The Management of Obstructive Azoospermia: AUA Best Practice Statement

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Table of Contents

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Abbreviations and Acronyms

AUA	American Urological Association
BOD	Board of Directors
CBAVD	congenital bilateral absence of the vasa deferentia
CFTR	cystic fibrosis transmembrane conductance regulator
ICSI	intracytoplasmic sperm injection
IUI	intrauterine insemination
IVF	in vitro fertilization
MESA	microsurgical epididymal sperm aspiration
PESA	percutaneous epididymal sperm aspiration
PGC	Practice Guidelines Committee
PESA	percutaneous epididymal sperm aspiration
TEFNA	testicular fine-needle aspiration
TESA	percutaneous testicular sperm aspiration
TESE	testicular sperm extraction
TURED	transurethral resection of the ejaculatory ducts

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Introduction

Azoospermia, defined as complete absence of sperm from the ejaculate, is present in less than 2% of all men[1] and in 15% of infertile men.[2] Although there are many causes of azoospermia, obstruction of the ductal system is responsible for approximately 40% of cases.[2] Obstructive azoospermia may result from epididymal, vasal, or ejaculatory duct pathology. Vasectomy is the most common cause of vasal obstruction. Severe genitourinary infections, iatrogenic injury during scrotal or inguinal surgical procedures and congenital anomalies are other common causes of obstructive azoospermia.

A limited evaluation of both partners is important before reaching a final decision on the management of the couple with infertility due to obstructive azoospermia. Other factors either unrelated or indirectly related to the obstruction may play a role in the decision regarding management. For instance, congenital bilateral absence of the vasa deferentia (CBAVD) is a common cause of obstructive azoospermia and is associated with mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.[3] Genetic testing and counseling should be considered in the management of these couples prior to treatment to allow the couple to make an informed decision as to whether or not to use the husband's sperm. Since female factors may also play a role, the female partner should be offered at least a limited evaluation prior to treatment of the infertile couple with obstructive azoospermia.

This review offers recommendations for management of couples with infertility due to obstructive azoospermia.

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Methodology

This best practice statement, *Management of Obstructive Azoospermia*, is part of an updated series on male infertility prepared by the Male Infertility Best Practice Statement Panel (Appendix 1). Other titles include: *Best Practice Statement on the Optimal Evaluation of the Infertile Male, Best Practice Statement on Evaluation of the Azoospermic Male,* and *Best Practice Statement on Varicocele and Infertility.* The first editions (2001) of these 4 reports were prepared by the Male Infertility Best Practice Policy Committee of the American Urological Association, Inc.® (AUA; Appendix 1) and the Practice Committee of the American Society for Reproductive Medicine. The two organizations agreed to collaborate to prepare documents of importance in the field of male infertility.

In October 2007, an updated assessment of the literature on male infertility by the AUA Practice Guidelines Committee (PGC) found insufficient outcomes data to support a formal meta-analysis and an evidence-based guideline. The evidence was generally of a low level, being derived overwhelmingly from nonrandomized studies. Thus, the Male Infertility Best Practice Statement Panel, which included many of the members of the 2001 Committee, was created by the Board of Directors (BOD) of the AUA. The Panel was charged with developing a best practice statement, based on the previous report, by employing published data in concert with expert opinion. The Panel co-chairmen and members were selected by the PGC. The mission of the Panel was to develop recommendations, based on expert opinion, for optimal clinical practices in the diagnosis and treatment of male infertility. It was not the intention of the Panel to produce a comprehensive treatise on male infertility.

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The initial Medline search that spanned 1999 through October 2007 was supplemented by review of bibliographies and additional focused searches. In all, 341 articles were deemed by the Panel members to be suitable for scrutiny. Three of the four original 2001 reports were updated with new findings and are presented in the documents in colored font. This updated document was submitted for peer review, and comments from 21 physicians and researchers were considered by the Panel in making revisions. The final document has been approved by the AUA PGC and the BOD. Funding of the Panel was provided by the AUA; members received no remuneration for their work. Each Panel member provided a conflict of interest disclosure to the AUA.

