the Y chromosome have severe oligozoospermia. Others with AZFc region deletions are azoospermic but may still produce sufficient numbers of sperm to allow testicular sperm extraction. Sperm production in such men appears to be stable over time, and the results of ICSI are not affected adversely by the AZFc deletion (47). In contrast, deletions involving the entire AZFb region appear to predict a very poor prognosis for sperm retrieval (48). The same may be true for men having deletions involving the entire AZFa region of the Y chromosome (49).

Sons of individuals with Y-chromosome microdeletions will inherit the abnormality and, therefore, may also be infertile (50). Although a microdeletion of the Y chromosome is not known to be associated with other health problems, few data exist regarding the phenotypes of the sons of fathers with such genetic abnormalities. A recent report showed that some men with Y-chromosome microdeletions had abnormalities of the pseudoautosomal regions (PARs) of the Y chromosome. Although most of these men had some sperm production, 16% of men had genetic aberrations of the short-stature-homeo-box (SHOX) gene, the best known gene in PAR1. SHOX gene abnormalities are associated with short stature, mental retardation, and arm and wrist deformities (51). It is important to note that a negative Y-chromosome microdeletion test result does not necessarily exclude a genetic abnormality, because there may be other, currently unknown, gene sequences on the Y or other chromosomes that also might be required for normal spermatogenesis. Conversely, some Y-chromosome microdeletions are rarely found in fertile or subfertile males who have fathered children (46, 52). Y-Chromosome analysis should be offered to men who have nonobstructive azoospermia or severe oligozoospermia before performing ICSI with their sperm.

SPERM CHROMOSOME ANEUPLOIDY

Sperm DNA aneuploidy can be assessed by fluorescent in situ hybridization technology (53). One study has reported that up to 6% of men presenting with infertility and a normal karyotype had an increased frequency of meiotic alterations detectable in their sperm (54). Men with the highest risk of sperm aneuploidy are those with karyotypic abnormalities, severely abnormal sperm morphology, and nonobstructive azoospermia (53). Patients with recurrent pregnancy loss and recurrent IVF failure also may benefit from sperm aneuploidy testing (55, 56). Currently, limitations to the routine use of this technology include cost, inability to screen the actual sperm used in ICSI, and difficulty of assigning a meaningful risk assessment to couples based on the test results (57).

SUMMARY

Men with nonobstructive azoospermia or severe oligozoospermia (<5 million/mL) are at increased risk for having a definable genetic abnormality and should be offered karyotype and Y-chromosome analysis before performing ICSI with their sperm. Genetic counseling may be offered when a genetic abnormality is suspected in either the male or the female partner and should be provided whenever a genetic abnormality is detected.

CONCLUSION

An initial screening evaluation of the male partner of an infertile couple is indicated when pregnancy has not occurred after 12 months of unprotected intercourse or after 6 months of failure to conceive when the female partner is >35 years old. Earlier evaluation may be warranted when medical history and physical findings indicate or suggest specific male or female infertility risk factors and for men who question their reproductive potential.

A thorough evaluation by a urologist or other specialist in male reproduction, including a complete medical and reproductive history and physical examination, should be performed if the initial screening evaluation reveals an abnormal male reproductive history or demonstrates abnormal semen parameters. Additional tests aimed at defining the cause may be required.

REFERENCES

1. Stephen EH, Chandra A. Declining estimates of infertility in the United States: 1982–2002. Fertil Steril 2006;86:516–23.

2. Thonneau P, Marchand S, Tallec A, Ferial ML, Ducot B, Lansac J, et al. Incidence and main causes of infertility in a resident population (1,850,000) of three French regions (1988–1989). Hum Reprod 1991;6:811–6.

3. Honig SC, Lipshultz LI, Jarow J. Significant medical pathology uncovered by a comprehensive male infertility evaluation. Fertil Steril 1994;62:1028–34.

4. Practice Committee of the American Society for Reproductive Medicine. Definitions of infertility and recurrent pregnancy loss. Fertil Steril 2013; 99:63.

