Counseling and Diagnostic Evaluation for the Infertile Couple

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KEYWORDS

- Infertility counseling • Optimizing natural fertility • Ovarian reserve testing
- Ovulatory dysfunction • Obstructive and nonobstructive male factor infertility
- Genetic causes of male factor infertility

KEY POINTS

- Proper counseling about the natural means to improve fertility should include a discussion about appropriate timing to initiate a diagnostic evaluation for infertility.
- Diagnostic evaluation of the infertile couple is best outlined by discussing the steps necessary for conception.
- Both male and female infertility factors should be investigated simultaneously to optimize all abnormalities for the best pregnancy outcomes.
- Coordination between gynecologists, reproductive endocrinologists, male reproductive urologists, and genetic counselors can be critical for conducting comprehensive diagnostic testing and determine safe and effective treatment options.

INTRODUCTION

Infertility is defined as a lack of pregnancy after 12 months of unprotected sexual intercourse with the same partner. The National Survey of Family Growth (NSFG) conducted by the Centers for Disease Control and Prevention indicates that, in the United States, the proportion of women aged 15 to 44 years who had ever accessed infertility care increased from 9% to 15% between 1982 and 1995, and then stabilized at 12% through 2010.[1,2] The upward trend in the rate for seeking infertility care most likely involves the decline in natural fertility with female age, an increased incidence of sexually transmitted infections, higher exposure to environmental toxins, and lifestyle factors such as smoking and obesity.

An estimated 75% of infertile couples will achieve conception after evaluation and treatment for infertility.[3] The success of therapeutic interventions depends on proper counseling and diagnostic evaluation of the infertile couple.

The author has nothing to disclose.
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Obstet Gynecol Clin N Am 42 (2015) 1–14
http://dx.doi.org/10.1016/j.ogc.2014.10.001 **obgyn.theclinics.com**
0889-8545/15/$ – see front matter

COUNSELING THE INFERTILE COUPLE

Initial counseling of infertile couples can naturally enhance their chance for conception and will dispel myths about unproven practices. Approximately 85% of couples should expect to become pregnant within 12 months of unprotected intercourse. Although the chance for pregnancy will be highest in the first 3 months, approximately 80% of couples destined to become pregnant within 1 year will achieve this goal by 6 months.[4] Women who are 35 to 40 years of age will have approximately one-half the cycle fecundity of women between 20 and 30 years of age.[5,6] Thus, earlier infertility evaluation is warranted after 6 months of unsuccessful efforts to conceive in women aged 35 years and older.[7] An infertility diagnostic evaluation does not need to be delayed in the presence of obvious menstrual irregularity, persistent sexual dysfunction, history of pelvic inflammatory disease, previous cancer chemotherapy, or male factor issues, including prior use of anabolic steroids or genital surgery.

NATURAL MEANS FOR ENHANCING CONCEPTION

The optimal frequency of intercourse during the fertile window is every 3 days or less and may begin 5 days before ovulation.[8] The male partner does not need to have ejaculatory abstinence for greater than 2 days in the periovulatory period, and in fact abstinence for greater than 5 days may adversely affect sperm quality.[9] In men with low sperm densities, daily ejaculation can actually increase sperm count.[10]

No evidence shows that the use of methods to predict ovulation increases the chance for conception in couples able to have regular intercourse. Ovulation predictor methods may produce false-positive and false-negative readings.[11] Of all the methods for ovulation detection, peak cervical mucus production predicts the fertile window more accurately than basal body temperature graphing, urinary luteinizing hormone (LH) monitoring, and use of a menstrual calendar.[12] If these methods are improperly performed or applied, they could actually impair fertility by causing couples to miss the timing for their fertile window.