Treatment methods for obstructive azoospermia

Men with obstructive azoospermia may father children either by 1) surgical correction of the obstruction, which may produce pregnancy by intercourse and obviate the need for assisted reproductive technology; or 2) retrieval of sperm from the male reproductive system for in vitro fertilization/intracytoplasmic sperm injection (IVF/ICSI).

Surgical treatment

Surgical correction may be accomplished by microsurgical reconstruction of the vas and/or epididymis or, in cases of ejaculatory duct obstruction, by transurethral resection of the ejaculatory ducts (TURED). Prior to performing microsurgery in the male, the female partner should be evaluated to determine if female infertility factors are present.

Microsurgical reconstruction of the reproductive tract

Microsurgical reconstruction of the reproductive tract often is successful in patients with obstructive azoospermia. Following vasectomy reversal, for example, return of sperm to the ejaculate occurs in 70-95% of patients, and pregnancies are obtained without the need for assisted reproduction in 30-75% of couples. A very important factor influencing the likelihood of

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sperm returning to the semen and of pregnancy after vasectomy reversal is the number of years between vasectomy and attempted reconstruction.[4] The length of the obstructive interval and the chance for successful outcome of vasectomy reversal are inversely related. Other factors influencing the success of vasectomy reversal include: the presence or absence of sperm in the intraoperative vas fluid; the gross appearance of the vas fluid; the quality of the sperm in the vas fluid; the length of the vas segment between the epididymis and the vasectomy site; and the presence or absence of a sperm granuloma at the vasectomy site. The likelihood of pregnancy after vasectomy reversal is also heavily influenced by the age of the female partner.

Vasoepididymostomy is performed for congenital, infectious, postvasectomy or idiopathic epididymal obstruction. Following this type of microsurgery, 20-40% of couples achieve pregnancy through intercourse. Accuracy and delicacy of microsurgical technique affect the outcome of reconstructive procedures on the male reproductive system. The best results are achieved by surgeons with training and on-going experience in microsurgery. In order to maximize successful outcomes, surgeons performing vasectomy reversal should be comfortable with anastomoses involving extremely small luminal diameters and must be competent and comfortable with both vasovasostomy and vasoepididymostomy, because the latter may be unexpectedly necessary in many cases.

In rare cases, obstruction of the male reproductive tract occurs in the inguinal portion of the vas deferens. Obstruction in this location is usually caused by an injury to the vas during inguinal hernia repair and should be considered in azoospermic men who have a history of previous inguinal surgery. Some of these injuries can be corrected by vasovasostomy performed in the

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inguinal canal, provided that the ends of the vas can be located and approximated without tension.

Sperm retrieval and cryopreservation may be performed at the time of microsurgical reconstruction in order to avoid a second procedure in the event that the microsurgical reconstruction does not reverse a patient's azoospermia.

Transurethral resection of the ejaculatory ducts

The possibility of ejaculatory duct obstruction should be considered in the differential diagnosis of obstructive azoospermia. This condition is uncommon, but can be treated by transurethral resection of the ejaculatory duct at the point where the duct enters the distal prostatic urethra near the veru montanum. Transurethral resection of the ejaculatory duct results in the appearance of sperm in the ejaculate in about one-half to three-fourths of cases. The pregnancy rate achieved by this surgery is about 25%.

Sperm retrieval techniques and in vitro fertilization/intracytoplasmic sperm injection

Intracytoplasmic sperm injection

Intracytoplasmic sperm injection is an adjunct to standard IVF. ICSI must be used in almost all cases in which sperm are retrieved from the testes or epididymides of a man with obstructive azoospermia, because the sperm retrieval techniques that must be employed to obtain sperm from these men very rarely produce enough motile sperm for intrauterine insemination (IUI) or standard IVF.[5-6] ICSI provides fertilization rates of 45-75% per injected oocyte when surgically retrieved epididymal or testicular spermatozoa are used.[7-13] Clinical pregnancy rates reported in the recent literature range from 26-57% and delivery rates range from 18- 75%.[9-13]At most reproductive centers, it is reasonable to expect clinical pregnancy rates of 30-40% and delivery rates of 25-30% when surgically retrieved epididymal or testicular sperm are used for ICSI.

