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The Evaluation and Management of the Azoospermic Patient

Review

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The incidence of azoospermia in infertile men is between 5% and 20%, while in the general population, it is about 2% (Jarow et al, 1989; Jarow, 1992). In the past, the main purpose of the evaluation of the azoospermic patient was to differentiate between excurrent duct obstruction and testicular failure. If the patient had uncorrectable obstruction or testicular failure, the couple's choices for parenting were donor insemination or adoption, with no options available for having their own biological children. In addition, the underlying cause was poorly understood.

The field of male factor infertility has changed dramatically in the last 10 years. First, the introduction of intracytoplasmic sperm injection (ICSI) and specialized sperm retrieval procedures have made it possible to circumvent some of the most severe forms of male factor infertility (Palermo et al, 1992). If at least 1 viable sperm per oocyte is available, the pregnancy rate with ICSI is dependent on female age and the number of oocytes retrieved (Sherins et al, 1995; Silber et al, 1997). Second, advances in basic science have improved our understanding of the etiology of both obstructive and nonobstructive azoospermia (NOA) (Anguiano et al, 1992; Foote et al, 1992; Vollrath et al, 1992; Reijo et al, 1995; Saxena et al, 1996; Lahn and Page, 1997). The purpose of this report was to provide an update on the evaluation and management of the azoospermic man.

Definition

''Azoospermia'' is defined as the absence of sperm in a centrifuged semen sample, while ''aspermia'' refers to an absent ejaculate. Azoospermia is classified as either obstructive or nonobstructive. Obstructive azoospermia is characterized by a testis biopsy demonstrating sufficient spermatogenesis and a physical occlusion of the reproductive tract distal to the testis that prevents sperm from entering the semen. Nonobstructive azoospermia (NOA) is caused by severely reduced sperm production, resulting in the absence of sperm in the semen. Even if sperm retrieval and intracytoplasmic sperm injection (ICSI) are being employed, this distinction is still important for 2 reasons. First, successful sperm retrieval is far more likely with obstructive azoospermia. Second, the potential underlying genetic defects is different in the 2 types of azoospermia.

Evaluation

The evaluation of the azoospermic man consists of a complete history, a physical examination, and the appropriate laboratory testing (Figure). Most men will have either ductal obstruction or testicular failure. Endocrine abnormalities such as Kallmann syndrome will be confirmed with endocrine testing. Ejaculatory dysfunction would not be expected to present with azoospermia but rather, with a low volume or absent ejaculate (Jarow, 1992; Sigman et al, 1997).

History and Physical Examination—A careful history can help identify the underlying cause of azoospermia in some cases. Specific questioning about prior fertility, age of sexual maturation, and history of congenital anomalies is important and may help to determine the underlying diagnosis. In addition, a thorough history and physical may be able to differentiate between obstructive azoospermia and NOA. Anosmia or a history of visual disturbances may suggest an underlying pituitary etiology. A history of prior inguinal or scrotal surgery or epididymitis raises the possibility of an obstructive etiology (Jarow, 1992; Sigman et al, 1997). The combination of chronic bronchitis, bronchiectasis, and azoospermia is consistent with Young syndrome (Hughes et al, 1987). A history of cryptorchidism, spermatic cord torsion, or cytotoxic chemotherapy treatment would suggest NOA. Anabolic steroid use can cause azoospermia, which, in some cases, is reversible (Turek et al, 1995). Medications associated with impaired sperm production or function are listed in Table 1 (Sigman et al, 1997).

The physical examination can contribute important information about the underlying cause of azoospermia. The head, neck, lung, heart, and abdominal examination are important for assessing the overall health of the patient. Hair and fat distribution, presence of gynecomastia, and overall virilization can provide clues about the patient's hormonal status. Inguinal surgical scars, possibly not recognized by the patient, suggest the possibility of obstruction from previous surgery. Because the majority

