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Overview of Current Approaches To the Evaluation and Management Of Male Infertility

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Infertility, the inability to conceive after one year of regular, unprotected intercourse, is secondary to male-only factors in 20% and a combination of male and female factors in 30% to 40% of cases. Advances in the identification and management of male factor infertility have provided new and often successful options for paternity.

Key Words: **Infertility, hypogonadism, assisted reproduction, semen analysis.**

Objectives:

1. Define infertility.
2. Discuss the importance of a thorough history of a patient with issues of infertility.
3. Explain the general examination of a patient with issues of infertility, to include physical examination, semen analysis, hormonal assessment, radiology, and post-ejaculatory urinalysis.
4. Describe the treatment options for male infertility.
5. Explain assisted reproductive technology and its impact on couples experiencing infertility.

Infertility is clinically defined as the inability of a couple to achieve conception after one year of regular, unprotected intercourse. It is currently believed that male factors contribute to 40% to 60% of infertility cases (Schlegel, 2009). This article seeks to provide an overview of the evaluation and management of male factor infertility. There are many different possible etiologies of impaired fertility in men, and because treatment efforts must be closely tailored to individual presentations, it is important to conduct a thorough initial evaluation of each case, which typically involves a focused history, physical examination, and laboratory testing.

History

A thorough history can provide many useful insights into possible causes of a patient's infertility. In obtaining a detailed sexual and fertility history, it is important to assess how long the couple has been trying to conceive, frequency of intercourse, and any previous fertility of either partner, as well as to pose questions regarding the use of any lubricants. The presence of any sexual dysfunction, such as erectile dysfunction or premature ejaculation, should be elicited as a part of the sexual history. Developmental history is also relevant, with a focus on onset of puberty and any history of undescended testes. Late-onset puberty may be indicative of endocrinologic dysfunction or andro-

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Note: *Objectives and CNE Evaluation Form appear on page 295.*

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gen receptor abnormality (Kulin, 1997; Sigman & Jarow, 2007), while cryptorchidism has been shown to result in decreased fertility (Cendron et al., 1989; Sigman & Jarow, 2007). A history of congenital anomalies should be evaluated; a variety of congenital anomalies are associated with hypogonadotropic hypogonadism, including Prader-Willi syndrome, Lawrence-Moon-Biedl syndrome, and Kallman syndrome. Klinefelter's syndrome is the most common genetic form of male hypogonadism, with a live birth prevalence rate of 4.3 to 15.0 per 10,000 live births or 8.4 to 29.0 male births (Buckton et al., 1980; Friedrich & Nielsen, 1975; Hamerton, Canning, Ray, & Smith, 1975; Hansteen, Varslot, Sleen-Johnsen, Langard, 1982; Jacobs, Melville, Ratcliffe, Keay, & Syme, 1974; Nielsen & Wohlert, 1991). Bojesen, Juul, and Gravholt (2003) noted Klinefelter's syndrome to be present in 153 per 100,000 babies tested prenatally. Klinefelter's syndrome is among the most frequent genetic causes of human infertility, occurring in 11% of azoospermic men and 4% of infertile men (Van Assche et al., 1996).

The past medical and surgical history focuses on a history of scrotal trauma or injury, such as testicular torsion, which could result in testicular atrophy or predispose the patient to develop anti-sperm antibodies (Cerasaro, Nachtsheim, Otero, & Parsons, 1984; Heidenreich, Bonfig, Wilbert, Strohmaier, & Engelmann, 1994; Sigman & Jarow, 2007). Infections such as mumps orchitis, sexually transmitted infections, recurrent urinary tract infections, and recent febrile illness could also impact fertility and should be noted (Sigman & Jarow, 2007). Also relevant to past medical history is a history of cancer, particularly testicular cancer, and prior chemotherapy or radiation therapy, which are known to impair spermatogenesis (Costabile, 1993; Orecklin, Kaufman, & Thompson, 1973; Rustin, Pektasides, Bagshawe, Newlands, & Begent, 1987; Sigman & Jarow, 2007). Retrograde ejaculation accounts for less than 2% of cases presenting to a fertility clinic (Jefferys, Siassakos, & Wardle, 2012). It may occur as a result of congenital abnormality, spinal trauma, retroperitoneal lymph node dissection (RPLND), bladder neck surgery, and diabetes mellitus; it can also be idiopathic.

