The management of obstructive azoospermia: a committee opinion

Practice Committee of the American Society for Reproductive Medicine in collaboration with the Society for Male Reproduction and Urology

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Infertility due to obstructive azoospermia may be treated effectively by surgical reconstruction or by retrieval of sperm from the epididymis or testis, followed by in vitro fertilization with intracytoplasmic sperm injection. This replaces the ASRM documents titled "Sperm retrieval for obstructive azoospermia" and "The management of infertility due to obstructive azoospermia," last published in 2008. (Fertil Steril® 2019;111:873–80. ©2019 by American Society for Reproductive Medicine.)

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OBSTRUCTIVE AZOOSPERMIA

Obstructive azoospermia is the result of a blockage of the male reproductive tract, leading to a complete absence of sperm in the ejaculate, and accounts for approximately 40% of all cases of azoospermia (1). Obstruction may be congenital or acquired and may include one or more segments of the male reproductive tract: epididymis, vas deferens, and ejaculatory ducts. Congenital causes of obstructive azoospermia include congenital bilateral absence of the vas deferens (CBAVD) and idiopathic epididymal obstruction. Acquired causes of obstructive azoospermia include vasectomy, infection, trauma, or iatrogenic injury. The evaluation of nonobstructive azoospermia is covered in another document (2).

MICROSURGICAL RECONSTRUCTION

Microsurgical techniques for the treatment of obstructive azoospermia were first introduced by Silber and Owen in 1977 and are considered the gold standard for reconstructive surgery involving the male reproductive tract (3–5). Scrotal or inguinal vasovasostomy may be employed for vasal obstruction secondary to vasectomy, iatrogenic vasal injury due to inguinal or scrotal surgery such as herniorrhaphy or hydrocelectomy, or solitary vasal obstruction secondary to infection or trauma. Vasovasostomy is not feasible in the setting of multifocal obstruction along the vas deferens.

Vasoepididymostomy is indicated for idiopathic epididymal obstruction, secondary epididymal obstruction due to long-standing vasal obstruction, or iatrogenic epididymal obstruction following interventions such as epididymal aspiration. Naturally, multifocal epididymal obstruction necessitates that the level of the anastomosis be proximal to all sites of obstruction.

The primary indication for vasovasostomy or vasoepididymostomy is to restore fertility in the setting of obstructive azoospermia. Although the use of these procedures has been described for the treatment of postvasectomy pain syndrome (6), affected men should be offered counseling or conservative methods of pain management prior to consideration of these reconstructive procedures.

SURGICAL TECHNIQUE

Incision

Scrotal vasovasostomy and vasoepididymostomy are usually performed through 2–3 cm vertical incisions in the anterior aspect of the hemiscrotum. When greater exposure or mobilization of the vas is required, for example, following a high vasectomy or loss of a large segment of the scrotal vas deferens, the scrotal incisions can be extended into the inguinal region. Alternatively, the surgeon can use an infrapubic incision to better mobilize the vas deferens (7) to perform a tension-free anastomosis.

Inguinal vasovasostomy may be performed via an inguinal approach if the vasal obstruction is focal and easily identified in the inguinal canal, as for example, following iatrogenic injury to the vas during inguinal surgery. Alternatively, laparoscopic or robotic assistance may be required for identification and dissection of the abdominal vas deferens prior to performing a microsurgical anastomosis.

Intraoperative Considerations

For men undergoing vasectomy reversal, the decision to perform either a vasovasostomy or a vasoepididymostomy is made intraoperatively. As such, vasectomy reversal should ideally be

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undertaken by surgeons who are skilled in both vasovasostomy and vasoepididymostomy. Although obstructive interval (8), length of the testicular vasal remnant (9), sperm granuloma (10), vasectomy site (11), prior vasectomy reversal, and surgeon skill are all factors to consider when making this decision, the quality of the vasal fluid remains the single most important determinant of whether vasovasostomy or a vasoepididymostomy should be performed. Testicular vasal fluid may be watery and copious or thick and creamy in consistency and have one of the following microscopic characteristics:

