Examining Male Infertility

Susanne Quallich

An increasing number of couples seek evaluation and treatment for infertility, especially as more couples delay childbearing in order to establish their careers. A male factor alone is the cause of infertility in up to 20% of infertile couples and a contributing factor in another 30% to 40% of all couples presenting for infertility evaluations (American Urological Association [AUA] & American Society for Reproductive Medicine [ASRM], 2001a; ASRM, 2004). Problems with infertility affect approximately 6.1 million people in the United States, or roughly 10% of the reproductive-age population. For these couples, a lack of success with conception is not just an inconvenience but rather a disease of their reproductive system(s). Understanding the basics of male infertility is an important part of providing complete urologic care to male patients.

There are causes of male infertility that are treatable, either through medical or surgical management, and causes that can be corrected, or improved, to the point where the couple is able to conceive naturally or to take advantage of less-costly assisted reproductive technologies.

Problems of male infertility can seem like minor issues within the larger realm of urology. But many male infertility diagnoses can be successfully treated, allowing the couple to conceive naturally or with minimal medical assistance. Some patients presenting with male infertility can have more significant disease. Treatments for male infertility will continue to progress, and as an increasing number of couples seek infertility services, the need to provide basic information grows as well.

Development of Sperm

Males do not begin to produce sperm until puberty, when testosterone begins to exert its influence on overall male development and growth. Spermatogenesis is driven by testosterone production in the Leydig cells of the testes. Under the influence of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), which are released from the anterior pituitary, the testes begin to produce sperm in a four-step process of development: spermagonia, spermatocyte, spermatid, spermatozoon. This cycle takes roughly 74 days to complete, with an additional 12 days for final maturation as the sperm traverse the length of the epididymis (Sigman, Lipshultz, & Howards, 1997). The duration of this cycle is important, as any changes in the semen analysis following medical or surgical intervention will not be reflected for at least 3 months.

This process is governed by a negative feedback loop, with testosterone acting as the primary negative feedback component that slows LH and FSH secretion. Inhibin, released during spermatogenesis, also specifically inhibits activity or down-regulates FSH. This feedback system can be overridden by the administration of exogenous testosterone, or medications such as luteinizing hormone-releasing
hormone antagonists, both of which stop the body's own production of testosterone (and halt spermatogenesis as well).

**History**

**General history and review of systems.** The general history of a male patient during an infertility evaluation begins with the duration of the attempts at pregnancy or reason for the evaluation (such as to establish if spermatogenesis has returned after chemotherapy). It includes many questions regarding the reproductive status of his partner, including her age, the duration of the couple's attempts at pregnancy, if they have had children or a positive pregnancy test together, and the results of any semen analyses prior to the current encounter. The history addresses whether or not either partner has conceived with another partner, and should include previous evaluation and treatment for male or female factor infertility in the past. Not every male patient is accompanied by his partner, but this information should be collected as completely as possible.

The male general history includes a discussion of any recent (within the last 6 months) systemic illness, particularly if it was a febrile illness, and any recent weight gain or loss. The patient should be asked if there are any complaints specific to the genitourinary (GU) structures. This may reveal complaints of a dull ache or fullness to the scrotum, or pain on one side that does not radiate. The review of systems will specifically include fevers, colds, sinus infections, anosmia (loss or impairment of the sense of smell), peripheral field visual problems, breast pain or secretions, and scrotal pain. It should establish that puberty started in the early or middle teens to confirm normal physiologic male development.

The general history includes any potential exposure to environmental toxins, either through occupation or hobbies. These include excessive heat, radiation, heavy metals, and glycol ethers or other organic solvents.

**Medical history.** The evaluation should then proceed to a history of any condition that would potentially affect erectile function, the testes, or the hormonal status of the patient (including such things as cryptorchidism, epispadias surgeries; orchitis, diabetes, hypothyroidism, varicocele, or pituitary malfunction). It will also include a review of additional medical conditions for which the patient is being followed, including any condition that would require radiotherapy or chemotherapy. Any history of treatment for malignancy, regardless of site, should be documented. Diabetes, chronic obstructive pulmonary disease, sleep apnea, renal insufficiency, hemochromatosis, and hepatic insufficiency are known possible contributors to male subfertility (Burrows, Schreperman, & Lipshultz, 2002). Infertility in the male can, in fact, be a hallmark symptom for other medical conditions in an apparently healthy adult male.

**Surgical history.** The surgical history during the male infertility visit focuses on any history of GU surgeries at any point during the life of the male undergoing evaluation. These include such diverse procedures as orchidopexy; Y-V plasty to the bladder neck; inguinal hernia repair as infant, small child, or adult; epispadias or hypospadias repair; prostate surgery; bladder reconstructions; bladder surgeries; or testicular surgeries. The surgical history should ask about procedures which impair retroperitoneal sympathetic nerve function, such as retroperitoneal lymph node dissection (RPLND). The patient should be asked specifically about previous treatment for testicular or GU malignancies, either with surgery or radiation. The patient should be asked specifically if there is a history of a vasectomy.