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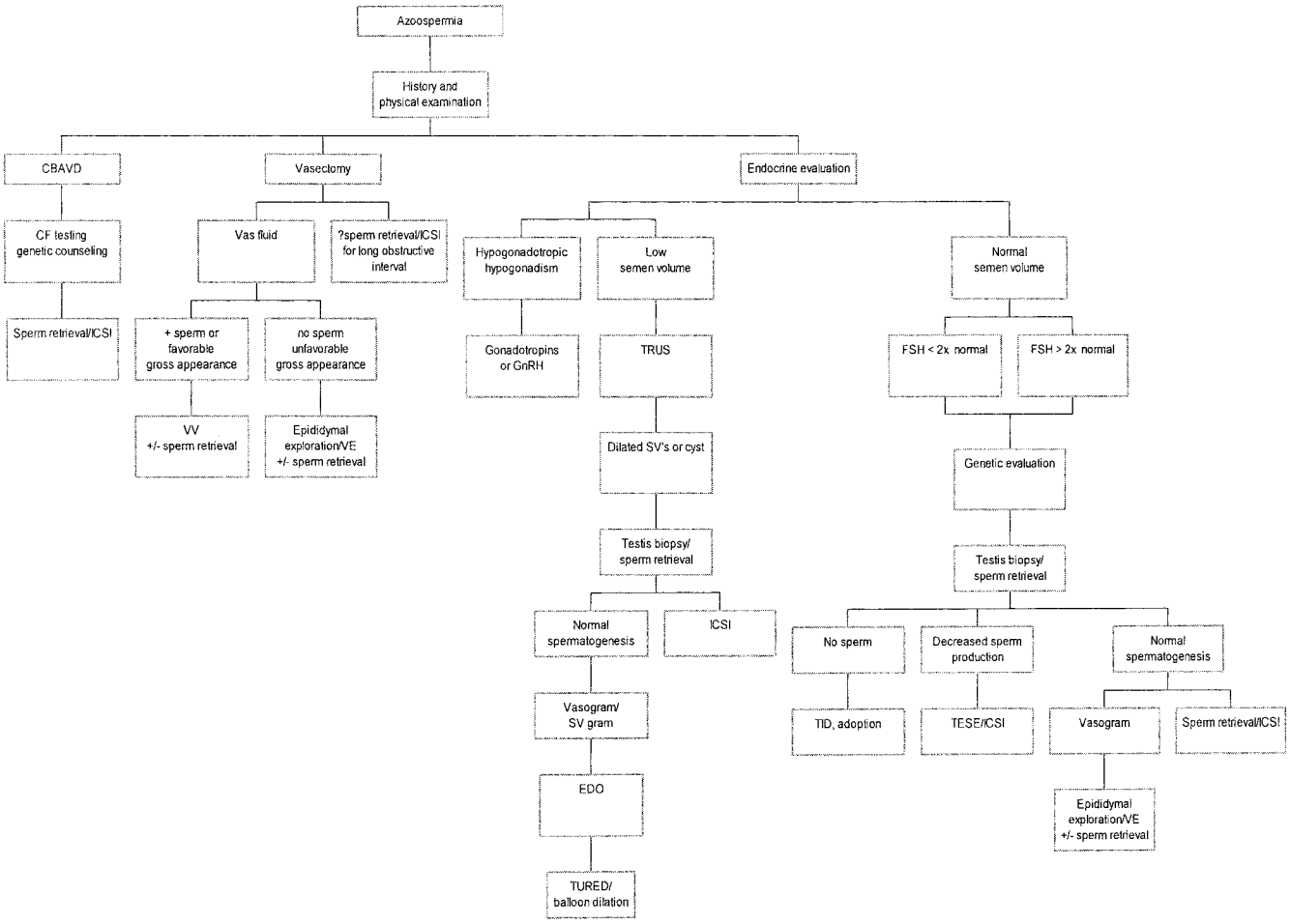

CBAVD indicates congenital bilateral absence of the vas deferens; CF, cystic fibrosis; ICSI, intracytoplasmic sperm injection; VV, vasovasostomy; VE, vasoepididymostomy; GnRH, gonadotropin releasing hormone; TRUS, transrectal ultrasound; SVs, seminal vesicles; EDO, ejaculatory duct obstruction; TURED, transurethral resection of the ejaculatory ducts; FSH, follicle-stimulating hormone; TID, therapeutic insemination with donor sperm; and TESE, testicular sperm extraction.

Table 1. *Drugs that can affect sperm production or function (Sigman et al, 1997)*

Alcohol
Alkylating agents
Allopurinol
Anabolic steroids
Cimetidine
Cocaine
Colchicine
Cyclosporine
Erythromycin
Gentamicin
Marijuana
Neomycin
Nitrofurantoin
Spironolactone
Sulfasalazine
Tetracyclines

of the testis is composed of the seminiferous epithelium, small testes are suggestive of spermatogenic failure. Careful palpation of the testes for masses is important because testicular tumors are more common in infertile men (Honig et al, 1994). Careful scrotal examination for presence or absence of the vas deferens is critical, and palpable induration or fullness of the epididymis, though a subjective finding, can indicate epididymal obstruction. With the patient in the standing position, palpation of dilated veins of the spermatic cord confirms the diagnosis of a varicocele. In an azoospermic man, a varicocele may be a cause of azoospermia, but it may also be only an incidental finding (Pryor et al, 1997; Matthews et al, 1998; Kim ED et al, 1999). On digital rectal examination (DRE), abnormalities of the prostate, such as induration or nodules, and seminal vesicles, such as enlargement, may be appreciated. As more couples delay parenting, men at risk for prostate cancer may be seen in consultation for infertility. Thus, early detection of prostate cancer

and palpation of seminal vesicle abnormalities suggestive of ejaculatory duct anomalies provide justification for the DRE in appropriate cases. This is particularly true for men seen regarding vasectomy reversal who tend to be older.

Laboratory Evaluation—The semen analysis establishes the diagnosis of azoospermia and is the foundation of the laboratory evaluation. Two samples, collected after at least 2 or 3 days' abstinence, should be examined. The sample should be centrifuged and the pellet resuspended and reexamined for sperm (Jaffe et al, 1998). Measurement of the semen volume (normal, >1.5 mL) directs further evaluation. The most common cause of low semen volume is incomplete collection, so it should be confirmed on at least 2 samples with sufficient abstinence time. Most of the seminal fluid is produced by the prostate and seminal vesicles, while the testis and epididymis contribute less than 5% of the total semen volume (Jarow, 1992). Therefore, low semen volume may reflect an abnormality of the prostate or seminal vesicles (see below). Fructose is produced by the seminal vesicles, so the absence of fructose indicates either ejaculatory duct obstruction or seminal vesicle aplasia/hypoplasia. The latter can be seen with congenital bilateral absence of the vas deferens (CBAVD), which can be differentiated from ejaculatory duct obstruction by physical examination.