Grade 1 – mainly normal motile sperm

Grade 2 – mainly normal non-motile sperm

Grade 3 – mainly sperm heads

Grade 4 – only sperm heads

Grade 5 – no sperm

Vasovasostomy should be performed for grades-1–4 vasal fluid (12, 13). When no sperm are observed in the vasal fluid, the likelihood of return of sperm to the ejaculate is greatest when the fluid is watery and copious, and lowest when it is thick and creamy (12). Therefore, for grade-5 vasal fluid, vasovasostomy should be performed if the fluid is watery and copious. If the fluid is thick and creamy, careful inspection of the epididymis under magnification can reveal a discolored or indurated area in the epididymis, signifying tubule rupture due to back pressure, or a demarcation between collapsed and dilated tubules. Vasoepididymostomy should be performed in both these circumstances.

Prior to anastomosis, patency of the distal length of the vas deferens should be confirmed by performing a saline vasogram, using a 24-gauge blunt-tipped peripheral venous catheter inserted directly into the lumen. Formal vasography is rarely necessary. Regardless of the location of the anastomosis, adequate mobilization of the vas, without devascularization, should be performed to ensure a tension-free anastomosis.

Anastomotic Methods

Although some surgeons have described satisfactory results using macrosurgical techniques or loupe-magnification (14), it is generally accepted that microsurgical anastomoses yield better outcomes than macrosurgical anastomoses, particularly for vasoepididymostomy.

Most surgeons perform vasovasostomy using a two-layer microsurgical anastomosis, by first placing 5–8 interrupted 10-0 nylon sutures in the inner mucosal edges of the vas, incorporating a small portion of the inner muscular layer, followed by 5–8 additional interrupted 9-0 nylon sutures in the outer muscular layer (3). A modified one-layer anastomosis using 4–6 interrupted 9-0 nylon sutures through the full thickness of the vas has also been described (15, 16). A meta-analysis showed no statistically significant difference in outcomes between the techniques (16).

Several different techniques have been described for microsurgical vasoepididymostomy, including an end-to-side anastomosis (17), triangulation (18), tubular invagination (19), and tubular intussusception techniques (20). In all techniques, the epididymal tubule is pulled up into the lumen of the vas deferens. The intussuscepted end-to-side vasoepididymostomy is currently the most commonly employed technique.

Robotic-assisted surgery has been applied for scrotal vasovasostomy and vasoepididymostomy as an alternative to microsurgery, but its use is not widespread at present (21). Robotic-assisted intra-abdominal vasovasostomy, using the formal two-layer anastomosis discussed above, has also been described as a novel approach for repairing intra-abdominal vasal defects that minimizes morbidity and obviates the need for an operating microscope (22, 23).

Sperm Retrieval and Cryopreservation

Patients should be counseled about the option of intraoperative sperm retrieval for cryopreservation via testicular biopsy or aspiration at the site of a vaso-vasal or vaso-epididymal anastomosis if microsurgical reconstruction is unsuccessful. This option may be more relevant for patients with a high preoperative likelihood of requiring a bilateral vasoepididymostomy. Costs of cryopreservation should also be discussed preoperatively.

POSTOPERATIVE CARE

Most surgeons will advise patients to use ice packs in the immediate postoperative period to minimize pain and scrotal swelling. A scrotal supporter should continue to be used for 3–4 weeks after surgery. Heavy physical activity, including weight lifting, straddle-type activities, sexual intercourse, and ejaculation, should also be avoided for 3–4 weeks after surgery. Pain is usually well controlled with oral analgesics, both nonsteroidal anti-inflammatory drugs (NSAIDs) and narcotics.

COMPLICATIONS

Complications after microsurgical reconstructive procedures are rarely reported in the published literature. Expected complications of scrotal surgery, such as scrotal hematomas, can usually be managed expectantly.

MONITORING

Sperm may return to the ejaculate as early as 1 month after surgery, especially in the case of vasovasostomy. Semen analyses may be obtained every 8–12 weeks in the postoperative period until sperm concentration and motility return to normal or until a pregnancy occurs. Even after sperm parameters return to normal, semen analysis may be performed at least every 12 weeks until pregnancy occurs to promptly identify patients who may again become obstructed due to anastomotic failure or scarring.