The patient's past surgical history should reveal any prior prostatic, spinal, inguinal, scrotal, or retroperitoneal surgeries, which may affect ejaculatory function and/or cause vasal obstruction. In particular, a prior history of hernia and/or hydrocele repair as a child could result in vasal injury (Sigman & Jarow, 2007). Finally, a social history should be obtained to investigate any additional fertility risk factors, such as drug use. Nicotine and marijuana have been shown to impair spermatogenesis (Kolodny, Masters, Kolodner, & Toro, 1974; Marshburn, Sloan, & Hammond, 1989; Sigman & Jarow, 2007). Exogenous androgen excess caused by the use of anabolic steroids can impair spermatogenesis by suppressing gonadotropin-releasing hormone (GnRH), thus decreasing luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels. This causes a resultant decrease in intratesticular testosterone (McLachlan et al., 2002) and decreased serum testosterone levels. Patients may not consider testosterone therapy a "medication" given that it is a topical therapy, though exogenous testosterone replacement therapy may have an adverse effect on fertility (Hwang, Walters, & Lipshultz, 2011). Environmental exposures, such as pesticides, may be gonadotoxic (Sigman & Jarow, 2007), and exposure to heat from sources, such as saunas and hot tubs, may elevate testicular temperatures, also impairing spermatogenesis (Procopé, 1965; Sigman & Jarow, 2007).

Evaluation and Analysis

General Physical Examination

A general physical examination should first be conducted with an eye towards assessment of secondary sex characteristics, confirming virilization, as well as identifying signs of hormonal imbalance. For example, the presence of gynecomastia may suggest a decreased testosterone/estrogen ratio or excess prolactin (Sigman & Jarow, 2007). The majority of the physical examination should then be focused on the genital examination. The penis should be examined for hypospadias, which could interfere with proper semen deposition during intercourse (Sigman & Jarow, 2007). Testicular volume should be measured next because decreased testicular size can be an indication of impaired spermatogenesis (Lipshultz & Corriere, 1977; Sigman & Jarow, 2007).

Each testis can be measured using an orchidometer or calipers. The normal adult testis is greater than 20 ml in volume (Sigman & Jarow, 2007). Examination of the spermatic cords should verify that the vas deferentia are palpable bilaterally to rule out congenital bilateral absence of the vas deferens (CBAVD), which would result in ductal obstruction (Sigman & Jarow, 2007). Next, the patient should be carefully examined for varicoceles, which are best assessed by having the patient Valsalva in the standing position (Hwang et al., 2011). Varicoceles are detected in up to 40% of men presenting with infertility (Lipshultz, Thomas, & Khera, 2007). They may cause infertility by a variety of mechanisms, ranging from elevation of intrascrotal temperatures to venous reflux of renal and adrenal toxic metabolites (Comhaire & Vermeulen, 1974; Sigman & Jarow, 2007). Lastly, a digital rectal examination should note the sphincter tone, prostate size and consistency, and the presence of a

palpable midline cyst or enlarged seminal vesicles (Hwang et al., 2011).

Semen Analysis

Semen analysis is a routine component of the laboratory evaluation of the infertile male. Key parameters assessed by the standard semen analysis include semen volume, total sperm number, sperm concentration, sperm motility, sperm vitality, and sperm morphology (World Health Organization [WHO], Department of Reproductive Health and Research, 2010). The WHO has recently released revised guidelines for semen analysis, which establish the lower reference limits (see Table 1). By WHO guidelines, semen samples should be collected after 2 to 7 days of sexual abstinence (WHO, Department of Reproductive Health and Research, 2010). Abstinence periods are important because sperm density increases by 25% for each day of abstinence, up to four days (Carlsen, Petersen, Andersson, & Skakkebaek, 2004). Additionally, at least two samples should be collected and analyzed over a period of several weeks to provide an adequate assessment of the patient's baseline spermatogenesis (Carlsen et al., 2004; Sigman & Jarow, 2007).

Table 1.
Lower Reference Limits Used in Semen Analysis

Parameter	Lower Reference Limit (95% Confidence Interval)
Semen volume (ml)	1.5 (1.4 to 1.7)
Total sperm number (x 10^6)	39 (33 to 46)
Sperm concentration (x 10^6 per ml)	15 (12 to16)
Progressive motility (%)	32 (31 to 34)
Total motility (Progressive + Non-progressive, %)	40 (38 to 42)
Vitality (% live spermatozoa)	58 (55 to 63)
Morphology (% normal forms)	4 (3.0 to 4.0)

Note: Adapted with permission from WHO, Department of Reproductive Health and Research, 2010. Copyright 2010 WHO.