**Sexual history.** The history should include the overall pattern of sexual activity during the period of time the couple has been trying to conceive, specifically in relation to ovulation. This includes questions regarding the use of ovulation-predictor kits or ovulation-promoting medications such as clomiphene citrate, a nonsteroidal anti-estrogenic. The optimal window for pregnancy occurs in the 6 days before ovulation, with day 6 being the actual day of ovulation (Wilcox, Weinberg, & Baird, 1995). Simply adjusting the timing of intercourse can result in a significantly increased chance for pregnancy.

Both partners should be asked about a history of sexually transmitted infections. Each patient should be queried regarding erectile function, ejaculation, and libido; these issues can be superimposed onto fertility concerns. Erectile difficulties may be accompanied by a history of declining erectile function, usually insidious and progressive, and may span the course of several years (as is a common scenario with diabetic patients). Alternatively, the patient may provide a history of relatively rapid or recent onset of a decline to erectile function, such as may be associated with the history of recently starting new medication or the stress of the fertility evaluation. The history should include several points specific to the patient's sexual functioning: the precise nature of the dysfunction (for example, whether the problem is attaining or sustaining an erection, insufficient rigidity, difficulty with penetration); the presence or absence of nocturnal and morning erections and their quality; and any treatments (pharmacologic and nonpharmacologic) that the patient has tried.

If the patient complains of low libido, he may also describe
moodiness, loss of interest in his usual activities, a decline in erectile function, fatigue, and even complaints of diminished muscle bulk. It should be established if these complaints are new or long-standing.

If there are issues with ejaculation, the patient may have complaints of cloudy urine after ejaculation, decreased volume of ejaculate, hematospermia, difficulty with bowel movements, anejaculation, oligospermia (low sperm count), or azoospermia (no sperm in ejaculate) with a low-volume ejaculate on semen analysis. The patient may have complaints of pain on ejaculation, usually of relatively recent onset, and it may localize to a specific scrotal structure. These complaints can be the result of a variety of surgical procedures, progressive neurologic disease, or pre-existing treatment with certain antidepressants (see the article, “Premature Ejaculation” elsewhere in this issue for a more detailed description of ejaculation issues).

The couple must also be asked about the use of lubricants: saliva, K-Y® jelly, surgilube, and hand lotions are known to impair sperm motility (Burrows et al., 2002).

Medication history. A careful medication history is a mandatory component of the initial evaluation of male-factor infertility. Prescription drugs can affect sperm count, motility, and morphology, and the dose and duration of use should be documented. Common antibiotics can temporarily contribute to a decline in the semen analysis quality. Calcium channel blockers and spironolactone can contribute to a decreased fertilization capacity and a decline in spermatogenesis respectively (Brugh, Matschke, & Lipshultz, 2003) (see Table 1). Anabolic steroid use can result in a profound decline in sperm counts that may not recover with the cessation of the exogenous steroid, leaving the patient azoospermic or with persistently decreased counts. The patient must also be asked about the ingestion of nutraceuticals and other over-the-counter medications, certain steroid hormones, or other harmful substances that may contribute to semen analysis derangements as well.

Social history. Cigarette smoking, excessive alcohol consumption, and consistent marijuana use are all known to be gonadotoxins (Burrows et al., 2002). A careful history of the use of these agents and other illicit drug use must be part of the complete male infertility evaluation. Cigarette smoking has been implicated as leading to changes in morphology, sperm production, and motility while chronic alcohol use contributes to feminization, erectile dysfunction, and hypogonadism (Nudell, Monoski & Lipshultz, 2002). Marijuana use can decrease sperm morphology over time (Nudell et al., 2002). Simply eliminating these agents can improve semen parameters in the absence of other physical findings.

Patients should be asked about recreational activities, as some activities, such as long-distance cycling, may put pressure on the perineal area and may result in possible impairment to erectile function.

Family history. The family history should include a discussion of testicular or other GU malignancies and specifically any cancer history, prostate or bladder problems in other family members (including female relatives with bladder conditions). It is helpful to include a history of maternal medication/drug use while pregnant with patient, if this information is known. The patient should be queried regarding siblings or extended family members who may have had fertility problems or diagnoses that are genetic in nature (such as cystic fibrosis).

Female partner history. The history of the patient’s partner should include details of any previous pregnancies (including miscarriages or elective terminations), menstrual cycle length, whether she is undergoing evaluation for fertility issues, and any medical or surgical management that has been necessary. It is also helpful to include comments regarding the expected next step in her management (if known) if the male evaluation is negative.