The initial hormonal evaluation includes a measurement of serum follicle-stimulating hormone (FSH) and testosterone (T). If both are normal, then no further hormonal evaluation is required. If the T level is low, then it should be repeated, and serum–luteinizing hormone (LH) and prolactin levels should be measured. Determining the prolactin level is also indicated in the setting of any other history or findings suggestive of hyperprolactinemia (Sigman and Jarow, 1997). Inhibin B is produced by the Sertoli cells of the testis and thus may be a more direct measure of spermatogenesis than serum FSH (Illingworth et al, 1996; Anderson et al, 1997; Klingmuller and Haidl, 1997). Currently, though, inhibin B is not considered part of the standard evaluation of male infertility.

Although most men with an elevated FSH have spermatogenic failure, there is no FSH level above which obstruction can be ruled out (Jarow, 1992). Azoospermic men with an FSH less than 2 times normal and at least 1 palpable vas deferens potentially have an obstruction. Testis biopsy is indicated in these men (Jarow et al, 1989). Azoospermic men with an FSH greater than 2 times normal were previously discouraged from undergoing testis biopsy because the chance of excurrent ductal obstruction was low. These men, although they likely have testicular failure, may have sperm present in their testes and can potentially establish a pregnancy with testicular sperm extraction (TESE) and ICSI (Chen et al, 1996; Kim et al, 1997; Jezek et al, 1998). Men with suspected testicular failure may therefore still benefit from testis biopsy.

Low FSH, T, and LH values suggest hypogonadotropic hypogonadism. Pituitary imaging should be performed to rule out a mass lesion. Azoospermic men with low semen volume, a normal FSH, and at least 1 palpable vas deferens should undergo transrectal ultrasonography (TRUS) to evaluate for ejaculatory duct obstruction (Jarow et al, 1989).

Genetic Evaluation—An abnormal karyotype is found in 13.7% of azoospermic men (Van Assche et al, 1996). The genetic evaluation of the azoospermic man therefore begins with this test, which has 2 purposes. First, the test may diagnose genetic abnormalities such as Klinefelter syndrome, translocations, monosomies, or inversions. Second, these men who were previously infertile are now potentially fertile with TESE and ICSI. If a karyotypic abnormality is discovered, then appropriate genetic counseling is required because there are potential genetic consequences for any offspring (Van Assche et al, 1996; Rucker et al, 1998).

Up to 2% of male infertility is caused by CBAVD (Lissens et al, 1996). A relationship between cystic fibrosis (CF) and CBAVD was suggested by Holsclaw et al (1971) and confirmed in later studies (Anguiano et al, 1992; Dumur et al, 1996). Over 70% of men with CBAVD have at least 1 mutation in the CF transmembrane conductance regulator (CFTR) genes currently tested for (Jaffe and Oates, 1997). CBAVD in most men can therefore be viewed as a mild form of CF, with the vasal anomaly as its only manifestation (Anguiano et al, 1992). Men with CBAVD should therefore undergo evaluation for CF gene mutations. The carrier frequency for CF in Northern Europeans is 5%, so it is important to test the man's partner as well, especially if the man is a carrier. The most common combinations associated with CBAVD are a compound heterozygote for CF or a combination of a CFTR mutation and the intron 8 5T splice variant. Therefore, testing for the 5T variant is also clinically useful in counseling patients about their risk of having a child with CBAVD (Lissens et al, 1996).

In some cases, congenital unilateral absence of the vas deferens (CUAVD) can also be related to CFTR mutations, as illustrated by Mickle et al (1995). This is particularly true in those patients with an obstruction of their solitary vas deferens. In 9 patients with CUAVD and an obstructed vas deferens at the inguinal or pelvic level, 8 of 9 (89%) had 1 CF mutation but no renal anomalies. These patients can therefore be viewed as having CFTR abnormalities that do not allow an intrinsically normal mesonephric duct to develop fully after the separation between the urinary and reproductive portions of the mesonephric duct. Other forms of CUAVD are simply mesonephric abnormalities unrelated to CF. In this same

study, those patients with CUAVD and a completely patent vas deferens did not have any CFTR mutations but were more likely to have renal anomalies. Of these patients, 5 of 12 (42%) had an ipsilateral renal anomaly on the side of the absent vas deferens. These patients can be viewed as having an intrinsic defect in mesonephric duct development and morphogenesis (Mickle et al, 1995). Men with CUAVD should therefore undergo CF testing and renal ultrasound, although it would be expected that the incidence of renal anomalies in men with a CF mutation would be low.

Our understanding of NOA has improved dramatically in the last 10 years. In 1976, Tiepolo and Zuffardi first noted deletions of the distal portion of band q11 on the Y chromosome, termed the ''azoospermia factor'' (AZF), in 6 azoospermic men. Additional molecular work has further defined the genes and gene families on the Y chromosome (Foote et al, 1992; Vollrath et al, 1992; Reijo et al, 1995; Kent-First et al, 1996; Qureshi et al, 1996; Saxena et al, 1996; Vogt et al, 1996; Kremer et al, 1997; Lahn and Page, 1997; Ferlin et al, 1999; Kim ED et al, 1999; Kleiman et al, 1999; Krausz et al, 1999). Reijo et al (1995) reported that 12 of 89 (13%) of men with NOA had deletions in a portion of Yq that has been termed the ''DAZ'' (deleted in azoospermia) gene.