Hormonal Assessment

Hormonal evaluation is another form of laboratory testing that can yield important clues regarding the etiology of a patient's infertility. Serum FSH, LH, and testosterone provide an overview of the patient's hypothalamic-pituitary-gonadal axis. Best practice American Urological Association (AUA) guidelines recommend that men with an abnormal semen analysis, particularly if sperm concentration is less than 10 million/ml, should have at least FSH and testosterone levels obtained (AUA, 2010). If an endocrinologic abnormality is suspected by history and physical examination, or if initial FSH and testosterone levels are abnormal, a more extensive hormonal evaluation is recommended, including measurements of LH, prolactin, thyroid stimulating hormone (TSH), sex hormone binding globulin (SHBG), cortisol, and estradiol levels (Hwang et al., 2011).

Elevated serum FSH levels are usually indicative of impaired spermatogenesis because the elevation results from a lack of feedback inhibition, which is normally provided by inhibin, a hormone secreted by Sertoli cells, which play a key role in spermatogenesis (Sigman & Jarow, 2007; Turek, Kim, Gilbaugh, & Lipshultz, 1995). Elevated serum FSH in conjunction with elevated serum LH and low serum testosterone is a sign of complete testicular failure and primary hypogonadism (Sigman & Jarow, 2007). Patients with decreased levels of serum FSH, LH, and testosterone are likely to have hypogonadotropic hypogonadism (Sigman & Jarow, 2007), such as seen with Klinefelter's syndrome. These patients should also undergo measurement of serum prolactin to check for possible prolactinoma (Carter et al., 1978; Sigman & Jarow, 2007). Hyperprolactinemia accounts for infertility in about 11% of oligospermic men, who may present clinically with erectile dysfunction, decreased libido, and possible gynecomastia (Singh, Singh, Cugati, & Singh, 2011).

Radiologic Evaluation

In most infertile males, a radiologic evaluation is not a component of the initial evaluation. However, in males in whom genital tract obstruction, which may arise from ejaculatory duct obstruction or congenital anomalies, is suspected, a transrectal ultrasound (TRUS) may be helpful. Obstruction of the ejaculatory ducts may be suggested by the sonographic findings of dilated seminal vesicles or ejaculatory ducts. Absence or atresia of the seminal vesicles supports a physical examination finding of nonpalpable scrotal vas deferentia (Schlegel, 2009). Scrotal ultrasound is helpful in identifying testicular pathology, such as tumors or torsion. Lastly, an MRI of the brain is indicated if a pituitary tumor is suspected.

Post-Ejaculatory Urinalysis

If retrograde ejaculation is suspected, a post-ejaculatory urine sample can be assessed to determine if sperm are present. The presence of sperm (greater than 10/hpf or 20% antegrade ejaculated sperm) in the urine is suggestive of retrograde ejaculation (Schlegel, 2009).

Treatment of Male Infertility

There are four primary approaches to the management of male factor infertility. The first is to treat the underlying cause of infertility in the male, if reversible, such as in the case of anabolic steroid-induced male infertility, to improve the inherent potential for fertility. Other options include surgical intervention, pharmacologic means, or minimally invasive therapies, such as electroejaculation for anejaculatory infertility.

Treatment of Anabolic Steroid-Induced Male Infertility

Infertility after anabolic steroid abuse frequently presents as oligozoospermia or azoospermia, with abnormalities in sperm motility and morphology (Dohle, Smit, & Weber, 2003). Most reports indicate that with cessation of anabolic steroid use, sperm quality tends to recover spontaneously within 4 to 12 months after cessation (Turek, Williams, Gilbaugh, & Lipshultz, 1995). In some patients, if seminal and hormonal levels do not improve with time, patients can be treated in a manner similar to that used for other forms of hypogonadotropic hypogonadism infertility. In this case, reinduction of spermatogenesis is attempted with the administration of gonadotropins or gonadotropin analogues (de Souza & Hallak, 2011). The use of human chorionic gonadotropin (hCG) alone or in combination with human menopausal gonadotropin (HMG) has been shown to be successful in such patients (Menon, 2003).