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In reproductive centers managing men with obstructive azoospermia, it is essential for the IVF team to have ICSI capability. Individuals with specific clinical and technical expertise must be available for all of the phases of IVF/ICSI. Sperm retrieval is best performed by a surgeon trained in this procedure, because the possible postoperative complications of sperm retrieval include bleeding and infection may require surgical intervention.

Sperm retrieval

Sperm retrieval for use in assistive reproductive techniques may be viewed as primary treatment for obstructive and nonobstructive azoospermia, or as an adjunct to microsurgical reconstructive procedures in cases of obstructive azoospermia. Common methods of sperm retrieval are listed in Table 1.[14] The goals of sperm retrieval are to obtain the best quality sperm possible in adequate numbers for immediate use and/or potential cryopreservation while minimizing the damage to the reproductive tract. The choice of sperm retrieval method depends primarily on the experience and preference of both the physician who performs the retrieval and the IVF laboratory embryologist who will be handling the specimen. There is not adequate evidence that either fertilization or pregnancy rates are different using either fresh or thawed cryopreserved sperm from patients with either obstructive or nonobstructive azoospermia.[15-16] Therefore, the timing of sperm retrieval in relation to oocyte retrieval should be based upon local preferences and expertise.

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Table 1 : Obstructive Azoospermia: Sperm Retrieval Techniques		
	Advantages	**Disadvantages**
Microsurgical epididymal sperm aspiration (MESA)	• Large quantity of sperm obtained suitable for several IVF/ICSI cycles in one procedure	• Requires microsurgical skills • Incision with post-op discomfort • Higher cost compared to percutaneous procedures
Percutaneous epididymal sperm aspiration (PESA)	• No microsurgical skills required • Fast • Minimum post-op discomfort	• Fewer sperm retrieved • Risk of epididymal damage
Testicular sperm extraction (TESE) and microTESE	• No microsurgical skills required except when micro TESE performed	• Risk of testicular damage with multiple biopsies • Incision with post-op discomfort • Higher cost compared to percutaneous procedures
Percutaneous testicular sperm aspiration (TESA)	• No microsurgical skills required • Fast and easy • Minimum post-op discomfort • Minimally invasive	• Fewer sperm retrieved

Open surgical testicular sperm retrieval with (TESE) or without microscopic magnification (microTESE) is recommended for patients with nonobstructive azoospermia. In contrast, there is not adequate evidence that the source or method of sperm harvesting affects the outcome of IVF with ICSI for patients with obstructive azoospermia.[17-18] Thus, the choice of sperm retrieval by either percutaneous or open surgery from either the testis or epididymis should be based upon local preferences and expertise.

Sperm retrieval may be performed sometime before or on the same day as the oocyte retrieval from the female partner. Many laboratories prefer to use freshly retrieved sperm rather then cryopreserved sperm, although there is no substantial evidence to indicate that fresh sperm yield superior results. Fresh sperm may be preferable for patients with nonobstructive azoospermia

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and very few sperm harvested because of the concern that there may not be any viable sperm available upon thawing. However, for logistical and financial reasons, it's often preferable to harvest and cryopreserve sperm well in advance of the oocyte retrieval since there is the possibility that no sperm will be obtained. This avoids putting the wife through superovulation unnecessarily.