Physical Examination

If this is a complaint in a man

### Table 1. Common Medications with an Effect on Sperm Function

<table>
<thead>
<tr>
<th>Medication</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spironolactone</td>
<td>Decreases spermatogenesis</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>Decreases fertilization capacity</td>
</tr>
<tr>
<td>Anti-androgens</td>
<td>Decreases spermatogenesis</td>
</tr>
<tr>
<td>Nitrofurantoin (high doses)</td>
<td>Decreases spermatogenesis</td>
</tr>
<tr>
<td>Cimetidine</td>
<td>Decreases spermatogenesis</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Decreases spermatogenesis</td>
</tr>
<tr>
<td>Colchicine</td>
<td>Decreases fertilization capacity</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>Decreases sperm density/motility</td>
</tr>
</tbody>
</table>

Source: Adapted from Brugh, Matschke, & Lipshultz, 2003.
with no other recognized medical conditions, a full physical examination is necessary. Examination of the male patient is best done in a warm room, in an attempt to avoid any exaggeration of the cremaster reflex (see Table 2). The examination should focus primarily on the genitalia (see Table 3), with consideration for the overall body habitus. For a detailed discussion of the complete male physical examination, refer to the physical assessment article that appears elsewhere in this issue. The structures that are evaluated include the penis, scrotum, testes, epididymis, spermatic cord and vas deferens, prostate, seminal vesicles, and Cowper’s gland; however, not all are easily palpated.

The patient should be examined for age-appropriate development of male secondary sex characteristics, gynecomastia, or hirsutism. He should be evaluated for lesions or scarring to the abdomen or groin (as patients may inadvertently neglect to mention surgery that happened in their remote past), any discoloration to the scrotum, asymmetry of the testicles, and the location and size of the opening of the penile meatus. Physical examination could reveal regression of secondary sexual characteristics such as hair loss and possible loss of muscle bulk. Patients using

### Table 2. Special Maneuvers for the Male Infertility Examination

<table>
<thead>
<tr>
<th>Maneuver</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>Cremasteric reflex</td>
<td>Brushing or touching the skin of the scrotum in a downward direction will result in the prompt elevation of the testicle on the same side. This reaction can be aggravated by a cool room; the reflex may be engaged prior to any contact with examiner.</td>
</tr>
<tr>
<td>Valsalva maneuver to evaluate for varicocele</td>
<td>Performed with patient standing, and in warm room; having patient perform Valsalva will reverse flow into the pampiniform plexus and result in palpable distention of the vessels (“bag of worms” if varicocele of sufficient size).</td>
</tr>
</tbody>
</table>

*Source: Quaillich, 2005.*

### Table 3. Physical Findings and Their Relationship to Male Infertility

<table>
<thead>
<tr>
<th>Visible Male Reproductive Structure</th>
<th>Normal Findings on Inspection/Palpation</th>
<th>Abnormalities Relevant to Infertility Evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penis</td>
<td>Soft and pliable along length of shaft. Meatus midline, central to glans. Foreskin should retract and draw forward easily.</td>
<td>Meatus not midline or central to glans – hypospadias, epispadias. Unilateral, uncomfortable swelling of the scrotum – varicocele.</td>
</tr>
<tr>
<td>Scrotum</td>
<td>Sac of skin partially covered with hair.</td>
<td>Mass associated with testicle – tumor, spermatocele. Solitary testis – maldescent of testicle or previous surgical removal. Small, soft testicle(s) – Klinefelter’s syndrome, history of infection, late orchidopexy, atrophy due to long-standing varicocele.</td>
</tr>
<tr>
<td>Testes</td>
<td>Two testes, freely movable within scrotum; should be nontender. Palpate between thumb and 1st two fingers of the hand. Firm, smooth, rubbery consistency. Average 6 cm x 4 cm in size, symmetrical. Right testicle may be slightly anterior to left. Separate from epididymis.</td>
<td>Cystic or nodular – spermatocele, previous infection, history of vasectomy. Large and/or fluctuant – spermatocele. Localized pain – epididymitis.</td>
</tr>
<tr>
<td>Vas deferens and spermatic cord</td>
<td>Soft, rubbery consistency. Trace vas deferens from epididymis to inguinal canal. Smooth along entire length.</td>
<td></td>
</tr>
</tbody>
</table>

*Source: Adapted from Quallich, 2005.*
anabolic steroids may also have skeletal muscle hypertrophy, acne, gynecomastia, and striae; there may be some noticeable testicular atrophy on examination.

Palpation is the most important component of the physical examination when assessing for male factor infertility. Because the tone of the tunica dartos muscle will determine the size of the scrotum, the examination should be performed in a warm room whenever possible. In a cool environment the tunica dartos muscle will cause the scrotum to contract. The scrotum must be carefully and thoroughly palpated, and the presence of all scrotal structures should be confirmed, along with their size and consistency. Masses may arise from the surface of the testicle, adjacent to or separate from the testes. There may be evidence of epididymal induration on physical examination. The patient may have a testicle that is palpable in the inguinal canal and can be tender on examination, that cannot be manipulated down into the scrotum, or that cannot be palpated at all. Physical examination may show complete absence of the vas deferens unilaterally or bilaterally, or a palpable gap in the vas deferens. The complete physical examination should also include a digital rectal examination when there are ejaculatory complaints.