Coital method or positioning for intercourse also has no apparent effect on conception rates. Women may remain supine or elevate their hips after intercourse to prevent the loss of semen from the vagina, but these practices have no benefit. Sperm can be found in the fallopian tubes within 15 minutes after intercourse around the time of ovulation.[13] Personal lubricants such as mineral oil, canola oil, or hydroxyethylcellulose-based lubricants have no known detrimental effect on sperm viability, whereas water-based lubricants such as K-Y or Astroglide have been shown to inhibit sperm motility in vitro.[14]

LIFESTYLE CONSIDERATIONS

Obesity is associated with ovulatory dysfunction, insulin resistance, and lower pregnancy rates after in vitro fertilization (IVF). Weight reduction of 10% to 15% of total body weight can improve ovulation rates and reduce the incidence of comorbid associations, such as hypertension and adult-onset diabetes mellitus, which as both risk factors for pregnancy complications. Women should be adequately supplementing their diet with 400 mcg of folate.[15] No specific dietary supplement for men or women has been proven to enhance fertility, but research remains active in this area.

Tobacco smoking has a detrimental impact on fertility and increases the risk of miscarriage.[16,17] Heavy use of alcohol should be avoided when attempting pregnancy, but an adverse effect of modest alcohol consumption (1 drink per day) on conception

has not been proven. Caffeine consumption at the equivalent of 1 to 2 cups of coffee per day has no known negative effect on fertility when consumed by men or women.[18]

HISTORY AND PHYSICAL EXAMINATION OF THE WOMAN IN THE INFERTILE COUPLE

A discussion of the process of reproduction and conception will help the infertile couple understand the basis for diagnostic testing. A helpful construct is to discuss the infertility evaluation with regard to (1) ovarian factors, (2) abnormalities of the pelvic organ anatomy and function, and (3) the male factor. In at least one-third of couples, more than 1 potential cause for the infertility will be detected, and in approximately 20% of couples baseline testing will show no abnormality.

A preconception evaluation should include comprehensive medical, reproductive, and family history, along with discussion of genetic carrier screening. Secondary infertility should prompt careful attention to acquired conditions, including the outcome and complications of prior pregnancies, possible adhesions from interval pelvic surgery, endometriosis, and sexually transmitted infections. Records of prior infertility testing and treatment will help save time and resources. **Table 1** provides a summary of relevant historical points for assessing ovarian factors and abnormalities of the pelvic organ anatomy recommended by the American Society for Reproductive Medicine.[19]

THE EVALUATION OF OVARIAN FACTORS

An investigation for ovarian factors should include an evaluation of the regularity of ovulation and an assessment of ovarian reserve. Ovulatory dysfunction accounts for up to 40% of female factor infertility.[20] Obvious menstrual irregularity indicates a frequency of ovulation that would reduce fertility potential. Ovarian reserve refers to the number and quality of the oocytes that remain in the ovary. Oocyte quality refers to the capability of the egg to sustain normal fertilization and growth of that embryo for implantation and development into the birth of a viable offspring. In contrast to women with ovulatory dysfunction, those with diminished ovarian reserve (DOR) most often

Table 1
Summary of relevant history and physical examination findings for determining female factors in the infertile couple

History	Physical Examination
• Duration of infertility • Menstrual history • Pregnancy history • Previous methods of contraception • Coital frequency and sexual dysfunction • Past surgery (procedures, indications) • Hospitalizations (illnesses or injuries) • Pelvic inflammatory disease (sexually transmitted diseases) • Thyroid disease, galactorrhea, hirsutism • Abnormal pap smears or cervical surgeries • Current medications and allergies • Family reproductive history • Exposure environmental hazards • Use of tobacco, alcohol, or illicit drugs	• Weight, body mass index, blood pressure, and pulse • Thyroid enlargement and presence of any nodules or tenderness • Breast secretions and their character • Signs of androgen excess • Vaginal or cervical abnormality or discharge • Pelvic or abdominal tenderness, organ size, or masses • Uterine size, shape, position, and mobility • Adnexal masses or tenderness • Cul-de-sac masses, tenderness, or nodularity

Adapted from Practice Committee of the American Society for Reproductive Medicine. Diagnostic evaluation of the infertile female: a committee opinion. Fertil Steril 2012;98(2):302–7; with permission.

have regular menses unless the severity of DOR has progressed to the point of severe ovarian insufficiency.

Ovulatory Dysfunction

Infrequent ovulation is associated with an intermenstrual interval of less than 25 days or greater than 35 days, or a variation in the intermenstrual interval of greater than 5 days.[21] Premenstrual symptoms, referred to as *moliminal symptoms* (breast tenderness, irritability, mild headache), are typically associated with ovulatory cycles.