Vogt et al (1996), on the basis of his laboratory's work, has proposed subdividing the AZF region into subregions A, B, and C. The DAZ gene is contained within the AZFc region. Men with AZFa and entire AZFb region deletions appear to have less favorable histology and poorer prognosis for successful sperm retrieval (Vogt et al, 1996; Brandell et al, 1998). In one report, no azoospermic men with deletions involving AZFb had sperm successfully retrieved, while both men with isolated AZFc deletions did (Brandell et al, 1998). Men with AZFc deletions can therefore have sperm retrieved from their testes (or may have sperm in their ejaculate), and these gene defects can be transmitted to offspring (Kent-First et al, 1996; Mulhall et al, 1997b; Brandell et al, 1998; Jiang et al, 1999; Page et al, 1999). Therefore, it is important to discuss this issue with patients and test for these gene defects prior to TESE. In general, it is possible for men with Y chromosome deletions to father children naturally, as illustrated by a father and 4 sons, all of whom had these deletions (Chang et al, 1999). Given that such deletions are associated with a widely variable phenotype, the site and location of Y chromosome deletions are critically important in any statement about fertility.

Testis Biopsy—Except in cases of vasectomy or the majority of cases of CBAVD, a testis biopsy is required to document obstruction. Biopsies may be indicated in selected patients with CBAVD, such as those with an elevated FSH (Meng et al, 2001). The technique for diagnostic testis biopsy is straightforward. An open biopsy can be performed through a small scrotal incision using a window technique. Delivery of the testis is usually not required for a standard diagnostic biopsy (Nagler and Thomas, 1987; Coburn et al, 1997). In addition, a touch imprint can yield useful information at the time of the biopsy. These preparations can help differentiate between late maturation arrest and normal spermatogenesis, which may be difficult on frozen or paraffin sections. This technique is performed by gently touching the biopsy specimen to a slide. The slide is then immediately sprayed with fixative (Coburn et al, 1987, 1997). The intratesticular arterial anatomy has been described by Jarow (1991). To avoid injury to significant branches of the testicular artery, the biopsies should be performed in either the medial or lateral aspect of the upper pole of the testis (Jarow, 1991). In one study, there was a 28% intraindividual difference in pathology when bilateral sampling was performed, suggesting that bilateral biopsies may be important, particularly in evaluating a man for possible sperm retrieval (Plas et al, 1999).

Pathological review is performed both to document the pattern of sperm production and to rule out underlying testicular pathology such as intratubular germ cell neoplasia (ITGCN), previously termed ''carcinoma in situ.'' This condition may occur in 0.4%–1.1% of infertile men (Coburn et al, 1997). Frank seminoma has also been discovered in patients with NOA at the time of TESE (Novero et al, 1996). The tissue for diagnostic biopsy should be fixed immediately in an appropriate fixative such as Bouin solution that does not destroy the testicular architecture. A diagnostic classification system devised by Levin (1999) is useful in describing the pattern of sperm production. A system described by Silber and Rodriguez-Rigau (1981) can be used to quantitate spermatogenesis. In the setting of azoospermia, more than 20 mature spermatids per round tubule on biopsy would be consistent with a sperm concentration of 10 million sperm per milliliter (Silber and Rodriguez-Rigau, 1981). The biopsy can also be examined intraoperatively. If sufficient numbers of sperm are noted, suggesting obstruction, then simultaneous microsurgical reconstruction can be performed in the same setting (Belker et al, 1996).

A testis biopsy can also be performed percutaneously with a biopsy gun or by fine needle aspiration. Fewer tubules may be seen on a percutaneous biopsy, making pathological interpretation more difficult (Harrington et al, 1996; Rosenlund et al, 1998). Both of these procedures are performed blindly, but there appears to be no increased risk for bleeding (Harrington et al, 1996).

Management

Endocrine Abnormalities—The most common endocrine abnormality associated with azoospermia is an elevated FSH with testicular failure. No specific therapy is avail-

Table 2. *Results of microsurgical vasovasostomy*

Authors	Year	# Patients	Patency Rate	Pregnancy Rate
Cos et al	1983	87	75% (66/87)	46% (32/69)
Requeda	1983	47	80% (38/47)	46% (18/39)
Owen and Kapila	1984	475	93% (439/475)	82% (390/475)
Lee	1986	324	90% (292/324)	51% (165/324)
Silber*	1989	282	91% (258/282)	81% (228/282)
Belker et al	1991	1247	86% (865/1012)	52% (421/808)
Fox	1994	103	84% (86/103)	48% (31/64)
Total		2565	88% (2044/2330)	62% (1285/2061)

* Excluding 44 patients with no sperm in the vasal fluid. Patency and pregnancy rates for the study population of 326 patients were 79% and 70%, respectively.

able for this condition, and TESE/ICSI may allow the patient to have his own biological children. Azoospermia secondary to anabolic steroid use may be reversed with withdrawal of the offending drug (Turek et al, 1995). Gonadotropin deficiency can be corrected with pharmacologic management. The most common correctable endocrine deficiency associated with infertility is hypogonadotropic hypogonadism (Sigman and Jarow, 1997). In these men, pituitary magnetic resonance imaging should be performed to rule out a mass lesion. If this is negative, then therapy with gonadotropins can initiate spermatogenesis. It can take longer than 1 year to induce production of acceptable semen parameters. Pregnancies can be established despite subnormal sperm concentrations in men with congenital hypogonadotropic hypogonadism (Jarow, 1992; Burgues and Calderon, 1997; Yong et al, 1997). Rare cases of isolated FSH deficiency have also been reported (Diez et al, 1994).