Recommendations:

1. **The timing of sperm retrieval in relation to oocyte retrieval should be based upon local preference and expertise because there is no evidence that either fertilization or pregnancy rates are different using either fresh or thawed cryopreserved sperm from patients with either obstructive or nonobstructive azoospermia.**
2. **The choice of sperm retrieval by either percutaneous or open surgery from either the testis or epididymis should be based upon local preferences and expertise since there is no evidence that the site or method of sperm retrieval affects outcome of in vitro fertilization with intracytoplasmic sperm injection for patients with obstructive azoospermia.**
3. **Open surgical testicular sperm retrieval with or without microscopic magnification is recommended for patients with nonobstructive azoospermia.**

Risks associated with IVF/ICSI

Any couple considering IVF/ICSI should be apprised of the risks associated with this treatment. These risks include the possibility of ovarian hyperstimulation, the potential complications of oocyte retrieval and multiple gestations.[19] The risk of congenital malformations in children conceived after ICSI, compared to results after IVF, have yielded conflicting results. Meta-analysis of studies after assisted reproductive treatments (IVF or ICSI) suggest less than 30%

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increase in the risk of congenital malformations relative to the rate of malformations in children conceived naturally (1-4% rate of malformations).[20] This information should be shared with couples considering IVF with or without ICSI. The prevalence of sex chromosome abnormalities in children conceived by ICSI is higher than that observed after routine IVF (0.8-1.0% vs. 0.2%). It is unclear whether this apparent increased risk results from the ICSI procedure or from a paternal effect related to abnormal sperm production in the male requiring ICSI.[21]

IVF carries a risk of mild ovarian hyperstimulation syndrome in up to 20% of patients. Moderate ovarian hyperstimulation occurs in up to 5% of women undergoing IVF. Severe ovarian hyperstimulation, which may require hospitalization and can be life threatening, occurs in 1% of women undergoing IVF.[22]

The risk of multiple gestations after ICSI in the United States is approximately 30% for twin gestations and less than 5% for triplets.[23] Multiple-gestation births are associated with increased infant morbidity and mortality rates due primarily to prematurity.[24] The neonatal and maternal morbidity induced by multiple gestations accounts for the increased perinatal expense associated with multiple gestations. Whereas the in-hospital costs for delivery of a singleton child are typically less than $10,000, perinatal care for triplets averages more than $100,000.[25]

Microsurgical reconstruction versus sperm retrieval with IVF/ICSI

Microsurgical vasovasostomy[26] and vasoepididymostomy[27] have been shown to be more cost-effective than sperm retrieval with IVF/ICSI, which requires intervention in both the male and female. In addition, microsurgical reconstruction, if successful, allows couples to have

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subsequent children without additional medical treatment. Therefore, in most cases, microsurgical reconstruction is more appropriate as an initial treatment for obstructive azoospermia.

There are situations, however, where sperm retrieval with IVF/ICSI may be the method of choice for couples in which the male has obstructive azoospermia. Financial factors are a legitimate concern in the management of this problem and may dictate the ultimate choice in treatment. If the situation involves a possible vasovasostomy, then the time that has elapsed since the vasectomy should also be taken into account. Sperm retrieval with ICSI may be preferable if the duration of obstruction is long. Pregnancy occurs in only 30% of couples managed by vasectormy reversal when the obstructive interval is greater than 15 years.[4]

Female infertility factors might also favor the selection of IVF/ICSI. The fertility status of the female partner is related to the presence or absence of specific risk factors, such as endometriosis or ovulatory dysfunction, and to age. When the female partner has tubal disease or has undergone tubal ligation, sperm retrieval with IVF/ICSI is clearly preferable because it avoids subjecting both partners to reconstructive microsurgery. The woman's age is important because a woman's fertility progressively decreases after age 35 years and is limited after age 40 years.[28] Due to the fact that the average interval until pregnancy after a successful microsurgical vasectomy reversal is 12 months[4], couples may consider sperm retrieval with ICSI when the female partner is greater than 37 years of age. However, in couples in which the female partner approaches age 40, the success rate of IVF with or without ICSI decreases dramatically as well.[23] Older women should be evaluated before any fertility treatment is undertaken. The choice of

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either sperm retrieval with IVF/ICSI or microsurgical reconstruction should also be influenced by the pregnancy rates achieved with ICSI by the IVF team when epididymal or testicular sperm is used and by the surgeon's results with microsurgical reconstructive procedures.