The only measure that proves ovulation has occurred is a positive pregnancy test after a conception cycle. Special diagnostic testing to confirm ovulation is not required in women with a history of regular cycles with premenstrual molimina. If an objective measure of ovulation is desired, a serum progesterone level can be obtained 7 days after a positive urinary LH determination. A concentration of progesterone of greater than 3 ng/mL is consistent with ovulation.[22]

When oligo-ovulation is present, a specific cause should be sought. The most common causes of ovulatory dysfunction include polycystic ovary syndrome, excessive psychological or physical stress, thyroid disorders, hyperprolactinemia, ovarian insufficiency, and medical conditions including obesity. Serum thyroid-stimulating hormone (TSH) and prolactin determinations will identify thyroid disorders and/or hyperprolactinemia. If hypothyroidism is suggested by an elevation of TSH along with an elevation in prolactin, levothyroxine replacement is indicated first to see if it will normalize an elevated prolactin level. Elevations of early follicular-phase follicle-stimulating hormone (FSH) levels greater than 10 mIU/mL are a threshold measure for DOR, whereas FSH levels of less than 4 mIU/mL may be encountered with hypothalamic oligo-ovulation.

Frequently no specific endocrine abnormality will be identified after the initial evaluation of women with ovulatory dysfunction. Most of the women with normal gonadotropin levels and no other known endocrine abnormality will be classified as having polycystic ovary syndrome (PCOS), exhibiting at least 2 of the 3 following characteristics: (1) hyperandrogenism (hirsutism, oily skin, acne), (2) irregular menses indicating oligo-ovulation, or (3) polycystic ovaries (>11 basal antral follicles, <10 mm in a single longitudinal image of each ovary by transvaginal ultrasound). This definition of PCOS, however, will also include some women with hypothalamic oligo-ovulation, because these women can exhibit PCOS-appearing ovaries with irregular menses. This distinction is important because the best method of ovulation induction will be different for these groups of women.

Ovarian Reserve

Testing to assess ovarian reserve includes early follicular phase FSH and estradiol levels, basal antral follicle (BAF) count measured with transvaginal ultrasound, and a serum anti-Müllerian hormone (AMH) level. For patient convenience, blood tests for ovarian reserve and ultrasound evaluation for BAF count can all be obtained in one visit on cycle day 2, 3, or 4 (with cycle day 1 the first day of full menstrual flow).

FSH and estradiol values should be correlated with the type of assay reported in the literature for levels indicating outcomes for normal ovarian reserve, diminished ovarian reserve, and ovarian insufficiency. Early follicular-phase levels of FSH levels are the most variable measure of ovarian reserve and should be obtained along with an estradiol level. An elevation in estradiol greater than 60 pg/mL with a normal range of FSH (<10 mIU/mL) is associated with both a poorer ovarian response during ovulation induction and a lower pregnancy rate with treatment.[23] The BAF count is measured as the sum of antral follicles in both ovaries less than 10 mm, as observed with

transvaginal ultrasonography during the early follicular phase. An average BAF count in reproductive aged women is approximately 15. A BAF count of less than 10 has been correlated with poor ovarian response to ovulation induction stimulation and low chances for conception in that treatment cycle.[24] AMH is a protein secreted by granulosa cells and is an indirect measure of egg number and quality. AMH may be obtained during any phase of the menstrual cycle and is a more consistent measure of ovarian reserve.[25] Obesity and oral contraceptive pill use will suppress AMH levels. An AMH level of less than 1 ng/mL is associated with reduced ovarian response and chance for pregnancy in cycles of IVF.[26]

Ovarian reserve testing can be recommended for all women in the initial diagnostic evaluation of infertility, but is especially important for women who are older than 35 years, or have a history of ovarian surgery, chemotherapy or pelvic radiation, or unexplained infertility, or a family history of early menopause.[27] The finding of DOR does not indicate that a patient will not conceive, but rather has its greatest value in predicting the ovarian response to gonadotropin stimulation and chances for pregnancy with IVF.[28] Oocyte quality is more difficult to ascertain through ovarian reserve testing, but AMH levels seem to have the best predictive value for this measure of fertility potential.[29]