5. Marshburn PB, Alanis M, Matthews ML, Usadi R, Papadakis MH, Kullstam S, et al. A short period of ejaculatory abstinence before intrauterine insemination is associated with higher pregnancy rates. Fertil Steril 2010;93:286–8.

6. Jurema MW, Vieira AD, Bankowski B, Petrella C, Zhao Y, Wallach E, et al. Effect of ejaculatory abstinence period on the pregnancy rate after intrauterine insemination. Fertil Steril 2005;84:678–81.

7. Raziel A, Friedler S, Schachter M, Kaufman S, Omanski A, Soffer Y, et al. Influence of a short or long abstinence period on semen parameters in the ejaculate of patients with nonobstructive azoospermia. Fertil Steril 2001; 76:485–90.

8. Centers for Medicare and Medicaid Services. Clinical laboratory improvement amendments. Available at: http://www.cms.hhs.gov/CLIA/. Accessed November 2014.

9. World Health Organization. WHO laboratory manual for the examination of human semen and sperm–cervical mucus interaction. 3rd ed. New York: Cambridge University Press; 1992.

10. World Health Organization. WHO laboratory manual for the examination and processing of human semen. Available at: http://whqlibdoc.who.int/publications/2010/9789241547789_eng.pdf; 2010. Accessed November 2014.

11. Kruger TF, Acosta AA, Simmons KF, Swanson RJ, Matta JF, Oehninger S. Predictive value of abnormal sperm morphology in in vitro fertilization. Fertil Steril 1988;49:112–7.

12. Menkveld R, Stander FS, Kotze TJ, Kruger TF, van Zyl JA. The evaluation of morphological characteristics of human spermatozoa according to stricter criteria. Hum Reprod 1990;5:586–92.

13. Pisarska MD, Casson PR, Cisneros PL, Lamb DJ, Lipshultz LI, Buster JE, et al. Fertilization after standard in vitro fertilization versus intracytoplasmic sperm injection in subfertile males using sibling oocytes. Fertil Steril 1999;71:627–32.

14. Keegan BR, Barton S, Sanchez X, Berkeley AS, Krey LC, Grifo J. Isolated teratozoospermia does not affect in vitro fertilization outcome and is not an indication for intracytoplasmic sperm injection. Fertil Steril 2007;88:1583–8.

15. Cooper TG, Noonan E, von Eckardstein S, Auger J, Baker HW, Behre HM, et al. World Health Organization reference values for human semen characteristics. Hum Reprod Update 2010;16:231–45.

16. Guzick DS, Overstreet JW, Factor-Litvak P, Brazil CK, Nakajima ST, Coutifaris C, et al. Sperm morphology, motility, and concentration in fertile and infertile men. N Engl J Med 2001;345:1388–93.

17. Kumanov P, Nandipati K, Tomova A, Agarwal A. Inhibin B is a better marker of spermatogenesis than other hormones in the evaluation of male factor infertility. Fertil Steril 2006;86:332–8.

18. Mehta A, Jarow JP, Maples P, Sigman M. Defining the "normal" postejaculate urinalysis. J Androl 2012;33:917–20.

19. Carter SS, Shinohara K, Lipshultz LI. Transrectal ultrasonography in disorders of the seminal vesicles and ejaculatory ducts. Urol Clin North Am 1989;16: 773–90.

20. Jarow JP. Transrectal ultrasonography of infertile men. Fertil Steril 1993;60: 1035–9.

21. Practice Committee of the American Society for Reproductive Medicine. Report on varicocele and infertility. Fertil Steril 2014;102:1556–60.

22. Wolff H, Anderson DJ. Immunohistologic characterization and quantitation of leukocyte subpopulations in human semen. Fertil Steril 1988;49:497–504.

23. Ayvaliotis B, Bronson R, Rosenfeld D, Cooper G. Conception rates in couples where autoimmunity to sperm is detected. Fertil Steril 1985;43:739–42.