Surgical Treatments

Anatomical abnormalities can often be addressed by surgical treatment. In the past, varicocele repair has been shown to result in improvement in seminal parameters in 70% of patients while yielding conception rates of 40% to 50% (Brown, 1976; Dubin & Amelar, 1977; Marks, McMahon, & Lipshultz, 1986; Marmar & Kim, 1994; Sigman & Jarow, 2007). However, a recent Cochrane review of the effect of varicocele repair (surgical or embolization) concluded there was insufficient evidence to support that varicocele repair in subfertile men improves couples' spontaneous pregnancy rates (Evers, Collins, & Clarke, 2009). In a meta-analysis review of the role of varicocele repair in male infertility, Baazeem et al. (2011) concluded there is insufficient evidence at present to demonstrate a beneficial effect of varicocele repair on spontaneous pregnancy rate. The procedure of varicocele repair has undergone major advancements with the introduction of the microsurgical approach to varicocelectomy. Through the use of a surgical microscope and intraoperative micro Doppler ultrasonic probe for arterial identification, the microsurgical technique allows for better preservation of the testicular artery and lymphatics. This has resulted in a decrease in post-operative complications, such as testicular artery injury, hydrocele formation, and varicocele recurrence (Khera & Lipshultz, 2008). Identification and isolation of the testicular artery by Doppler probe allows for more testicular veins to be ligated without concern for arterial injury (Khera & Lipshultz, 2008). The varicocele recurrence rate for non-microscopic inguinal varicocelectomy is reportedly 9% to 16% compared to a 1% to 2% recurrence rate for varicocele repairs performed microsurgically (Cayan, Kadioglu, Tefekli, Kadioglu, & Tellaloglu, 2000; Goldstein, Gilbert, Dicker, Dwosh, & Gnecco, 1992; Khera & Lipshultz, 2008; Marmar & Kim, 1994).

Vasovasostomy and vasoepididymostomy are two procedures used for vasectomy reversal, the latter of which can also be utilized in cases of epididymal obstruction. Following vasovasostomy, patency rates up to 99% have been reported with microsurgical vasovasostomy (Matthews, Schlegel, & Goldstein, 1995), while pregnancy rates range from 45% to 76% (Belker, Thomas, Fuchs, Konnak, & Sharlip, 1991; Boorjian, Lipkin, & Goldstein, 2004; Chan & Goldstein, 2004; Fox, 1994; Lipshultz et al., 2007). These rates have been shown to decline with increased interval from initial vasectomy (Belker et al., 1991). The risk of epididymal obstruction increases with duration since vasectomy, prompting the need for vasoepididymostomy rather than vasovasostomy (Chawla, O'Brien, Lisi, Zini, & Jarvi, 2004; Fuchs & Burt, 2002; Lipshultz et al., 2007). The decision to perform vasoepididymostomy is based on the quality of fluid expressed at the proximal vas deferens at the time of reversal. If the fluid is thick, pasty, and devoid of sperm, or if no fluid can be expressed from the cut end of the vas deferens, vasoepididymostomy may be indicated (Lipshultz et al., 2007). Patency and pregnancy rates following vasoepididymostomy vary widely depending on the degree of epididymal obstruction and skill of the surgeon (Lipshultz et al., 2007). They may be as high as 65% to 71.7%, with pregnancy rates of 11% to 56% (Matthews et al., 1995).

Pharmacologic Treatment For Low Testosterone in the Subfertile Male

In patients with idiopathic oligospermia, clomiphene citrate may be used as a form of empirical pharmacologic therapy. Clompihene citrate is an anti-estrogen agent that works by blocking the feedback inhibition of estrogen at the hypothalamus, serving to increase the production of FSH and LH (Sigman & Jarow, 2007). Although the use of clomiphene citrate in women can be associated with vasomotor flushing, visual blurring, abdominal bloat-

ing, and urticaria (Lobo, 2007), multiple studies have reported no adverse effects experienced by male patients undergoing clomiphene citrate therapy (Shabsigh et al., 2005; Taylor & Levine, 2010). A Cochrane database review concluded that although anti-estrogens appear to have a beneficial effect on endocrinologic outcomes, there is not enough evidence to evaluate their use for increasing the fertility of males with idiopathic oligoasthenospermia (Vandekerckhove, Lilford, Vail, & Hughes, 2000). However, in a small study of 60 infertile men with idiopathic oligoasthenozoospermia (having decreased sperm concentration and motility), the combination of clomiphene citrate (25 mg/day) and vitamin E (400 mg/day) significantly increased pregnancy rate and improved sperm count (Ghanem, Shaeer, & El-Segini, 2010). The odds ratio was 2.76, and the 95% confidence interval was 1.03 to 13.64, with a pregnancy rate of 36.7% (11/30) in the combination group compared to 13.3% (4/30) in the control group (Ghanem et al., 2010).