UTERINE AND PERITONEAL ABNORMALITIES AND INFERTILITY

The evaluation of uterine, tubal, and peritoneal factors is necessary to assess the likelihood of a favorable environment for gamete transport, fertilization, embryo implantation, and continued development of a pregnancy. Diagnostic procedures for evaluating the anatomy of the uterus, fallopian tubes, and peritoneal cavity provide different and complementary information. Hysterosalpingography remains the most versatile initial test for uterine cavity conformation, assessment of tubal patency, and evaluation of developmental abnormalities, such as a unicornuate, septate, or bicornuate uterus. Fluoroscopic or hysteroscopic selective tubal cannulation can confirm or exclude pathologic conditions causing proximal tubal occlusion determined on hysterosalpingography. This method uses an intrauterine catheter to selectively cannulate a fallopian tube and infuse dye or contrast to assess tubal patency or define intratubal disease.[30] Saline instillation sonography is superior to hysterosalpingography for evaluating endometrial polyps, submucosal fibroids, and adenomyosis.[31] Because of its increased expense and invasiveness, hysteroscopy is reserved for patients who require corrective intrauterine surgery.[32] The scheduling of hysteroscopy together with laparoscopy is an efficient way to evaluate and treat women with both intrauterine and peritoneal abnormalities. Laparoscopy is reserved for infertile women whose history, physical examination, and testing reveal the presence of certain adnexal masses, pelvic pain, or tubal abnormalities. With direct visualization of the peritoneal cavity, endometriosis and pelvic adhesions can be diagnosed and possibly corrected.

Table 2 summarizes the methods for assessing uterine, fallopian tube, and peritoneal abnormalities in women of the infertile couple, and outlines the relative advantages and disadvantages of each.

MALE REPRODUCTIVE HISTORY AND PHYSICAL EXAMINATION

A male factor contributes to infertility in up to 40% of couples.[33] Although the semen analysis remains the cornerstone for the initial male evaluation, other historical factors are important even when the semen analysis is normal. The approach for evaluating men with primary infertility (never having fathered a pregnancy) is the same as for men

Table 2
Methods for assessing uterine, fallopian tube, and peritoneal abnormalities in women with infertility

	Uterine Cavity	Tubal Patency	Peritoneal Cavity	Advantages	Disadvantages
Hysterosalpingogram	+++	+++	+	Defines size and shape of uterine cavity, detects Müllerian and intratubal anomalies, profertility effect	Cannot assess size or depth of uterine tumors, no tubo-ovarian proximity evaluation
Saline instillation Sonography	++++	+	–	Excellent judge of cavity conformation, size and depth of uterine tumors Simple office procedure with lower cost and less pain Can view ovaries for BAF count, cysts	May assess tubal patency by seeing pelvic fluid but not tubal anatomy, no tubo-ovarian proximity evaluation, poor for severe intrauterine adhesions
Hysteroscopy	++++	–	–	Gold standard for uterine cavity evaluation Corrective surgery possible Adjunctive procedures with laparoscopy	Expensive, more invasive, more intensive instrumentation Unable to evaluate tubal anatomy
Laparoscopy	–	++++	++++	Best to identify and correct uterotubal, ovarian and peritoneal factors Tubal patency can be assessed	Expensive, more invasive, more intensive instrumentation Unable to evaluate intrauterine anatomy

with secondary infertility. The infertile man may present with underlying medical conditions that secondarily result in an abnormal semen analysis. Failure to evaluate for conditions such as testicular cancer and pituitary tumors that are associated with male factor infertility can have serious health consequences if not detected and treated.[34]

For most gynecologists and reproductive endocrinologists, a careful history and semen analysis will help direct a referral to an urologist with specialty training in male reproductive medicine for further physical examination. **Table 3** provides a summary of relevant historical points for assessing male factors contributing to infertility recommended by the American Society for Reproductive Medicine.[35]

SEMEN ANALYSIS

Semen analysis is the essential initial test for male fertility potential. Unless a man has a history of reduced libido, erectile dysfunction, premature ejaculation, hypospadias, and/or the inability to achieve intravaginal ejaculation, the finding of normal semen parameters would prompt no need for further male diagnostic evaluation. Even with no other remarkable historical risk factors, however, a man with a normal semen analysis could still have abnormal sperm function. In couples undertaking in vitro fertilization, normal semen parameters may still be associated with poor fertilization and/or abnormal embryo growth. At least 2 semen analyses are recommended because of the known variability in the total number of motile sperm cells among specimens. An abnormal finding on semen analysis may also represent a problem with collection or lack of prompt analysis after collection (within 30 minutes).[36]