A varicocele can be exaggerated during physical examination by asking the patient to perform the Valsalva maneuver while standing; any distention of the pampiniform plexus should disappear when the patient lies down. If the varicocele is bulky enough, there may be resulting scrotal swelling that is noticeable to the patient, along with a bluish discoloration beneath the scrotal skin. A long-standing varicocele may cause testicular atrophy. If the varicocele is large, it may be visible during inspection (“bag of worms”).

### Table 4. Semen Parameters

<table>
<thead>
<tr>
<th>Semen Parameters</th>
<th>Normal Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphology (strict criteria)</td>
<td>≥ 15% normal forms</td>
</tr>
<tr>
<td>Motility</td>
<td>≥ 50%</td>
</tr>
<tr>
<td>Sperm concentration</td>
<td>≥ 20 million</td>
</tr>
<tr>
<td>Volume</td>
<td>2.0 ml - 5.0 ml</td>
</tr>
</tbody>
</table>

*Source: Adapted from Rowe, Comhaire, Hargreave, & Mahmoud, 2000.*

**Semen Analysis and Laboratory Evaluation**

The semen analysis yields a tremendous amount of information as to the potential causes of male infertility. The primary values that are evaluated are the volume of the ejaculate, sperm motility, total sperm count, and sperm morphology (shape) (see Table 4). Patients should receive notification in advance that they will need to provide a semen sample after a period of abstinence of 2 to 5 days. This sample is collected through masturbation, and must be collected into a container that is not toxic to sperm, or by using a special condom designed for semen collection (latex condoms alter sperm viability, especially if they are lubricated). Patients should be discouraged from attempting to collect a sample through intercourse as coitus interruptus is not a recommended, or reliable, means for sample collection (AUA & ASRM, 2001b). The ideal circumstances for specimen collection are in close proximity to the laboratory to prevent any delay in processing. If the sample is collected at home it should arrive to the lab within 60 minutes to ensure the accuracy of the results.

When determining a course of treatment, it is common to require serial analyses to avoid any spurious results, ideally with the same period of abstinence each time. For instance, patients could be scheduled for three specimens, with 3 days abstinence, a minimum of 3 weeks apart. It is common for patients to repeat their semen analysis every 3 months after starting any treatment, due to the length of time it takes sperm to mature. The results of the semen analysis can indicate any additional testing that might be useful.

There are several additional tests that can be performed on a semen sample, including a sperm penetration assay, peroxidase staining, direct immunobead testing, and computer-aided semen analysis. The clinical usefulness of specialized sperm testing remains controversial, however.

An endocrine evaluation can yield a great deal of information (see Table 5), and may be ordered if there is any suspicion of endocrinopathy or evidence of oligospermia. This will include total testosterone, free testosterone, LH, FSH, and prolactin levels; estradiol level may be included if the patient has a high body mass index.

If the semen analysis shows severe oligospermia or azoospermia and/or the physical examination yields abnormalities as far as testicular size or the male’s overall physical development, then karyotype analysis and Y-chromosome microdeletion testing are also indicated.

**Potentially Reversible Causes Of Male Infertility**

Varicocele. A varicocele is a
palpable or visible dilation of the vessels of the pampiniform plexus in the scrotum. It is the reflux of venous blood from the internal spermatic vein which dilates the pampiniform plexus and results in a varicocele. It is estimated that varicoceles may be present in 15% of the male population, and this number increases to 40% in men presenting for an infertility evaluation (AUA & ASRM, 2001c). Varicoceles are more common on the left, possibly due to the greater distance the internal spermatic vein must traverse to the left renal vein when compared with the distance on the right. If a varicocele is painful, there may be a history of a dull ache, fullness, pain that does not radiate, or pulling to the affected side of the scrotum after prolonged standing, exertion, or sitting. Pain from a varicocele is rare after prolonged recumbency or sleeping.

A varicocele might be suspected in the male with decreased semen parameters, as varicoceles represent a common cause of secondary male infertility. The etiology of varicoceles remains unclear, and there are no specific risk factors. The mechanism by which varicoceles alter the semen analysis is also uncertain, and may be the result of temperature elevation, venous congestion, or testicular hormone changes. It is unusual for males to exhibit a varicocele prior to adolescence, and the majority of varicoceles are asymptomatic, causing neither pain nor semen analysis changes. Adult males with a varicocele and some abnormalities of their semen parameters may benefit from treatment for the varicocele as a way to protect their future fertility and prevent any potential for future decline to their semen parameters (Chehval & Purcell, 1992).

A scrotal ultrasound is not necessary to diagnose a varicocele, but it will confirm the presence of a varicocele and eliminate other testicular or scrotal pathology. However, only those varicoceles palpable on physical examination have been documented as contributing to male infertility (AUA & ASRM, 2001c).

Treatment of a varicocele is possible either through surgical repair or percutaneous embolization. Surgical repair can be achieved with a variety of approaches, including microsurgical, inguinal, or subinguinal. Neither embolization nor surgery has been clearly shown to improve fertility (AUA & ASRM, 2001c). Any offered surgical correction will be secondary to the individual surgeon’s experience, while embolization requires interventional radiology. Surgical treatment has a high success rate (AUA & ASRM, 2001c). Both surgery and embolization have short recovery periods. The primary risks are infection, varicocele recurrence, and failure of the semen analysis to improve after the procedure. For those patients who do not show improvement or show only modest improvement over the course of a year, and in whom the varicocele has not recurred, intrauterine insemination (IUI) or in vitro fertilization (IVF) may be advised, depending on the total sperm count.