Obstructive Azoospermia: Vasal and Epididymal Obstruction—Obstructive azoospermia is correctable with microsurgery in many cases. Alternatively, sperm retrieval and ICSI can be employed if surgical correction is not possible or not desired by the couple. Vasal obstruction secondary to vasectomy can be corrected with microsurgical vasovasostomy (VV). Patency and pregnancy rates for VV range from 75% to 93% and from 46% to 82%, respectively (Cos et al, 1983; Requeda, 1983; Owen and Kapila, 1984; Lee, 1986; Silber, 1989b; Belker et al, 1991; Fox, 1994) (Table 2). In 1991, the Vasovasostomy Study Group (VVSG) published their report, which remains the most widely quoted study on the subject. This report demonstrated that experienced microsurgeons can perform this procedure with reproducible results and outlined predictive factors for success. In their study of over 1200 cases, the overall patency and pregnancy rates were 86% and 52%, respectively. The patency and pregnancy rates were related to the obstructive interval and quality of the fluid seen from the testicular end of the vas deferens. Results were equivalent using either formal 2-layer or modified 1-layer anastomoses and did not vary significantly between surgeons. Patency can take as long as 6 months for VV (Belker et al, 1991). The average time to achieve pregnancy was 1 year. Success rates for repeat reversals are lower than for first-time procedures. Patency rates for repeat reversals range from 64% to 79%, and pregnancy rates range from 27% to 44% (Belker et al, 1991; Fox, 1997; Matthews et al, 1997; Donovan et al, 1998; Hernandez and Sabanegh, 1999) (Table 3). Simultaneous sperm retrieval at the time of microsurgical reconstruction is possible in some cases (Belker and Bergamini, 1997). This may be more important during cases of vasoepididymostomy (VE) or in repeat reconstructions (Belker and Bergamini, 1997; Donovan et al, 1998; Hernandez and Sabanegh, 1999).

Vasal obstruction can also occur secondary to other scrotal surgery besides vasectomy, or lower abdominal or inguinal surgery, such as renal transplantation or herniorrhaphy. Reconstruction after renal transplantation is usually not feasible, as the abdominal end of the vas deferens retracts proximally in the retroperitoneum (Han-

Table 3. *Results of repeat microsurgical vasectomy reversals**

Authors	Year	# Patients	Patency Rate	Pregnancy Rate
Belkder et al	1991	222	75% (150/199)	43% (52/120)
Matthews et al	1997	64	67% (43/64)	30% (17/64)
Fox	1997	22	64% (14/22)	27% (6/22)
Donovan et al	1998	18	78% (14/18)	44% (8/18)
Hernandez and Sabanegh	1999	41	79% (26/33)	31% (10/31)
Total		367	74% (247/336)	36% (93/255)

* Where not explicitly stated in the respective manuscripts, numbers of patent or pregnant patients were calculated by multiplying the published percentage by the total number of patients.

Table 4. *Results of microsurgical vasoepididymostomy**

Authors	Year	# Patients	Patency Rate	Pregnancy Rate
Fogdestam et al	1986	41	85% (35/41)	37% (15/41)
Silber	1989	190	77% (146/190)	49% (94/190)
Schlegel and Goldstein	1993	91	70% (64/90)	27% (25/91)
Thomas (from Thomas and Howards, 1997)	1993	153	76% (116/153)	42% (64/153)
Matsuda et al	1994	26	81% (21/26)	38% (10/26)
Jarow et al	1997	131	67% (71/131)	27% (36/131)
Takihara	1998	14	71% (10/14)	29% (4/14)
Kim et al	1998	43	81% (35/43)	37% (16/43)
Total		689	72% (498/689)	38% (264/689)

* Where not explicitly stated in the respective manuscripts, numbers of patent or pregnant patients were calculated by multiplying the published percentage by the total number of patients.

delsman, 1984). Obstruction caused by hernia repair may be correctable, though these repairs are technically challenging (Matsuda et al, 1998; Sheynkin et al, 1998). Scarring from the previous surgery can be extremely dense, particularly if mesh was used for the hernia repair (Uzzo et al, 1997). Crossover transseptal procedures (VV or VE) are possible when a normal testis with unreconstructable obstruction is present on one side and an atrophic testis and patent ductal system are present on the contralateral side (Lizza et al, 1985; Sabanegh and Thomas, 1995).

When a secondary epididymal obstruction occurs after vasectomy, VE is required (Silber, 1979). The precise indications for VE are controversial. If sperm are seen on microscopic examination of the fluid from the testicular end of the vas deferens, then VV is performed. If sperm are not seen, then the gross appearance of the fluid (clear and watery, opalescent/cloudy, or thick and creamy) may also be important. Most surgeons would perform VE if thick, pasty fluid without sperm is noted. Whether VE should be performed with clear or opalescent fluid lacking sperm depends on many factors including the obstructive interval and microsurgical expertise of the surgeon. It is possible to have sperm return to the semen with VV, however, even when sperm are absent from the vasal fluid. Patency and pregnancy rates of 60% and 31% were reported by the VVSG when sperm were absent from the vas fluid bilaterally (Thomas, 1987; Belker et al, 1991).