24. Check ML, Check JH, Katsoff D, Summers-Chase D. ICSI as an effective therapy for male factor with antisperm antibodies. Arch Androl 2000;45: 125–30.

25. Lee R, Goldstein M, Ullery BW, Ehrlich J, Soares M, Razzano RA, et al. Value of serum antisperm antibodies in diagnosing obstructive azoospermia. J Urol 2009;181:264–9.

26. Liu J, Tsai YL, Katz E, Compton G, Garcia JE, Baramki TA. High fertilization rate obtained after intracytoplasmic sperm injection with 100% nonmotile spermatozoa selected by using a simple modified hypo-osmotic swelling test. Fertil Steril 1997;68:373–5.

27. de Mendoza MV, Gonzalez-Utor AL, Cruz N, Gutierrez P, Cascales F, Sillero JM. In situ use of pentoxifylline to assess sperm vitality in intracytoplasmic sperm injection for treatment of patients with total lack of sperm movement. Fertil Steril 2000;74:176–7.

28. Evenson DP, Jost LK, Marshall D, Zinaman MJ, Clegg E, Purvis K, et al. Utility of the sperm chromatin structure assay as a diagnostic and prognostic tool in the human fertility clinic. Hum Reprod 1999;14:1039–49.

29. Larson-Cook KL, Brannian JD, Hansen KA, Kasperson KM, Aamold ET, Evenson DP. Relationship between the outcomes of assisted reproductive techniques and sperm DNA fragmentation as measured by the sperm chromatin structure assay. Fertil Steril 2003;80:895–902.

30. Henkel R, Hajimohammad M, Stalf T, Hoogendijk C, Mehnert C, Menkveld R, et al. Influence of deoxyribonucleic acid damage on fertilization and pregnancy. Fertil Steril 2004;81:965–72.

31. Collins JA, Barnhart KT, Schlegel PN. Do sperm DNA integrity tests predict pregnancy with in vitro fertilization? Fertil Steril 2008;89:823–31.

32. Greco E, Scarselli F, Iacobelli M, Rienzi L, Ubaldi F, Ferrero S, et al. Efficient treatment of infertility due to sperm DNA damage by ICSI with testicular spermatozoa. Hum Reprod 2005;20:226–30.

33. Practice Committee of the American Society for Reproductive Medicine. The clinical utility of sperm DNA integrity testing: a guideline. Fertil Steril 2013; 99:673–7.

34. Fenichel P, Donzeau M, Farahifar D, Basteris B, Ayraud N, Hsi BL. Dynamics of human sperm acrosome reaction: relation with in vitro fertilization. Fertil Steril 1991;55:994–9.

35. Huszar G, Vigue L, Morshedi M. Sperm creatine phosphokinase M-isoform ratios and fertilizing potential of men: a blinded study of 84 couples treated with in vitro fertilization. Fertil Steril 1992;57:882–8.

36. Kim JG, Parthasarathy S. Oxidation and the spermatozoa. Semin Reprod Endocrinol 1998;16:235–9.

37. Said TM, Land JA. Effects of advanced selection methods on sperm quality and ART outcome: a systematic review. Hum Reprod Update 2011;17: 719–33.

38. Foresta C, Garolla A, Bartoloni L, Bettella A, Ferlin A. Genetic abnormalities among severely oligospermic men who are candidates for intracytoplasmic sperm injection. J Clin Endocrinol Metab 2005;90:152–6.

39. Anguiano A, Oates RD, Amos JA, Dean M, Gerrard B, Stewart C, et al. Congenital bilateral absence of the vas deferens. A primarily genital form of cystic fibrosis. JAMA 1992;267:1794–7.

40. McCallum T, Milunsky J, Munarriz R, Carson R, Sadeghi-Nejad H, Oates R. Unilateral renal agenesis associated with congenital bilateral absence of the vas deferens: phenotypic findings and genetic considerations. Hum Reprod 2001;16:282–8.