The incidence of postoperative re-obstruction ranges from 12% (12/98) after vasovasostomy to approximately 21% (11/52) after vasoepididymostomy (24). Surgery is considered to have failed if sperm do not return to the ejaculate by 6 months after vasovasostomy or by 18 months after vasoepididymostomy (25). Most pregnancies occur within

24 months after surgery without any further intervention (12). If pregnancy fails to occur, despite normal semen quality and the lack of any identifiable female infertility factors, evaluation for antisperm antibodies may be considered.

OUTCOMES

The Vasovasostomy Study Group reported a 97% patency rate (86/89) and 76% pregnancy rate (56/74) following vasovasostomy among patients who were less than 3 years out from vasectomy (12). In their report, these outcomes declined as the obstructive interval increased to a patency rate of 71% (32/45) and a pregnancy rate of 30% (11/37) at greater than 15 years (12). Although other studies have not shown a direct correlation between obstructive interval and patency rates after vasovasostomy, a significant decline in pregnancy rates has been noted for intervals greater than 15 years (26).

The Vasovasostomy Study Group also reported surgical success rates based on the quality of the vasal fluid. Patency and pregnancy rates ranged from 94% (116/123) and 63% (62/98), respectively, for quality of grade-1 fluid to 60% (50/83) and 31% (20/65), respectively, for quality of grade-5 fluid (12).

Techniques for vasoepididymostomy have evolved over time, with an evolution of surgical success rates as well. Patency rates for the currently used intussuscepted end-to-side vasoepididymostomy range from 80% (12/15) (20) to 84% (53/63) (27), with pregnancy rates of 40% (14/35) (27) to 44% (4/9) (20).

MANAGEMENT OF OPERATIVE FAILURES

Men who remain azoospermic may be offered a repeat operation but should be counseled that repeat procedures are usually more technically challenging. According to findings from the Vasovasostomy Study Group, sperm returned to the ejaculate after repeat vasovasostomy in 75% of men (150 of 199 patients) and 43% of their partners subsequently achieved pregnancy (52 of 120 couples) (12). Other groups have reported comparable results (28–30).

After a failed vasoepididymostomy, a repeat procedure may not always be technically feasible. However, in the hands of experienced surgeons, acceptable success rates after repeat vasoepididymostomy are possible, with one series reporting an overall patency rate of 67% (12/18 men) and a natural conception rate of 25% (3/12 couples) (31).

SPERM-RETRIEVAL TECHNIQUES

These techniques can be used in the setting of post-vasectomy obstruction, CBAVD, ejaculatory duct obstruction (EDO), and unreconstructable causes of obstructive azoospermia. These procedures do not yield sufficient sperm for intrauterine insemination (IUI) and rarely for assisted reproductive technology (ART), including in vitro fertilization (IVF) (32, 33). ART involves the manipulation of both ova and sperm outside the body and does not include IUI. Surgically retrieved testicular or epididymal sperm used for intracytoplasmic sperm injection (ICSI) have similar outcomes whether fresh or frozen sperm are used: fertilization rates between 45% and 60% (8/17, 93/157) per injected oocyte; clinical pregnancy rates from 23%–35% (23/100, 5/17), and live-birth rates of approximately 18%–36% (14/77 and 7/19) (34–36). This is comparable to the use of ejaculated sperm (37).

Percutaneous epididymal sperm aspiration (PESA) is conducted in the office or laboratory procedure room under local anesthesia or monitored anesthesia care. It can be repeated and does not require microscopic guidance. After a spermatic cord block, the epididymis must be stabilized between the surgeon's forefinger and thumb. A butterfly needle with a 20 mL syringe is inserted into the caput epididymis. With gentle suction pressure, the needle is withdrawn until fluid enters the tubing. This is continued until sperm of adequate quality and quantity are obtained. If no sperm is aspirated, microsurgical epididymal sperm aspiration (MESA), testicular biopsy, or aspiration can still be performed.