### Ejaculatory and Sexual Dysfunction

A secondary goal of the infertility evaluation is to identify any underlying health conditions that may be contributing to difficulties with conception. This could include any conditions that would contribute to problems with ejaculation, such as undiagnosed diabetes, or problems with erection, such as might be caused by a significant smoking history, severe hypercholesterolemia, or hypogonadism. A full discussion of the diagnosis and treatment of erectile dysfunction (ED) is beyond the scope of this article; however, it is not uncommon for men to report some stress-related ED during the course of the infertility evaluation and treatment.

### Table 5. Endocrine Abnormalities Seen with Male Infertility

<table>
<thead>
<tr>
<th>Condition</th>
<th>Testosterone level</th>
<th>LH level</th>
<th>FSH Level</th>
<th>Prolactin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal spermatogenesis</td>
<td>Normal</td>
<td>Normal</td>
<td>Elevated or normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Anabolic steroid use</td>
<td>Elevated or low (depends on specific chemical)</td>
<td>Decreased</td>
<td>Decreased</td>
<td>Normal</td>
</tr>
<tr>
<td>Hypogonadotropic hypogonadism</td>
<td>Decreased</td>
<td>Decreased</td>
<td>Decreased</td>
<td>Normal</td>
</tr>
<tr>
<td>Normal spermatogenesis</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Partial androgen resistance</td>
<td>Elevated</td>
<td>Elevated</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Testicular failure</td>
<td>Decreased or normal</td>
<td>Elevated</td>
<td>Normal</td>
<td>Normal</td>
</tr>
</tbody>
</table>
These patients may benefit from a prescription for a PDE-5 inhibitor. Alprostadil (Muse®) is not recommended since its potential effect on the ejaculate is not known.

Patients who complain of difficulty with ejaculation and climax may be taking psychotherapeutic agents that block dopamine production and consequently blunt the hypothalamic-pituitary axis and possibly decrease libido. Other psychotherapeutic agents can decrease vasodilation and decrease the quality of erections. Tricyclic antidepressants, selective-serotonin reuptake inhibitors, and monoamine oxidase inhibitors can lead to ED, anejaculation, and decreased libido. These patients can have their regimen changed, or may be offered other means of medically managing their complaints, such as a PDE-5 inhibitor.

**Endocrinopathy.** Hypogonadism represents the only cause of male infertility that can successfully be treated with hormone therapy, although the response is largely dependent on the length of time and causes of the hypogonadism. Hypogonadism is failure of the testes to produce normal levels of testosterone and/or sperm. Primary causes of hypogonadism are commonly due to testicular failure, while secondary causes are due to pituitary or hypothalamic causes, and combined hypogonadism is due to the combinations of the decreased pulsatility of the pituitary gonadotropins coupled with the decreased response of the testicular Leydig cells. Hypogonadism is more common in aging males who have passed through their reproductive stage.

Reversible endocrinopathies that directly contribute to male infertility are unusual (Kolettis, 2003). In the adult male, hypogonadism manifests with changes in sexual function, behavior, muscle mass, and some loss of secondary sexual characteristics. The patient may also report mood and behavioral symptoms (depression, irritability, loss of motivation) in addition to complaints of lethargy or loss of energy. Physical examination may demonstrate some regression of secondary sexual characteristics such as hair loss and possible loss of muscle bulk. There is no change to penis or prostate size, but the testes may be softer in consistency and smaller than might be expected from the patient’s chronologic age.

Obesity can lead to the aromatization of testosterone in fatty tissue to estradiol, leaving less testosterone available for maintenance and virilization functions. This will lead to a decline in sperm production, as the testes no longer receive an adequate hormonal signal to produce sperm. As a result of lowered testosterone, a clinically obese male may demonstrate evidence of feminization (such as gynecomastia) or regression of secondary male sexual characteristics on physical examination. Testosterone and free testosterone levels, along with estradiol, LH, and FSH levels will aid in determining the degree to which obesity may have upset the patient’s hormonal balance and contributed to alterations in the semen analysis.

The most definitive treatment is weight loss, but some patients may also respond well to treatment with clomiphene citrate, a synthetic nonsteroidal anti-estrogen.

All forms of hypogonadism can be confirmed by checking a testosterone level; morning values are preferred to afternoon blood samples because testosterone is secreted in the morning. This should include total testosterone, free testosterone, LH, and FSH. Estradiol should be obtained if the patient has a higher body mass index. Prolactin and a thyroid profile can also be useful in diagnosing secondary causes in selected cases.