Management of Retrograde Ejaculation

The goal of treatment methods for retrograde ejaculation is to restore antegrade ejaculation though medical therapy or with surgical procedures, or to retrieve sperm from the urine to be used with assisted reproduction.

Medical management aims to increase the tone of the bladder neck, preventing retrograde flow of semen into the bladder. This can be achieved either by stimulating sympathetic activity (closure of the bladder neck is under sympathetic control) or by blocking parasympathetic input (parasympathetic activity is responsible for bladder neck relaxation) (Jonas, Linzbach, & Weber, 1979; Stewart, & Bergant, 1974; Stockamp, Schreiter, & Altwein, 1974). Treatment of retrograde ejaculation includes antihistamines (brompheniramine), tricyclic antidepressants (imipramine), and other agents, including anticholinergic and adrenergic agents (Kamischke, & Nieschlage, 2002). Araja and Tabie (2008) noted in cases of males with diabetes mellitus with complete retrograde ejaculation that imipramine (25 mg twice a day) was successful in producing antegrade ejaculation in 10 patients (38.5%), while pseudoephedrine (120 mg twice a day) was successful in 11 patients (47.8%); both drugs given together were successful in 16 patients (61.5%). In those with partial retrograde ejaculation, significant increases in antegrade semen volume, total sperm count, and progressive motility were noted with either agent alone and in combination.

The goal of surgical intervention is restoration of bladder neck integrity. Limited data are available regarding the use of surgical intervention in the treatment of retrograde ejaculation. However, Reynolds, McCall, Kim, and Lipshultz (1998) successfully injected collagen into the bladder neck of a male with retrograde ejaculation, achieving antegrade ejaculation, two subsequent pregnancies, and one live birth. Electroejaculation is primarily used to achieve antegrade ejaculation in anejaculatory men following retroperitoneal lymph node dissection or spinal cord injury (Brackett, Lynne, Ibrahim, Ohl, & Sonksen, 2010; Hsiao, Deveci, & Mulhall, 2012).

Urinary sperm retrieval aims to obtain sufficient viable sperm from the post-ejaculatory urine for insemination, in-vitro fertilization (IVF), or intracytoplasmic sperm injection (ICSI) (Jefferys et al., 2012). In urinary sperm retrieval, a post-ejaculatory urine specimen is obtained either by voiding or catheterization, usually after alkalinization of the urine using oral sodium bicarbonate or by increasing oral fluid intake to dilute the urine. The sample is suspended in medium, centrifuged, and resuspended before being used for vaginal insemination, intrauterine insemination (IUI), IVF, ICSI, or intraperitoneal insemination (Jefferys et al., 2012). In a systematic review of the literature, Jefferys et al. (2012) noted a pregnancy rate of 13% per cycle in IUI cycles using this method. An alternative technique attempts to circumvent the problem of retrograde ejaculation by encouraging the patient to ejaculate when his bladder is full, in an attempt to promote antegrade ejaculation, which could then be used for IUI (Crich & Jequier, 1978; Templeton & Mortimer, 1982).

Assisted Reproductive Technology

The next step in the management approach is to attempt to achieve conception by utilizing assisted reproductive technology (ART). IUI is a technique by which a processed semen sample, washed to remove prostaglandins, leukocytes, and nonmotile sperm, is injected via catheter directly into the upper uterine cavity. IUI is useful in cases where normal deposition of semen cannot be achieved through intercourse, whether due to hypospadias, erectile dysfunction, or ejaculatory dysfunction (Sigman & Jarow, 2007). Men with abnormal semen parameters can also benefit from IUI because the procedure allows sperm to bypass the cervical mucus, thus increasing the chances of conception (Sigman & Jarow, 2007). The efficacy of IUI can be increased when combined with controlled ovarian hyperstimulation (COH) (Arici et al., 1994; Nulsen, Walsh, Dumez, & Metzger, 1993; Sigman & Jarow, 2007). Although pregnancy rates are to an extent dependent on motile sperm count, rates of 10% to 18% per IUI cycle have been reported (Ombelet, Campo, Bosmans, & Nijs, 2008). This method of ART is not an option for men with severe oligospermia (having de-

creased sperm concentration) or azoospermia (having no detectable sperm in the semen) (Mangoli, Dandekar, Desai, & Mangoli, 2008).