Assessment of semen and sperm characteristics should be performed in a laboratory with technicians certified by proficiency testing according to the guidelines of the Clinical Laboratory Improvement Amendments.[37] Semen collection is preferably performed via masturbation at the andrology laboratory after 2 to 3 days of ejaculatory abstinence. **Table 4** provides the lower limits of the accepted World Health Organization reference values for semen analysis.[38]

The significance of a single semen parameter must be evaluated with regard to the other semen and sperm characteristics. Retrograde ejaculation should be suspected

Table 3
Summary of relevant history and physical examination findings for determining male factors in the infertile couple

History	Physical Examination
• A history of prior fertility • Coital frequency and timing • Duration of infertility and prior fertility • Childhood illnesses • Developmental history • Systemic medical illnesses (eg, diabetes mellitus and upper respiratory diseases) • Previous surgery • Medications • Sexual history (including sexually transmitted infections) • Exposures to gonadal toxins (including environmental and chemical toxins and heat)	• Examination of the penis, noting the location of the urethral meatus • Palpation and measurement of the testes • Presence and consistency of both the vasa and epididymides • Presence or absence of a varicocele • Body habitus • Hair distribution • Breast development

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Table 4
Lower limits of the accepted World Health Organization reference values for semen analysis

Semen Parameter	Reference Value
Ejaculate volume	1.5 mL
pH	7.2
Sperm concentration	15×10^6 spermatozoa/mL
Total sperm number	39×10^6 spermatozoa/ejaculate
Percent motility	40%
Forward progression	32%
Normal morphology (Kruger strict)	4% normal
Sperm agglutination	Absent
Viscosity	$\leq$2 cm thread after liquefaction

in a man with low semen volume and a history of genital surgery, retroperitoneal lymph node dissection, or diseases that impair the autonomic nervous system, such as diabetes mellitus. In these cases, the patient should be asked to return for a repeat semen sample after emptying the bladder. Evaluation of the postejaculation urine may demonstrate the presence of sperm, confirming retrograde ejaculation.[39]

The most clinically useful determination of sperm morphology is provided by microscopically analyzing specially stained sperm to obtain a strict anatomic evaluation of the sperm head, neck, and tail.[39] Strict morphologic sperm reports of less than 4% normal forms are associated with lower oocyte fertilization in vitro.[40] Careful proficiency testing of laboratory technicians is critical for accurate strict morphology assessment of sperm.

The finding of round cells in the microscopic assessment of semen indicates the presence of leukocytes, immature germ cells, or degenerating epithelial cells.[38] The use of peroxidase staining can help differentiate among these cell types. Peroxidase-positive cells are polymorphonuclear leukocytes and may represent genital tract infection or inflammation. Immature germ cells in semen may reveal a disorder in spermatogenesis.

The finding of very low numbers or absence of motile sperm cells in the ejaculate can be devastating to the infertile couple. **Table 5** includes a summary of the potential implications of abnormal semen analysis parameters. Many men with extremely depressed sperm counts can still achieve a conception, although assisted reproductive technology may be required.

MALE REPRODUCTIVE UROLOGY

Defining the cause of the male factor infertility is often best achieved in consultation with a urologist with training and expertise in male reproductive medicine. A reproductive urologist will examine the male genitalia and, if indicated, order hormonal and genetic laboratory testing. A low testicular volume (<15 mL) is a significant determinant for sperm production and indicates that the seminiferous tubules are either atrophic from lack of gonadotropin stimulation or atrophic because of a primary testicular process.