Men who are diagnosed with hypogonadotropic hypogonadism (decreased testosterone, decreased LH, decreased FSH) can also benefit from treatment with exogenous hormones to stimulate their system into a more normal profile. Their prospects for recovery of spermatogenesis are modest; even with treatment it may be a year or more before sperm production returns. The most profound cases of this are caused by hypothalamic disorders such as Kallman’s syndrome. Men diagnosed with a form of hypogonadotropic hypogonadism may still sire genetic offspring, via testicular aspiration and IVF and intracytoplasmic sperm injection (ICSI).

**Obstructive azoospermia.** Patients who have previously had vasectomies suffer from obstructive azoospermia. These patients are usually otherwise healthy, and have normal GU examinations, with the exception of sperm granulomas as a result of the vasectomy, and varying degrees of induration and/or tenderness to their epididymis. These patients can be offered a vasectomy reversal as treatment for their infertility, and may be candidates for a vasovasostomy or vasoepididymostomy depending on their physical examination (AUA & ASRM, 2001b). The offered surgical approach will be based on the individual surgeon’s experience. Vasectomy reversals may become less successful as the time after the vasectomy increases. A microsurgical vasectomy reversal remains the most cost-effective option for fertility restoration after a vasectomy (Pavlovich & Schlegel, 1997).

A minority of patients presenting for a male infertility evaluation may have suffered an inadvertent vasectomy during surgery for another condition, such as an inguinal hernia repair as a child or adult. In some cases these patients can be successfully reconstructed.

**Ejaculatory duct obstruction.** Ejaculatory duct obstruction describes a condition in which one, or
both, of the ducts leading from the seminal vesicles into the prostate become(s) partially or completely blocked. This results in only prostatic fluids contributing to the ejaculate volume. As a result the semen analysis will show decreased volume, increased acidity, possible hematospermia, possible oligospermia, or azoospermia. The patient may provide a history of pain immediately following ejaculation. Digital rectal examination may show some tenderness to the prostate and/or epididymis, and possible distended seminal vesicles, but the diagnosis is more commonly made after a transrectal ultrasound. Treatment involves the transurethral resection of the ejaculatory ducts.

Chemotherapeutic agents. Men who have been treated with chemotherapeutic agents have varying chances of recovering spermatogenesis, depending on the specific agents involved. Damage is done directly to the germinal epithelium and Sertoli cells that support spermatogenesis. The most gonadotoxic agents are alkylating agents, antimetabolites, and vinca alkaloids (Nudell et al., 2002). Agents such as methotrexate, cisplatin, and 6-mercaptopurine offer better chances of sperm recovery (Nudell et al., 2002), but offering the opportunity to cryopreserve sperm prior to initiation of treatment should be considered whenever possible. Spermatogenesis can recover during the 2 to 4 years after the cessation of treatment; progress toward recovery can be monitored with yearly semen samples.

Male Infertility and Medical Management

Medical management of male infertility occurs when a specific contributing factor is potentially amenable to attempts at medical treatment is identified. This routinely includes the recommendation to remove any environmental toxins, such as smoking cessation, cessation of recreational drug use, and cessation of alcohol intake. Medical management is often related to addressing some endocrine abnormality; in the case of a specific hormone deficiency, administration of the hormone, or a substance that promotes its production, can restore the patient to normal hormone levels. After a period of time, 6, 9, 12 months or more, there can be improvements in overall semen parameters either to normal ranges or such that the couple becomes a candidate for low-tech interventions.

This is true for all attempts at hormone replacement except for testosterone. The patient who is given any form of testosterone replacement will suffer a progressive decline in the function of the testicles, as the exogenous testosterone is a powerful inhibitor of the feedback loop that governs spermatogenesis and testicular testosterone production. To boost testosterone levels in the subfertile male, clomiphene citrate (Clomid®), a synthetic nonsteroidal anti-estrogen is given, commonly at 25 mg daily. In men, it blocks feedback inhibition and so increases FSH and LH, thus increasing testosterone and sperm production. In part, because of its estrogenic effects, there is the potential for alterations in libido, gynecomastia, weight gain, and headache (see Table 6). There have been a variety of uncontrolled studies as to the effectiveness of clomiphene citrate in treating male subfertility, but when the outcome is measured as an increase in pregnancy rate, clomiphene citrate fares little better than placebo (Sokol, Steiner, Bustillo, Petersen, & Swerdloff, 1988). It will not have an effect on the male who has a normal testosterone level and a decreased semen analysis.

If there is retrograde or low-volume ejaculation, a trial of sympathomimetics can be useful. The goal of this therapy is to convert the retrograde ejaculation to antegrade or partially antegrade ejaculation; a variety of medications have been used, with varying degrees of success (Schuster & Ohl, 2002). This approach is more successful with patients who suffer a progressive decline in their ejaculatory function, such as that seen with neurologic disease, than with the abrupt onset seen as a result of a variety of surgeries, such as radical retropubic prostatectomy.