Microsurgical Epididymal Sperm Aspiration

Under general anesthesia or intravenous (IV) sedation, MESA techniques include individual epididymal incision and effluent aspiration or micropuncture of individual tubules (38, 39). Using an operating microscope, individual epididymal tubules are identified and then aspirated sequentially until optimal quantity and quality of sperm are obtained. Puncture sites are then closed or cauterized. Sperm of best quality are found near the testis in the proximal epididymis and are concentrated to about 1 million sperm/μL (40).

Open Testicular Biopsy

Though the epididymis is a richer source of motile sperm than the testicle, testis retrieval can still be useful. There is no appreciable difference in pregnancy rate with ART between testicular or epididymal sperm for men with obstructive azoospermia (37, 41). Though sperm retrieval is similar, MESA may provide higher live-birth rates (42). Ideally, only one tunical incision is necessary to obtain sufficient tissue and sperm. Care must be taken to avoid damage to the testicular blood supply within the tunical wall.

Percutaneous Testicular Sperm Aspiration (TESA)

After local cord block and stabilization of the testicle, a needle is inserted along the testicular long axis during TESA and then repeatedly redirected with gentle pressure and aspiration until tubules are sufficiently disrupted and adequate sperm are obtained. Fine-needle aspiration can also be used diagnostically and to procure sperm for ART.

Percutaneous Testicular Biopsy (PercBiopsy)

A local spermatic cord block and a 14-gauge biopsy gun is used during a PercBiopsy to remove a small cylinder piece of testicular tissue. Multiple passes can be performed if needed.

TABLE 1

Advantages and disadvantages of sperm-retrieval techniques.

Technique	Advantages	Disadvantages
PESA	No microsurgical expertise required Local anesthesia Few instruments Fast and repeatable Minimal postoperative discomfort	Few sperm retrieved Risk of hematoma Damage to adjacent tissue
MESA	Best clinical pregnancy rates Large number of sperm retrieved Excellent results with cryopreservation Reduced risk of hematoma	Requires microsurgical expertise Increased cost General or local anesthesia Incision required Postoperative discomfort
TESE	No microsurgical expertise required Local or general anesthesia Few instruments Fast and repeatable	Relatively few sperm retrieved Limited risk of testicular atrophy (with multiple biopsies)
PercBiopsy, TESA	No microsurgical expertise required Local anesthesia Few instruments Fast and repeatable Minimal postoperative discomfort	Few sperm retrieved Risk of testicular atrophy Risk of hematoma

Complications/Risks

Techniques for sperm retrieval are generally very safe, even under local anesthesia. The incidence of hematoma, persistent pain, swelling, or infection is low (43–45). The risk of associated birth defects after sperm retrieval with ICSI is similar to ICSI using ejaculated sperm (37).

Cryopreservation

Sperm retrieved with these sperm-retrieval methods can be freshly used for IVF/ICSI. Alternatively, the sperm can be frozen and used later after thawing. Couples should be counseled that sperm can be lost in the freeze-thaw process, typically 10%–30%, although complete loss or damage is possible (45–47) (Table 1).

Ejaculatory Duct Obstruction (EDO)

EDO is rare. When the ducts are obstructed in the urethra, transurethral resection of the ejaculatory ducts (TURED) relieves the obstruction where the distal ejaculatory duct terminates in the prostatic urethra (48). Resection may be guided by synchronous transurethral ultrasound (TUUS) to confirm obstruction location and avoid rectal injury (49). Relief of obstruction can often be seen immediately when cloudy fluid drains immediately on resection. Alternatively, seminal vesicle methylene blue chromotubation will release blue fluid upon resection (50). Sperm returns to the ejaculate in up to 70% (30/46) of men, and 20% (9/46) of couples will achieve unassisted pregnancy thereafter. Complications occur in up to 20% of patients and include urinary tract infection, epididymitis, hematuria, hematospermia, or watery ejaculate due to reflux of urine into the now widely patent ducts (51,52). When a midline cyst, not in connection with the ejaculatory duct system, causes the obstruction, aspiration of the cyst can relieve the blockage. This relief may be temporary or permanent and can be verified on a semen analysis soon after the aspiration. Any sperm in the aspirated fluid can be cryopreserved if needed and suggests the need for resection.