Table 5. *Sites/types of obstruction in patients with obstructive azoospermia; from Hendry et al (1983)**†

Location of Obstruction	# Patients (%)
Caput epididymis	48 (29)
Cauda epididymis	34 (20)
CBAVD	29 (17)
CUAVD	8 (5)
Vas deferens	23 (14)
Empty epididymis	25 (15)
Ejaculatory duct	1 (0.6)

* Total number of patients = 168.
† CBAVD indicates congenital bilateral absence of the vas deferens; CUAVD, congenital unilateral absence of the vas deferens.

VE is more technically demanding and less successful than VV. Patency rates range from 67% to 85%, and pregnancy rates range from 27% to 49% (Fogdestam et al, 1986; Silber, 1989a; Schlegel and Goldstein, 1993; Matsuda et al, 1994; Jarow et al, 1995; Thomas and Howards, 1997; Kim et al, 1998; Takihara, 1998) (Table 4). Patency can take as long as 1 year following VE (Jarow et al, 1995; Matthews et al, 1995). The pregnancy rate decreases as the anastomosis is performed more proximally on the epididymis (Thomas, 1987; Silber, 1989; Jarow et al, 1997).

The most popular technique for VE has been the end-to-side technique described by Thomas (1987). Recent modifications address one of the main technical difficulties encountered in VE, that is, suture placement in an open collapsed epididymal tubule. These newer intussusception techniques involve placement of sutures in a distended epididymal tubule before it is opened. The technique reported by Berger (1998) uses three 10-0 sutures and that by Marmar (2000) uses 2. The main theoretical advantage of these newer intussusception techniques is that the resultant invagination of the epididymis may reduce leakage from the anastomosis. Whether these modifications will translate into improved pregnancy rates is not known (Berger, 1998; Marmar, 2000). Patency may occur earlier, however. In the small series by Marmar, 6 of 9 (67%) patients had sperm in the semen at 3 months.

Epididymal obstruction can also be congenital, inflammatory, or idiopathic. In an azoospermic man with normal semen volume, normal size testes, bilateral palpable vasa, and a testis biopsy that demonstrates sufficient spermatogenesis, the most likely site of obstruction is the epididymis (Hendry et al, 1983; Thomas, 1987) (Table 5). Prior to performing VE, vasography should be performed to document vasal patency. Vasography should only be performed at the time of a planned surgical reconstructive procedure. If vasography is performed as a separate pro-

cedure, then an additional site of obstruction can be created. Vasography can be performed with either an open or a puncture technique (Nagler and Thomas, 1987; Poore et al, 1997). The puncture technique eliminates the need for closure of the vas deferens (Poore et al, 1997). Radiographic contrast can be injected distally toward the abdomen, and a plain x-ray is taken to define the anatomy of the vas deferens. A Foley catheter with air in the balloon on gentle traction can eliminate contrast reflux into the bladder and provide a better quality film. Alternatively, the bladder can be catheterized following injection of a mixture of saline and methylene blue. If blue fluid is noted, then patency of the vas deferens is confirmed. Patency of the vas deferens can also be verified by simply injecting saline distally. If it flows easily, then the vas deferens is assumed to be patent. Injection should not be performed toward the epididymis, as this could cause injury.

Ejaculatory Duct Obstruction—Azoospermic men with low semen volume, a normal FSH, and at least 1 palpable vas deferens should be evaluated for ejaculatory duct obstruction with TRUS. Endorectal coil magnetic resonance imaging can also be useful in making the diagnosis (Goluboff et al, 1995). Causes of ejaculatory duct obstruction include trauma, infection, congenital atresia or stenosis, and utricular, Mullerian, or Wolffian duct cysts (Pryor and Hendry, 1991; Meacham et al, 1993; Goluboff et al, 1995). A seminal vesicle greater than 1.5 cm in greatest diameter is suggestive of ejaculatory duct obstruction, though there is no definite threshold for making the diagnosis (Meacham et al, 1993). TRUS may also demonstrate a midline cyst or visible dilation of the ejaculatory ducts (Goluboff et al, 1995). Traditionally, ejaculatory duct obstruction has been diagnosed by vasography following a testis biopsy demonstrating normal spermatogenesis. Recently, seminal vesiculography, either via a transrectal or transperineal approach, has been developed as an alternative to vasography. The potential advantage is that it does not risk creating an additional site of obstruction at the vasogram site (Jones et al, 1997).

Ejaculatory duct obstruction treatment has traditionally been accomplished with transurethral resection of the ejaculatory ducts (TURED). A limited resection of the prostate is performed at the level of the verumontanum, either to unroof a cyst or to open a narrowed ejaculatory duct (Pryor and Hendry, 1991; Meacham et al, 1993; Goluboff et al, 1995; Turek et al, 1996; Cornel et al, 1999; Schroeder-Printzen et al, 2000). A mixture of saline and methylene blue is simultaneously injected distally in the vas deferens. Endoscopic visualization of blue fluid confirms opening of the ejaculatory duct. A new alternative to TURED is balloon dilation of the ejaculatory duct at the time of seminal vesiculography (Jarow and Zagoria, 1995).