In-vitro fertilization (IVF) is an alternate form of ART. Conventional IVF involves mixing a processed semen sample with oocytes harvested from the female partner, looking for fertilization to occur, and placing the resultant embryos into the uterus. The efficacy of IVF is improved by the technique of intracytoplasmic sperm injection (ICSI), in which a single sperm is directly injected into the cytoplasm of a mature oocyte. The technique was developed by Gianpiero Palermo in 1991 (Palermo, Joris, Devroey, & Van Steirteghem, 1992). The success of ICSI is believed to depend on 1) the viability of spermatozoon, 2) the quality of the oocyte, 3) effective activation of the oocyte, and 4) the ability of the oocyte to tolerate intracytoplasmic manipulation (Schlegel & Girardi, 1997). Unlike conventional IVF, IVF with ICSI allows for the circumvention of key steps of the standard fertilization process, including the sperm having to bind and penetrate the zona pellucida of the oocyte (Liu, Garrett, & Baker, 2004). Thus, ICSI drastically improves the fertility prognosis of men who are severely oligospermic or asthenospermic (having decreased sperm motility). Although strict criteria for ICSI have not been fully defined, sperm concentration less than 2 x 10^6 sperm/ml, sperm motility less than 5%, strict criterial normal morphology less than 4%, use of surgically retrieved spermatozoa, and failure of fertilization with a prior IVF cycle are often used as indications for ICSI (Schlegel & Girardi, 1997).

In the case of azoospermic men, it is possible that some sperm may be present in the testes or the ductal system and could be retrieved by a variety of surgical procedures (Sigman & Jarow, 2007). These procedures include microsurgical epididymal sperm aspiration (MESA), in which the epididymis is opened under an operating microscope and fluid is aspirated and examined for the presence of motile sperm; testicular sperm aspiration (TESA), in which testicular tissue is aspirated by a needle and examined for sperm; and testicular sperm extraction (TESE), in which the testis is opened by a single incision and a biopsy is obtained and examined for sperm. In an updated variant of the latter procedure, known as microdissection TESE (micro-TESE), the exposed seminiferous tubules are examined under an operating microscope in a systematic search to identify fuller tubules that may contain sperm, which are then extracted and examined (Lipshultz et al., 2007). Sperm retrieved from any of these procedures may be used for ICSI. Pregnancy rates of IVF with ICSI range from 20% to 37% per cycle (Sigman & Jarow, 2007).

Treatment options provided by IVF and ICSI do not come without their share of inherent risks. Current guidelines recommend the transfer of anywhere from one to five embryos per cycle, depending on maternal age and developmental stage of the embryo (Practice Committee of the Society for Assisted Reproductive Technology & Practice Committee of the American Society for Reproductive Medicine, 2006); thus, 32.5% of all resultant pregnancies are multiple gestations, with 3.5% of pregnancies being triplet or higher-order gestations (Centers for Disease Control and Prevention [CDC], 2010). In addition, the risk of passing on genetic defects to potential offspring is a primary area of concern, as there is evidence of increased sex chromosomal abnormalities among children conceived through ICSI (Tarlatzis & Bili, 2000). The relationship of ICSI to sex chromosomal abnormalities in the offspring may be related to the association between Y chromosomal abnormalities and severe male factor infertility (Kim et al., 2010). The rates of non-sex chromosomal abnormalities in the ICSI population, however, have not been found to exceed the rates seen in the general population (Schlegel & Girardi, 1997).

In addition to the potential for genetic abnormalities, researchers have also questioned the effects of ICSI on the cognitive and motor development of ICSI-conceived children. An earlier Australian study reported a significantly lower mental developmental index for ICSI-conceived babies than for both conventional IVF-conceived babies and naturally conceived babies (Bowen, Gibson, Leslie, & Saunders, 1998). However, a more recent European study identified no differences between the groups of ICSI, IVF, and naturally conceived children with respect to either full scale IQ or motor scale scores (Ponjaert-Kristoffersen et al., 2005).