The final decision concerning microsurgical reconstruction versus sperm retrieval with IVF/ICSI is ideally made by the well-informed couple together with both partners' reproductive specialists.

Recommendations: Microsurgical reconstruction of the reproductive tract is preferable to sperm retrieval with in vitro fertilization/intracytoplasmic sperm injection in men with prior vasectomy if the obstructive interval is less than 15 years and no female fertility risk factors are present. If epididymal obstruction is present, the decision to use either microsurgical reconstruction or sperm retrieval with in vitro fertilization/intracytoplasmic sperm injection should be individualized. Vasoepididymostomy should be performed by an expert in reproductive microsurgery.

Sperm retrieval/ICSI is preferred to surgical treatment when (1) advanced female age is present, (2) female factors requiring IVF are present (3) the chance for success with sperm retrieval/ICSI exceeds the chance for success with surgical treatment or (4) sperm retrieval/ICSI is preferred by the couple for financial reasons.

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Conflict of Interest Disclosure

All panel members completed Conflict of Interest disclosure. Those marked with (C) indicate that compensation was received; relationships designated by (U) indicate no compensation was received; (A) indicates affiliation.

Consultant or Advisor: Larry I. Lipshultz, Humagen (C), Pfizer (C), Lilly ICOS (C), Allergan (AU), Auxilium (AC); **Scientific Study or Trial:** Larry I. Lipshultz, Auxilium Prostate/T Study (AU), Auxilium Registry Study (AU); **Meeting Participant or Lecturer:** Larry I. Lipshultz, Solvay (C); Pfizer (C); Auxilium (AC**); Investigator:** Mark Sigman**,** GlaxoSmithKline (AC), **Other:** Peter Niles Schlegel, Theralogix (C), American Board of Urology (AU)

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Acknowledgements and Disclaimers

The Management of Obstructive Azoospermia: Best Practice Statement

The supporting systematic literature review and the drafting of this document were conducted by the Infertility Best Practice Statement Panel (the Panel) created in 2007 by the AUA. The PGC of the AUA selected the Panel chair who in turn appointed the additional Panel members with specific expertise in evaluation of the infertile male. The mission of the Panel was to develop either analysis- or consensus-based recommendations, depending on the type of evidence available and Panel processes, to support optimal clinical practices concerning the infertile male. This document was submitted to 58 urologists and other health care professionals for peer review. After revision of the document based upon the peer review comments, the best practice statement was submitted to and approved by the PGC and the BOD of the AUA. Funding of the Panel and of the PGC was provided by the AUA. Panel members received no remuneration for their work. Each member of the PGC and of the Panel furnished a current conflict of interest disclosure to the AUA. The final report is intended to provide medical practitioners with a current understanding of the principles and strategies for the management of obstructive azoospermia. The report is based on review of available professional literature as well as clinical experience and expert opinion. This document provides guidance only and does not establish a fixed set of rules or define the legal standard of care. As medical knowledge expands and technology advances, this best practice statement will change. Today they represent not absolute mandates but provisional proposals or recommendations for treatment under the specific conditions described. For all these reasons, this best practice statement does not preempt physician judgment in individual cases. Also, treating physicians must take into account

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variations in resources, and in patient tolerances, needs and preferences. Conformance with the best practice statement reflected in this document cannot guarantee a successful outcome.

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This best practice statement is intended to provide medical practitioners with a consensus of principles and strategies for the care of couples with male infertility problems. The document is based on current professional literature, clinical experience and expert opinion. It does not establish a fixed set of rules or define the legal standard of care and it does not preempt physician judgment in individual cases. Physician judgment must take into account variations in resources and in patient needs and preferences. Conformance with this best practice statement cannot ensure a successful result.

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