Alternative therapies for EDO include endoscopic laser-assisted resection of the ducts, seminal vesicoscopy or balloon dilation, or even antegrade seminal vesicle lavage to remove debris or calculi (53–55).

TREATMENT SELECTION

Vasectomy Reversal vs. IVF/ICSI: Therapeutic Options

Both microsurgical reconstruction and sperm retrieval combined with IVF/ICSI can be effective treatments for infertility due to obstructive azoospermia. Several factors affect the decision; ultimately the choice must be based on the needs and preferences of the individual couple. Success rates and costs often are the factors weighted most heavily, but other considerations are relevant including risks of complications and the baseline fertility of each partner.

In experienced hands, microsurgical vasectomy reversal results in return of sperm to the ejaculate in 46.7% (n=30) to 98.1% (n=50) of patients (mean of 89%, N=6,633) (16), and up to 65%–75% of couples may achieve pregnancy without ART (12). Between 40% (n=14/35) (27) and 46% (n=6/13) (20) of couples may conceive naturally after bilateral end-to-side vasoepididymostomy.

The technique of sperm retrieval and the source of sperm (testis, epididymis, or vas deferens) have no significant effect on pregnancy rates achieved with IVF/ICSI (56). All methods generally provide sufficient numbers of viable sperm for ICSI and often also for cryopreservation. As long as viable sperm can be retrieved, neither the duration of obstruction (57, 58) nor the motility of the sperm affect the outcomes achieved with IVF/ICSI (59). When surgically retrieved frozen epididymal or testicular sperm are used for ICSI, fertilization rates range between 45% (n=1,335) and 74% (n=1,255) per injected oocyte (35, 56, 60–62). Fertilization rates for fresh epididymal or testicular sperm are similar to frozen and range from 48% (n=242) to 72% (n=1,429) (35, 36, 56, 60), as with fertilization rates from two small studies of testicular sperm which did not specify fresh or frozen, 59% (N=21) to 81% (N=118) (56, 63). Clinical pregnancy rates from epididymal and testicular sperm (fresh and frozen) range from 22% (n=9 cycles) to 74% (n=24 cycles), with the largest reported groups from frozen epididymal and frozen epididymal sources, 24% (N=100 cycles) and 40% (n=145 cycles), respectively (36, 45, 64, 65). Delivery rates are less reported and range from 19.5% (testicular, n=41) to as high as 70.4% (epididymal, n=27) (64, 66).

Impact of Female Factors

Clinical pregnancy and live-birth rates following vasectomy reversal or with sperm retrieval and IVF/ICSI are significantly impacted by characteristics of the female partner that correlate with female fertility. Outcomes are better in couples with the same female partner as before vasectomy. This advantage persists across the spectrum of female age and despite the duration of the obstructive interval (67).

Female age has been an independent predictor of success for both vasectomy reversal, with a younger age associated with better outcomes (68, 69). Studies find post-reversal pregnancy rates significantly worse when performed in men whose partners were 40 years or older (~15%) (70, 71), compared with under 39 years of age (55.7%) (71). Even after long obstructive intervals, female age is still the most profound predictor of success. In men with obstructive intervals greater than 15 years, the live-birth rates decreased with spousal age over 35. For spousal age <30 years, 30–35 years, 36–40 years, and >40 years, live-birth rates were 45% (n=22), 49% (n=39), 29% (n=29), and 14% (n=14), respectively (72).

An analysis of the Society for Assisted Reproductive Technology (SART) data demonstrates that among women undergoing ICSI/IVF for a male factor (a category that would include vasectomy), live-birth rates drop steadily with maternal age. The live-birth rate in 2014 varied by age for women under age 35 (48.7%), 35–37 (38.4%), 38–40 (24.3%), 41–42 (12.3%), and >42 years (3.8%), respectively (73). Ovarian reserve testing can help to select which option to choose when the female partner is age 34–40 when ART may shorten the time to pregnancy compared with vasectomy reversal, or in the 40 years-and-above population when ART success is diminished (74). The average time to pregnancy after a successful microsurgical vasectomy reversal is 12 months, although this may be impacted by female age (12). Consequently, sperm retrieval and IVF/ICSI may be the better option when the female partner is older and the window of opportunity to conceive is short. However, even with ART, fewer than 20% of women may be expected to achieve a successful pregnancy after age 40 (73). Sperm retrieval and IVF/ICSI also may be preferable to vasectomy reversal for couples having coexisting female infertility factors. When the female partner has significant tubal disease or a previous tubal sterilization procedure and both partners would require reconstructive microsurgery, sperm retrieval with IVF/ICSI is the obvious choice.