ART in the Setting of Genetic Abnormalities

Klinefelter's syndrome (47, XXY) represents the most common karyotype abnormality in azoospermia and severe male factor infertility, followed by Y chromosome terminal deletions (Yq-) and structural autosomal abnormalities (Krausz, 2011). Many patients with Klinefelter's syndrome do not have the classic phenotype; thus, underdiagnosis is common. Only one out of four adult males with Klinefelter's syndrome are diagnosed, and less than 10% of the expected number are diagnosed before puberty (Abramsky & Chapple, 1997; Bojeson et al., 2003; Van Assche et al., 1996). Testicular biopsy of prepubertal boys with Klinefelter's syndrome shows preservation of seminiferous tubules with a decrease in the number of germ cells, but nor-

mal-appearing Sertoli and Leydig cells. The testes in adult males with Klinefelter's syndrome have extensive fibrosis and hyalinization of the seminiferous tubules and hyperplasia of the interstitium. However, there may be residual foci of spermatogenesis (Wikstrom & Dunkel, 2011). Although patients with Klinefelter's syndrome are traditionally thought to be infertile, using TESE combined with ICSI, fertility is possible. The initial success rate of TESE in adult males with Klinefelter's syndrome in small series has been 40% to 50% (Lanfranco, Kamischke, Zitzmann, & Nieschlag, 2004). However, microdissection TESE has yielded sperm recovery rates as high as 70% (Schiff et al., 2005). Currently, testicular ultrasound, chromosomal analysis, degree of virilization, testicular volume, serum testosterone, FSH, LH, and inhibin levels have all failed to be predictive of TESE outcome in patients with Klinefelter's syndrome (Vernaeve et al., 2004; Westlander et al., 2001).

Impairment of fertility is an evolving phenomenon in Klinefelter's syndrome. Thus, there is an option for cryopreservation of sperm in adolescents with Klinefelter's syndrome (De Sanctis & Ciccone, 2010). It is recommended that in such cases, pediatricians inform parents and patients about potential strategies for preservation of future fertility and that assent from the adolescent is obtained. Ideally, ejaculated sperm are obtained and stored for subsequent use. If ejaculated sperm cannot be obtained, an early morning urine sample can be evaluated for sperm. Spermaturia is present in 1% to 2% of boys 11 years of age, 15% to 37% at 12 to 13 years of age, and 24% to 69% at 14 years of age (Fallat & Hutter, 2008). The role of cryo-TESE in young patients is not addressed well in the literature, and thus, careful counseling should ensue (Krausz & Forti, 2006).

Y chromosome microdeletion is the most frequent known molecular genetic cause of severe impairment of spermatogenesis (Krausz, 2011). Its frequency is about 10% in non-obstructive azoospermia, and 3% to 5% in idiopathic severe oligozoospermia (Krausz & Degl'Innocenti, 2006). The identification of Y chromosome microdeletions is important not only for diagnosis, but also because it has a prognostic impact on TESE (Brandell et al., 1998; Krausz, Quintana-Murci, & McElreavey, 2000). If AZFa and AZFb deletions on the Y chromosome are noted, the chance of finding sperm on testicular biopsy is virtually zero (Krausz, 2011). Furthermore, those Y chromosomal deletions compatible with the presence of sperm in the testis or ejaculate are transmitted to male offspring, and thus, genetic counseling is necessary (Krausz, 2011).

Alternatives to Treatment

Lastly, the final approach in the management of male infertility would be to bypass the affected male entirely, through the use of either donor sperm or adoption. This option may bear consideration in certain individual cases, such as in men with no identifiable sperm on TESE or testicular biopsy, or in men with certain Y chromosome microdeletions.

Summary

The advancements of present day medical technology have afforded infertile men with a notably improved prognosis for biological paternity. For many years, azoospermic and severely oligospermic men were offered donor sperm or adoption as their only options for parenthood. However, the realization that viable sperm may still be retrieved in these men, in combination with advances in ART, has made it possible for these individuals to conceive, revolutionizing the field of male infertility in the process. Nevertheless, the technology represented is still relatively new, and researchers are far from reaching a consensus regarding the safety and long-term outcomes of procedures such as ICSI. Given the notable risks involved, it remains advisable for couples considering ART to receive comprehensive genetic counseling prior to deciding on a plan of action. Ultimately, the technology at hand serves to provide these couples with a new hope and the opportunity to start a family, which when considering the issues involved, may prove to be well worth the risk.

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continued on page 304

Management of Male Infertility

continued from page 294

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