The physical examination by the male reproductive urologist can be assisted by ultrasonography of the male genital system. In the case of low semen volume (<1 mL) with no evidence of retrograde ejaculation, transrectal ultrasonography can reveal dilated seminal vesicles or ejaculatory ducts, suggesting partial or complete ductal

Table 5
Implications of abnormal semen parameters in the evaluation of male factor infertility

Parameter	Implication
Volume	• Low volume with decreased or absent sperm numbers: partial genital tract obstruction, androgen deficiency • Low volume with normal sperm concentration: problems with semen collection, partial retrograde ejaculation • High volume: possible genital tract infection
Sperm concentration	• Low numbers of sperm cells per milliliter: hypogonadism from hypothalamic/pituitary insufficiency or primary testicular dysfunction • Azoospermia (absent sperm): complete genital tract obstruction, primary testicular failure, complete hypothalamic/pituitary insufficiency, complete retrograde ejaculation
Motility	• Isolated severe low motility: toxins in seminal plasma or delayed analysis of specimen, prolonged period of ejaculatory abstinence • Low motility with global semen parameter abnormality: see causes listed previously for low or absent sperm concentration.
Morphology	• Total morphologic abnormality of a single type: possible rare genetic abnormality • Multiple abnormalities by strict morphology staining: most often unexplained
White or round cells	• Leukocytes: possible genital tract infection of inflammation • Immature sperm cells: possible disorder of spermatogenesis

obstruction.[41] Careful physical examination of the scrotum can identify a varicocele (enlarged testicular veins), absent vas deferens, firmness and pain of the epididymis, and testicular masses. Scrotal ultrasonography can help with ill-defined abnormalities detected through scrotal palpation, including small varicoceles, small testes located in the upper scrotum (cryptorchid), or testicular neoplasm that could be cancer.

A hormonal evaluation should be performed in men with oligozoospermia (sperm count <10 million/mL), diminished libido, erectile dysfunction, or phenotypic characteristics of endocrinopathy or genetic abnormality. An initial evaluation should include a measurement of serum FSH, LH, and testosterone. For men exhibiting a low serum testosterone level (<300 ng/mL), another level should be obtained along with a prolactin measurement. Some men with abnormal spermatogenesis have a normal serum FSH level, but an elevated serum FSH concentration (>14 mIU/mL) indicates primary testicular insufficiency, whereas a depressed FSH level (<4 mIU/mL) indicates hypogonadism from low gonadotropin production caused by pituitary or hypothalamic dysfunction.

Azoospermia (no sperm) or severe oligoasthenozoospermia (sperm count <5 million/mL) may be divided into one of the following diagnostic categories: (1) genital tract obstruction, (2) hypogonadotropic, nonobstructive azoospermia/oligoasthenozoospermia, or (3) testicular insufficiency, nonobstructive azoospermia/oligoasthenozoospermia. The diagnosis of azoospermia may be determined only after a semen specimen is centrifuged at 300 g for 15 minutes, with microscopic examination of the pellet. Identifying even a few spermatozoa in the ejaculate is useful because it indicates a higher rate of success with testicular sperm extraction (TESE) for IVF plus intracytoplasmic sperm injection (ICSI).[42] **Table 6** provides a reference for counseling men with severe azoospermia/oligoasthenozoospermia.

Table 6
Diagnostic evaluation for men with obstructive and nonobstructive azoospermia or severe oligoasthenozoospermia

Category	Physical Findings	Hormonal Evaluation	Other Testing
Obstructive	Possible congenital bilateral absence of the vas deferens, congenital or acquired obstructive stone or stricture of excurrent ductal system, normal testicular size	T: normal LH: normal FSH: normal	Dilated seminal vesicles on transrectal ultrasonography; postejaculatory urine analysis if absent semen on ejaculation; cystic fibrosis carrier screening
Nonobstructive: testicular insufficiency	Small testicular size, possible male eunuchoid habitus	T: low or normal LH: normal FSH: elevated	Karyotype, azoospermia factor microdeletion testing (AZF a, b, and c)
Nonobstructive: hypogonadotropic	Small testicular size, possible male eunuchoid habitus	T: low LH: low FSH: low	Possible brain MRI for lesion or tumor; gonadotropin replacement

Abbreviations: MRI, magnetic resonance imaging; T, testosterone.