The patency rate for TURED is about 50%, and the overall pregnancy rate is about 25% (Schlegel, 1997). Potential complications from TURED are significant. The resection can cause urinary and ejaculatory symptoms secondary to urinary reflux into the vasa. Other potential complications include injury to the external sphincter and rectum (Vazquez-Levin et al, 1994; Goluboff et al, 1995; Schlegel, 1997).

CBAVD—The introduction of ICSI with epididymal and testicular sperm has revolutionized the management of men with CBAVD and other forms of uncorrectable obstruction. Clinical or ongoing pregnancy rates for ICSI and obstructive azoospermia range from 17% to 56%. Prior to the sperm retrieval procedure, the patient and his partner should be tested for CF mutations (Tournaye et al, 1994, 1998, 1999; Craft et al, 1995; Gil-Salom et al, 1995; Hovatta et al, 1995; Silber et al, 1995; Oates et al, 1996; Abuzeid et al, 1997; Mansour et al, 1997; Meniru et al, 1997; Dohle et al, 1998; Friedler et al, 1998; Madgar et al, 1998; Palermo et al, 1999a; Prins et al, 1999). The sperm retrieval procedure of choice varies between centers. Some centers prefer epididymal sperm because it is generally easier to process and freeze. Many centers, however, routinely use testicular sperm with excellent results. Microepididymal sperm aspiration (MESA) reliably provides adequate numbers of sperm that can also be cryopreserved for future cycles but is also the most invasive retrieval technique. It usually requires an operating room, microsurgical skills, and anesthesia, though there are reports of the procedure being performed with local anesthesia (Nudell et al, 1998; Sheynkin et al, 1998b). Percutaneous epididymal sperm aspiration (PESA) is an alternative to open epididymal sperm aspiration and can be performed in the office with local anesthesia (Craft et al, 1995; Meniru et al, 1997). Testicular sperm can also be reliably obtained percutaneously or with an open biopsy in men with obstructive azoospermia (Gil-Salom et al, 1995; Hovatta et al, 1995; Silber et al, 1995; Abuzeid et al, 1997; Belker et al, 1998; Madgar et al, 1998; Tournaye et al, 1998; Prins et al, 1999). Cryopreserved sperm, either epididymal or testicular, can be used with ICSI, and several reports suggest that pregnancy rates are not significantly compromised (Oates et al, 1996; Friedler et al, 1998; Prins et al, 1999; Tournaye et al, 1999; Janzen et al, 2000).

Microsurgical Reconstruction vs Sperm Retrieval and ICSI—All forms of obstructive azoospermia can be circumvented with sperm retrieval and ICSI. In the case of CBAVD, there is no realistic alternative for the couple to have their own biologic children. In cases where the obstruction is correctable, such as after a vasectomy, these couples' management is a matter of some controversy. Vasectomy reversal can allow natural conception, which most couples prefer. In vasectomy-induced obstruction of

shorter intervals, vasectomy reversal has a higher success rate than the nationally published live delivery rate (24.9%) for in vitro fertilization (Belker et al, 1991; US Department of Health and Human Services, 1998). Pregnancy rates for ICSI and obstructive azoospermia may be higher, though, than for other causes of infertility and have been reported to be as high as 51% (Palermo et al, 1999a). Other series of ICSI with obstructive azoospermia have reported more modest clinical or ongoing pregnancy rates between 17% and 42% (Tournaye et al, 1994, 1998, 1999; Craft et al, 1995; Gil-Salom et al, 1995; Hovatta et al, 1995; Silber et al, 1995; Oates et al, 1996; Abuzeid et al, 1997; Mansour et al, 1997; Meniru et al, 1997; Dohle et al, 1998; Friedler et al, 1998; Madgar et al, 1998; Palermo et al, 1999a; Prins et al, 1999). With longer obstructive intervals, the pregnancy rate for ICSI may therefore equal or exceed that of vasectomy reversal. Fuchs and Burt (2000) have recently presented data, however, that showed improved success for vasectomy reversal with even prolonged obstructive intervals. They reported a 45% pregnancy rate and a 38% delivery rate for an obstructive interval of 15 years or greater. In this study, 62% of patients required a VE on at least 1 side. In addition, ICSI cost per delivery can be as much as 5 times greater than vasectomy reversal (Kolettis and Thomas, 1997; Pavlovich and Schlegel, 1997; Heidenreich et al, 2000). Furthermore, in vitro fertilization/ICSI is associated with complications such as ovarian hyperstimulation and an increased risk of multiple births (Bergh and Lundkvist, 1992; Callahan et al, 1994; Neumann et al, 1994; Schenker and Ezra, 1994). These considerations support the application of vasectomy reversal even in cases of prolonged obstructive intervals.

NOA—The first pregnancy with testicular sperm and ICSI was reported in 1993 in a patient with unreconstructable obstructive azoospermia (Schoysman et al, 1993). TESE/ICSI has been applied to NOA and represents an extraordinary treatment advance for one of the most severe forms of male factor infertility. In brief, the TESE procedure involves extracting sperm from testis tissue removed with open or percutaneous biopsy or by percutaneous aspiration. Men previously regarded as sterile can now establish a pregnancy with TESE/ICSI. Successful sperm retrieval has been achieved in large series in as many as 77% of cases (Turek et al, 1997; Amer et al, 1999, 2000; Lewin et al, 1999; Schlegel, 1999; Schulze et al, 1999; Meng et al, 2000). One series of TESE cases guided by fine needle mapping resulted in successful retrieval in 95% (20 of 21) of cases (Turek et al, 1999). Even men with nonmosaic Klinefelter syndrome and severe testis atrophy have fathered children with TESE/ICSI (Tournaye et al, 1996; Nodar et al, 1999; Palermo et al, 1999b; Ron-El et al, 1999).