Secondary Male Infertility

A small proportion of men presenting for vasectomy reversal may have secondary infertility due to factors such as longstanding varicoceles, or internal injury, trauma, surgery, radiation, chemotherapy, or other spermatotoxic medication regimens since their last successful conception. For these men, the restorative potential of microsurgical reconstruction is compromised but sperm retrieval may still be possible, making IVF/ICSI the appropriate choice. Some men will be exposed to exogenous testosterone, which typically suppresses sperm production and creates a condition of nonobstructive azoospermia that is typically reversible but may take months to recover once testosterone is withheld. Gonadotropin support has been demonstrated to reverse this suppression successfully and allow for similar success rates of vasectomy reversal as unaffected men (75).

Cost-effectiveness Comparisons

Microsurgical vasovasostomy (76) and vasoepididymostomy (77, 78) may be more cost-effective than sperm retrieval and IVF/ICSI, particularly for couples who hope to conceive more than a single pregnancy, because a successful reconstruction allows the couple to conceive naturally without further intervention. Even a repeated attempt at microsurgical reconstruction may be less costly than sperm retrieval and IVF/ICSI (79). Over the past several years, studies of cost-effectiveness have consistently demonstrated lower costs with microsurgical reconstruction. Such analyses include expected patency rates of at least 79% following reconstructive surgery, obstructive intervals, maternal age, and increased indirect costs from factors such as multiple conception seen with IVF/ICSI (76, 77, 80–84).

Advanced maternal age (above 40 years) combined with diminishing ovarian reserve typically moves the cost-effectiveness advantage toward IVF/ICSI, but as ovarian reserve drops below a threshold of advantage with ART, vasectomy reversal may again be more cost-effective due to the ability to attempt conception repeatedly without assistance (85). As the proficiency with ART has increased, live-birth outcomes with IVF/ICSI have improved and multiple gestations have decreased making ART more cost-effective. However, this cost advantage may be offset by expenses associated with the increased use of preimplantation genetic testing for aneuploidy (PGT-A). In circumstances of parental genetic-carrier states where the birth outcome may be seriously impacted, the indirect costs push the decision easily toward IVF/ICSI.

Ultimately, the results achieved with microsurgical reconstruction must be compared directly with those achieved with ART in the individual center. Furthermore, certain factors including the man's desire to maintain his vasal contraception or the couple's desire for having (an)other child(ren) may override financial calculations. Ideally, the final choice of treatment will be made by a well-informed couple in consultation with the reproductive specialists caring for both partners.

For some individuals, the costs associated with retrieval of sperm and ART may be a barrier to treatment. In those cases, adoption and the use of donor sperm are other options that should be presented and discussed.

SUMMARY

- Infertility due to obstructive azoospermia may be treated effectively by surgical reconstruction or by retrieval of sperm from the epididymis or testis, followed by IVF/ICSI.
- Sperm-retrieval techniques in general are minimally invasive and have a low complication risk. Successful sperm retrieval should be the expected outcome in the vast majority of obstructed men.

CONCLUSIONS

- When obstructive azoospermia results from a vasectomy and there are no coexisting female infertility factors, microsurgical reconstruction of the reproductive tract is generally preferred over sperm retrieval and IVF/ICSI.
- Sperm retrieval with IVF/ICSI is generally the best choice of treatment for obstructive azoospermia when [1] the female partner has rapidly diminishing ovarian reserve due to age or other conditions, [2] there are coexisting female infertility factors that require IVF, [3] there is a concomitant secondary male infertility condition in the male partner, and [4] the likelihood for success with sperm retrieval/ICSI is greater than with surgical treatment.

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