Use of the supplement L-carnitine, either by itself or in a mix-

### Table 6. Discussion of Clomiphene Citrate (Selective Estrogen Receptor Modulator)

<table>
<thead>
<tr>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Action</td>
<td>Functions at level of pituitary: causes increased FSH secretion</td>
</tr>
<tr>
<td>Result</td>
<td>Increased testosterone production, likely increased sperm count, and concentration</td>
</tr>
<tr>
<td>Potential adverse effects</td>
<td>Dizziness, Gynecomastia, Headache, Lightheadedness, Mental depression, Vision problems (rare)</td>
</tr>
</tbody>
</table>
tility of additional substances, has been proposed as a supplement that can improve overall sperm motility and the total sperm count, and enabling a patient to avoid invasive procedures such as varicocele repair or testicular biopsy. However, its use remains somewhat unfounded. Although carnitine serves a role in the maturation of sperm, there have been no prospective, randomized, double-blind, placebo-controlled trials to evaluate this supplement’s utility in improving male-factor infertility (Siddiq & Sigman, 2002).

Generally, attempts at medical treatments for male infertility have been limited by poorly designed research studies, and by wide variations in dosage and duration of therapy, lack of a placebo-control arm, and a failure to control for the variation seen in semen quality with time.

**Irreversible Causes of Male Infertility**

Klinefelter's syndrome. Klinefelter’s syndrome is the most common abnormality of sexual differentiation, and occurs in approximately 1 in 500 live births. It is one of the most common causes of primary hypogonadism, and is the most common sex chromosome abnormality seen in infertile men. Patients will present with a typical triad of small, firm testes; gynecomastia; and elevated urine gonadotropins. Variants of Klinefelter’s may also result in increased height, diabetes mellitus, obesity, and decreased intelligence. The infertility evaluation may be the first time the patient has a complete physical examination as an adult.

During the history, patients may describe the delayed completion of puberty and delayed virilization. There are usually few physical complaints associated with Klinefelter’s syndrome. There will be a lack of development of secondary sexual characteristics on physical examination (atrophy (< 2.0 cm) testes, small phallus, diminished body hair, diminished muscle bulk), and a feminine, or truncal, rather than male, fat distribution that often includes gynecomastia. Patients may be tall, due to a delay in the fusion of the epiphyseal plates in the long bones.

Clinical suspicion after the physical examination will usually lead to a karyotype analysis, which will show 47, XXY or a mosaic pattern such as 46, XY/47, XXY, indicating a diagnosis of Klinefelter’s syndrome. Serum hormone studies will demonstrate a decreased or normal testosterone, decreased free testosterone, elevated estradiol, normal or elevated LH, and elevated FSH.

Treatment for infertility in the patient with Klinefelter’s can take a variety of forms (see Table 7). It is only recently, with the advent of the microTESE (microsurgical testicular extraction) procedure, that patients diagnosed with Klinefelter’s syndrome were given the potential to father genetic offspring via microTESE and ICSI (intracytoplasmic sperm injection).

**Congenital bilateral absence of the vas deferens.** Congenital bilateral absence of the vas deferens is a genetic abnormality that is seen with cystic fibrosis (CF) and its multiple variants. If not previously diagnosed with cystic fibrosis, the patient may have one of the less-severe CF mutations, and report a history of chronic bronchitis that may have required hospitalization, recurrent respiratory infections as a child and adolescent, asthma or an asthma-like condition, or even have no symptoms at all (most common). There are usually no other physical complaints; but there may be a family history of infertility or persistent respiratory illnesses.

Males with CF frequently demonstrate malformation of the epididymis. The vas deferens, seminal vesicles, and ejaculatory ducts are generally atrophic or absent. Physical examination may show complete absence of the vas deferens unilaterally or bilaterally, or a palpable gap in the vas deferens. Testosterone levels in these patients will be normal. Spermatogenesis is usually normal as well, and so testes size and consistency are normal, with the patient describing normal libido and demonstrating appropriate secondary sexual characteristics. It is possible that the patient may have a much more rare unilateral absence of the vas deferens, which is usually associated with Wolffian duct abnormalities and renal malformations.

The physical examination and history are sufficient to confirm a suspicion of CF; the patient will be sent to a genetics clinic for additional counseling and testing. Males with CF have the option to sire genetic offspring via testicular aspiration and IVF.

**Anejaculation after a spinal cord injury or surgery.** Approximately 80% of spinal cord injured (SCI) men will demonstrate some preservation of their erectile function (Schuster & Ohl, 2002). Men with a T9 level injury or above can have reflex erections that do not persist long enough or are reliable for sexual activity. In men who have suffered lower motor neuron injuries (below T9), erectile activity is absent.

Ejaculatory function in men with SCI is a separate challenge. Only 5% to 15% of men will have any evidence of ejaculation after their injury (Biering-Sørensen & Sønksen, 2001) and this represents a major aspect contributing to infertility. This is complicated further by a significant decline in overall sperm quality. Sperm obtained from men who are unable to ejaculate demonstrate a variety of abnormalities that include significantly decreased...
motility and viability, decreased ability to penetrate cervical mucus, and decreased fertilizing capability. Only 5% of men with SCI will be able to initiate a pregnancy without some degree of medical intervention (Schuster & Ohl, 2002).