Predicting successful sperm retrieval is difficult. In fact, the best predictor of success is the histologic pattern on a previous biopsy (Mulhall et al, 1997a; Tournaye et al, 1997; Gil-Salom et al, 1998; Ezeh et al, 1999; Su et al, 1999). TESE is not an altogether benign procedure, as testis atrophy can occur following multiple biopsies. The data of Schlegel and Su (1997) suggest that if a repeat procedure is required, then the procedures should be performed at least 6 months apart to reduce the chance of testicular injury.

Successful sperm retrieval in NOA depends on adequate sampling of the testis. Most reports of TESE in NOA describe an open approach (Mulhall et al, 1997a; Tournaye et al, 1997; Turek et al, 1997, 1999; Gil-Salom et al, 1998; Hauser et al, 1998; Amer et al, 1999, 2000; Ezeh et al, 1999; Schlegel, 1999; Schulze et al, 1999; Su et al, 1999). Direct comparisons of open and percutaneous TESE approaches have generally demonstrated that the open approach has a higher chance for successful sperm retrieval (Friedler et al, 1997b; Ezeh et al, 1998; Westlander et al, 1999; Mercan et al, 2000). One recent report describing a percutaneous fine needle approach, however, suggested that successful sperm retrieval is also possible with this technique. Despite an average of 15 needle punctures, no scrotal hematomas occurred (Lewin et al, 1999).

Two innovative techniques have been developed to improve chances for successful sperm retrieval and limit the amount of testis tissue removed in TESE. A fine needle aspiration mapping procedure has been described by Turek. This mapping procedure can be used to identify pockets of spermatogenesis within the testis that can be sampled at the time of TESE (Turek et al, 1997, 1999). In a recent small cohort of patients, this technique enabled successful sperm retrieval in 95% of cases (20 of 21) (Turek et al, 1999).

The second sperm retrieval procedure recently introduced is the microdissection technique developed by Schlegel (1999). In this procedure, the tunica albuginea is opened widely to expose the testis parenchyma. Under the operating microscope, dilated tubules bearing sperm can be identified and differentiated from the sclerotic ones that do not contain sperm. The dilated tubules are then sampled, limiting the amount of tissue removed and improving chances for successful retrieval (Schlegel, 1999).

Clinical pregnancy rates between 11% and 49% per cycle have been reported for TESE/ICSI in NOA (Devroey et al, 1995; Kahraman et al, 1996; Mansour et al, 1997; Gil-Salom et al, 1998; Madgar et al, 1998; Lewin et al, 1999; Palermo et al, 1999; Prins et al, 1999; Kupker et al, 2000). It is possible to perform ICSI with cryopreserved testicular sperm, and several studies suggest that pregnancy rates are not compromised (Gil-Salom et al, 1996; Friedler et al, 1997; Liu et al, 1997; Oates et al, 1997; Ben-Yosef et al, 1999; Kupker et al, 2000).

Azoospermia and Varicocele—Two recent reports have

examined outcomes following varicocele ligation in the setting of azoospermia (Matthews et al, 1998; Kim et al, 1999). Both series had a large percentage of bilateral lesions. Sperm returned to the semen in 43% (12 of 28) and 55% (12 of 22) of patients. A total of 2 unassisted pregnancies occurred for 50 patients (4%) in the 2 studies. Three pregnancies resulted from ICSI in the 2 studies, one using testicular sperm. Thus, the main potential benefit of varicocele ligation in these patients appears to be reducing the likelihood of TESE and its potential complications. Testis biopsy findings of Sertoli cell–only or early maturation arrest were predictive of a negative outcome in one of the studies (Kim et al, 1999).

Round Spermatid and Elongated Spermatid Injection—In cases for which no mature sperm are available, sperm precursors, obtained from either the ejaculate or the testis, have been injected into oocytes. Round spermatid and elongated spermatid injection (ROSNI and ELSI, respectively) have resulted in pregnancies. At the present time, these procedures would be considered experimental by most investigators (Fishel et al, 1995; Tesarik et al, 1996; Antinori et al, 1997; Araki et al, 1997; Bernabeu et al, 1998; Kahraman et al, 1998; Sofikitis et al, 1998; Tsai et al, 2000).

Other Alternatives—Despite the recent technological advances outlined above, some couples may not wish to pursue treatment with assisted reproductive techniques. Reasons for this may include financial limitations or religious objections. These couples may pursue other alternatives, including therapeutic insemination with donor sperm (TID), adoption, or child-free living.

Conclusions—Recent advances have dramatically changed the evaluation and treatment of the azoospermic man. An underlying genetic cause can be identified in a significant proportion of these men. Men with NOA or uncorrectable obstruction, previously regarded as sterile, can now father their own biological children with sperm retrieval and ICSI. Improved understanding of underlying genetic defects that cause some of the more severe forms of male infertility may lead to new therapies. The application of assisted reproductive technologies to these more severe forms of male factor infertility necessitates appropriate genetic evaluation and counseling.

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