GENETIC SCREENING OF MEN WITH MALE FACTOR INFERTILITY

Men with nonobstructive azoospermia or severe oligozoospermia have a higher risk of genetic abnormalities than fertile men.[43] Genetic abnormalities that result in aberrant spermatogenesis may be detected through karyotype and special testing for Y-chromosome microdeletions. Approximately 10% to 15% of men with nonobstructive azoospermia and 5% with severe oligozoospermia will have chromosomal abnormalities.[44,45] More than 50% of men with nonobstructive azoospermia/oligozoospermia who demonstrate structural or numerical chromosomal abnormalities will be found to have a karyotype of 46, XXY or Klinefelter syndrome.[46]

Specific microdeletions of the long arm of the Y chromosome are associated with azoospermia or severe oligozoospermia. Three regions on the Y chromosome have been named the azoospermia factor (AZF) regions: AZFa, AZFb, and AZFc. Men with the AZFc deletion are more likely to have sperm in their ejaculate and have a much higher chance of sperm retrieval via TESE. Very poor results are obtained from TESE in men with AZFa and AZFb deletions.[47,48] A convenient way to remember the most favorable prognosis for men with AZFc deletions is: AZF"a" is awful, AZF"b" is bad, and AZF"c" has conception. Couples should be counseled that sons of men with Y-chromosome microdeletions will inherit this chromosome and are very likely to have severe male factor infertility.[49]

Obstructive azoospermia from congenital bilateral absence of the vas deferens (CBAVD) is associated with a high risk of cystic fibrosis carrier status in affected men.[50] It is imperative, therefore, to test the female partner of a man affected by CBAVD. The safest measure is to sequence the cystic fibrosis gene in the female partner because some of the less common mutations may be missed on routine testing for cystic fibrosis carrier status.

All couples with severe male factor and either chromosomal or Y chromosomal microdeletions should receive genetic counseling to discuss prognostic information for offspring and choice of treatment options. With the advent of IVF and preimplantation genetic screening, the transfer of a single euploid embryo could be of great

benefit to men with severe male factor infertility and structural or numerical chromosomal abnormalities.

SPECIALIZED CLINICAL TESTS OF SPERM FUNCTION

The availability of ICSI has greatly reduced the utility of testing for sperm–cervical mucous interaction and the acrosome reaction, and assays to determine sperm/oocyte penetration. Antisperm antibodies (ASA) may impair sperm motility, prevent the penetration of cervical mucous, and prevent oocyte fertilization.[51] The greatest utility for ASA testing is before IVF to determine whether direct sperm injection via ICSI is indicated.[52] A direct immunobead test is recommended, because it determines whether ASA are bound directly to the spermatozoa.

Future investigation may ultimately reveal clinically relevant testing of sperm function that improves the management of infertile couples. Men with abnormally high sperm DNA fragmentation have lower pregnancy rates after intrauterine insemination or IVF and ICSI.[53] Unfortunately, no treatment for abnormal DNA integrity has yet shown benefit, and the prognostic value of DNA integrity testing has not been clinically proven.[54] Excessive reactive oxygen species levels in semen generated by leukocytes and senescent sperm cells are correlated with sperm membrane damage and male factor infertility.[55] The development of a clinically practical test for excessive reactive oxygen levels in semen could allow for targeted treatment, such as shortening the period of ejaculatory abstinence before insemination or treatment with reducing vitamins such as vitamins E and C.[56]

THE CASE OF UNEXPLAINED INFERTILITY

How should infertile couples be counseled when the results of their diagnostic evaluation are all normal? This potentially frustrating circumstance can be approached by explaining the practical limitations of diagnostic testing. A more accurate description of their condition would be a status of having “underdiagnosed” infertility. The most likely factors contributing to unexplained infertility are issues relating to reduced sperm and egg quality, fertilization, or occult abnormalities of the fallopian tubes and the peritoneal cavity not diagnosed by hysterosalpingography or laparoscopy. The utility of IVF to diagnose problems with fertilization, sperm and egg quality, and embryo growth is obviously not practical. In this situation of unexplained infertility, the chance for pregnancy per menstrual cycle with continued natural attempts for pregnancy will be approximately 4% per cycle,[57] and this chance decreases with increased periods of infertility before evaluation and with the age of the female partner.[58] Couples with unexplained infertility can be reassured that they will have increased pregnancy rates with empiric ovulation induction and intrauterine insemination followed by IVF if necessary.[59]

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