41. McPherson E, Carey J, Kramer A, Hall JG, Pauli RM, Schimke RN, et al. Dominantly inherited renal adysplasia. Am J Med Genet 1987;26:863–72.

42. van Assche E, Bonduelle M, Tournaye H, Joris H, Verheyen G, Devroey P, et al. Cytogenetics of infertile men. Hum Reprod 1996;11(Suppl 4):1–25.

43. Ravel C, Berthaut I, Bresson JL, Siffroi JP. Genetics Commission of the French Federation of CECOS. Prevalence of chromosomal abnormalities in phenotypically normal and fertile adult males: large-scale survey of over 10,000 sperm donor karyotypes. Hum Reprod 2006;21:1484–9.

44. de Braekeleer M, Dao TN. Cytogenetic studies in male infertility: a review. Hum Reprod 1991;6:245–50.

45. Debiec-Rychter M, Jakubowski L, Truszczak B, Moruzgala T, Kaluzewski B. Two familial 9;17 translocations with variable effect on male carriers fertility. Fertil Steril 1992;57:933–5.

46. Pryor JL, Kent-First M, Muallem A, Van Bergen AH, Nolten WE, Meisner L, et al. Microdeletions in the Y chromosome of infertile men. N Engl J Med 1997;336:534–9.

47. Oates RD, Silber S, Brown LG, Page DC. Clinical characterization of 42 oligo-spermic or azoospermic men with microdeletion of the AZFc region of the Y chromosome, and of 18 children conceived via ICSI. Hum Reprod 2002;17: 2813–24.

48. Brandell RA, Mielnik A, Liotta D, Ye Z, Veeck LL, Palermo GD, et al. AZFb deletions predict the absence of spermatozoa with testicular sperm extraction: preliminary report of a prognostic genetic test. Hum Reprod 1998;13:2812–5.

49. Krausz C, Quintana-Murci L, McElreavey K. Prognostic value of Y deletion analysis: what is the clinical prognostic value of Y chromosome microdeletion analysis? Hum Reprod 2000;15:1431–4.

50. Kent-First MG, Kol S, Muallem A, Ofir R, Manor D, Blazer S, et al. The incidence and possible relevance of Y-linked microdeletions in babies born after intracytoplasmic sperm injection and their infertile fathers. Mol Hum Reprod 1996;2:943–50.

51. Jorgez CJ, Weedin JW, Sahin A, Tannour-Louet M, Han S, Bournat JC, et al. Aberrations in pseudoautosomal regions (PARs) found in infertile men with Y-chromosome microdeletions. J Clin Endocrinol Metab 2011;96:E674–9.

52. Kent-First M, Muallem A, Shultz J, Pryor J, Roberts K, Nolten W, et al. Defining regions of the Y-chromosome responsible for male infertility and identification of a fourth AZF region (AZFd) by Y-chromosome microdeletion detection. Mol Reprod Dev 1999;53:27–41.

53. Carrell DT. The clinical implementation of sperm chromosome aneuploidy testing: pitfalls and promises. J Androl 2008;29:124–33.

54. Egozcue S, Blanco J, Vendrell JM, Garcia F, Veiga A, Aran B, et al. Human male infertility: chromosome anomalies, meiotic disorders, abnormal spermatozoa and recurrent abortion. Hum Reprod Update 2000;6:93–105.

55. Carrell DT, Wilcox AL, Lowy L, Peterson CM, Jones KP, Erickson L, et al. Elevated sperm chromosome aneuploidy and apoptosis in patients with unexplained recurrent pregnancy loss. Obstet Gynecol 2003;101:1229–35.

56. Petit FM, Frydman N, Benkhalifa M, Le Du A, Aboura A, Fanchin R, et al. Could sperm aneuploidy rate determination be used as a predictive test before intracytoplasmic sperm injection? J Androl 2005;26:235–41.

57. Tempest HG, Martin RH. Cytogenetic risks in chromosomally normal infertile men. Curr Opin Obstet Gynecol 2009;21:223–7.