Surgical procedures in the pelvis or retroperitoneum can result in neurogenic impairment of the ejaculatory process by damaging peripheral nerves. This can manifest as an incompetent bladder neck and retrograde ejaculation, or total anejaculation. Men with testis cancer, in particular, are at risk for this type of injury with a RPLND. Men who suffer from surgically induced anejaculation will experience decreases to their semen quality similar to that of men with SCI.

Anejaculatory men can still father their own children: both penile vibratory stimulation (PVS) or electroejaculation (EEJ) are successful options for specific groups of patients and allows the possibility for IUI (see Table 8). Alternatively, anejaculatory men have the option to proceed with testes aspiration with IVF or IVF and ICSI.

### Table 7.
Examples of Treatment Options for Male Infertility Diagnoses

<table>
<thead>
<tr>
<th>Diagnosed Condition</th>
<th>Treatment Option A</th>
<th>Treatment Option B</th>
<th>Treatment Option C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antisperm antibodies</td>
<td>IUI</td>
<td>IVF + ICSI</td>
<td>Donor insemination + IUI</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>Testicular sperm extraction with IVF</td>
<td>Donor insemination + IUI</td>
<td>Adoption</td>
</tr>
<tr>
<td>Diabetes with anejaculation</td>
<td>Trial of sympathomimetic to promote antegrade ejaculation</td>
<td>Testicular sperm extraction with IVF</td>
<td>Donor insemination + IUI</td>
</tr>
<tr>
<td>Failed vasectomy reversal</td>
<td>Testicular sperm extraction with IVF</td>
<td>Donor insemination + IUI</td>
<td>Adoption</td>
</tr>
<tr>
<td>Hypergonadotropic hypogonadism</td>
<td>Possible hormone replacement</td>
<td>Testicular sperm extraction with IVF</td>
<td>Donor insemination + IUI; Adoption</td>
</tr>
<tr>
<td>Idiopathic male infertility</td>
<td>IUI +/- donor insemination (depends on count)</td>
<td>IVF +/- ICSI (depends on count)</td>
<td>Adoption</td>
</tr>
<tr>
<td>Klinefelter’s syndrome</td>
<td>MicroTESE and IVF</td>
<td>Donor insemination + IUI</td>
<td>Adoption</td>
</tr>
<tr>
<td>Persistent low sperm count after medical or surgical treatment</td>
<td>IUI</td>
<td>Donor insemination + IUI</td>
<td>IVF</td>
</tr>
<tr>
<td>Retrograde ejaculation</td>
<td>Trial of sympathomimetic to promote antegrade ejaculation</td>
<td>IUI</td>
<td>Testicular sperm extraction with IVF</td>
</tr>
<tr>
<td>Varicocele</td>
<td>Varicocele repair</td>
<td>IUI</td>
<td>IVF</td>
</tr>
</tbody>
</table>

IUI: Intrauterine insemination
IVF: In vitro fertilization
ICSI: Intracytoplasmic sperm injection

Other genetic causes. There are other less-commonly seen genetic causes of male infertility that include conditions such as Kallman’s syndrome, Y-chromosome microdeletions, various neuromuscular conditions, immotile cilia syndromes, and Kartagener’s syndrome. Depending on sperm counts, these patients can be offered sperm aspiration with IVF or IVF and ICSI.

Antisperm antibodies (immunologic infertility). Some men will demonstrate antisperm antibodies that are associated with their sperm. These can be antibodies that are attached to the head, tail, or all parts of the sperm, and their presence inhibits the fertilizing ability of the sperm. It is unclear precisely why these antibodies form, but it can be the result of vasectomy and reversal, testis injury or infection, or cancer; it can also be idiopathic. Past attempts at treatment of this condition with such medications as corticosteroids have met with little success.
Fertility Preservation

The future of infertility treatment continues to evolve. This is partly a response to changes in technology as a whole, but is also inspired by the increasing survival rates of cancers that affect young people during their reproductive years and the trend for couples to delay pregnancy. There are currently available options for preservation of fertility for men, primarily sperm cryopreservation; this can be a reasonable option for men planning to undergo chemotherapy or radiotherapy treatment and can serve as a “backup” in the event that spermatogenesis does not rebound after treatment. But it is also an option for those at risk for exposure to toxins or even those being deployed in the military. The future may see options for the storage of testicular tissue, autologous spermatogonial stem cell transplantation, or gene therapies to treat genetic causes of male infertility.

Conclusions

The discussion of treatments for a variety of male infertility diagnoses requires a basic understanding of male GU anatomy and function, as well as understanding of the hormonal processes that control spermatogenesis. The male infertility evaluation often represents the first time an otherwise healthy male is faced with the concept that he is somehow “not normal.” Not only can this be an affront to his masculinity, but depending on the larger religious and/or cultural context, failure to have children can impact his standing in his comm...
community. This can be heightened by the fact that the outcome is not always predictable, even with the use of assisted reproductive technologies. As technologies continue to progress, there will be new options that become available to couples whose only options currently are donor insemination or adoption.

References

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