[Frontiers in Bioscience E1, 381-389, June 1, 2009]

Advances in microsurgery and assisted reproduction for management of male infertility

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1. ABSTRACT

Microsurgical techniques are often used for reconstruction of the male genital tract in order to restore fertility. Advances in technology have led to improved outcomes for patients and men previously felt to be incapable of fathering children are now biologic parents. Use of the operating microscope has led to improved outcomes in vasectomy reversal and has made possible the connection of the vas deferens to a single delicate epididymal tubule. In addition to advances in the area of magnification, novel techniques such as robotic assisted surgery or use of biologic sealants hold promise for further refinement. New surgical techniques and high power magnification has enabled surgeons to find isolated areas of sperm production in testicles of patients that previously were felt to make no sperm at all. In this article we will review the indications, outcomes, and technological advances in the various microsurgical procedures to treat male infertility are.

2. INTRODUCTION

Microsurgical reconstruction of the male reproductive tract has shown dramatic advances over the past twenty years. Today it is an essential component of the management of male infertility. Up to 14 percent of patients presenting with primary infertility will have ductal obstruction, a condition which is potentially correctable with microsurgical techniques (1). Vasectomy is safe, effective and durable, but its popularity is a double-edged sword as about 6 percent of men will eventually request a restoration of their fertility due to changing life circumstances such as re-marriage, a change in plans, or the death of a child (2). In addition, a significant number of patients presenting with infertility without a prior history of vasectomy will be found to have azoospermia (absence sperm in the ejaculate) and will have an occult genital tract obstruction.

Soon after the recognition of ductal obstruction, innovative approaches to restore genital tract patency began to appear. Martin, in 1903 first reported his technique to treat epididymal obstruction in a patient with a history of gonococcal epididymitis. He used fine silver wire to perform anastomosis of the vas deferens to the epididymis in a side-to-side fistula fashion (3). Over three decades later, Hagner reported over 60 percent patency rates in his series of patients treated using Martin's technique (4). In another innovative effort, Quinby performed the first reportedly successful vasectomy reversal using silkworm gut as a stent in 1919. For over 75 years, these techniques remained the standard for reconstruction until advances in technique and instrumentation made possible precise multi-layer anastomosis.

Early pioneers in reconstructive surgery have provided a foundation upon which the latest techniques and innovations have been built. Since these initial efforts, incremental improvements in surgical decision making and technique have been validated by careful and critical analysis of outcomes. This article will focus on the main microsurgical procedures used to treat male infertility. An emphasis will be placed on identification of the proper candidates for each procedure as well as a critical review of outcomes for each procedure. Only a brief description of each procedure will be included in lieu of technical details. Finally, the role and contributions of microsurgery in the modern era of assisted reproduction (using techniques such as in-vitro fertilization) will be discussed.

3. BODY

3.1. Anatomy, physiology, and pathology of the excurrent ducts

To appreciate the advances in microsurgical techniques used to restore the patency of the male genital ducts or identify small areas of sperm production within the testis, a review of the male reproductive system is necessary. As germ cells become spermatozoa, they are released into the lumen of the seminiferous tubules. If obstruction is not the cause of azoospermia, it is in these tubules where isolated sites of spermatogenesis can be found for sperm harvest. The terminal ends of these tubules drain into the rete testis, which is an area in the posterior mediastinum of the testis where a nexus of anastomosing ducts coalesce into six to eight efferent ducts. These efferent ducts then converge into the single epididymal tubule in the caput, or head, of the epididymis. The epididymal tubule is a convoluted thin-walled structure of about 3 meters in length that is coiled into the 4-5 centimeter epididymis which lies on the postero-lateral surface of the testis. The epididymis is divided into 3 sections: the caput or head, corpus or midbody, and the tail or cauda. As the tubule exits the cauda epididymis, the wall becomes thick and muscular, marking the beginning of the vas deferens. During ejaculation, the sympathetic nervous system mediates contraction of this thick muscular wall, propelling sperm towards the ampulla of the vas. From the epididymis, the vas travels along the spermatic cord, up through the inguinal canal and then enters the retroperitoneum. At this point the vas crosses anterior to the ureter towards the posterior base of the bladder and prostate. Within this rectovesical space, it becomes more dilated to form the ampulla of the vas deferens. The terminal segment, called the ejaculatory duct, traverses through the prostate to empty into the urethra.

The epididymis has four vital functions: sperm maturation, transport, concentration, and storage. The fact that sperm mature in the epididymis has significant implications on microsurgical outcomes. While the exact mechanism of maturation is unknown, it is well recognized that transit through the proximal portion of the epididymis is essential for the fertilization potential of that sperm. Animal studies have shown that sperm extracted from the cauda of the epididymis have superior motility and fertilizing capacity when compared to sperm extracted from the caput of the epididymis (5-6). Similar studies in humans have shown that chances for fertility after vaso-epididymostomy, a microsurgical bypass that directly connects the vas deferens to the epididymis, are directly correlated with the length of epididymis the sperm were able to traverse (7-8). The cauda epididymis functions primarily for storage of sperm prior to ejaculation.

Obstruction may occur anywhere along the course of these ducts. The etiologies of the obstruction can be divided into groups based on their causative nature: congenital, inflammatory, traumatic, iatrogenic, and idiopathic.

Hypoplasia of the seminal vesicles, absence of the vas deferens, and absence of most of the distal epididymis is found in a form of congenital obstruction called vasal agenesis. Vasal agenesis can be unilateral or bilateral. About two thirds of men with bilateral vasal agenesis are found to have at least one mutation of the cystic fibrosis transmembrane regulator gene, but most will not manifest the phenotypic findings of cystic fibrosis (9). Because the majority of semen volume normally comes from the seminal vesicles, patients with hypoplasia of the seminal vesicles will have low ejaculate volume and azoospermia. Most of these patients will require surgical or percutaneous extraction of sperm for use with in-vitro fertilization (IVF) and possible intracytoplasmic sperm injection (ICSI), a type of IVF where a single sperm is directly injected into an egg.

In contrast, obstruction at the level of the epididymal duct secondary to infection may be surgically reversible. Though rare, tuberculous epididymitis can result in epididymal occlusion and azoospermia. Tuberculous and gonorrheal epididymitis had been major causes of obstructive epididymitis, but they have become quite rare in the antibiotic era. Bacterial epididymitis from organisms such as Chlamydia is a much more common cause of infection-derived epididymal obstruction at this time. Trauma to the epididymis, blunt or penetrating, can also lead to obstruction. It is more common to have iatrogenic injuries occurring after procedures such as spermatocelectomy, hydrocelectomy or even testis biopsy (10).

Elective sterilization via vasectomy is by far the most common cause of obstructive azoospermia and subsequent infertility. Though vasectomy initially results in only a single, focal obstructive site, high intraluminal pressures from the obstruction can result in rupture of the upstream delicate epididymal tubule and a secondary obstruction of the epididymal tubule. The likelihood of this phenomenon increases when the vasectomy was performed greater than ten years prior or if vasectomy reversal has been attempted once and failed (11).

Men with vasal or epididymal obstruction will have azoospermia with normal testicular size, normal ejaculate volume and normal hormone levels. Nevertheless, restoration of genital tract patency does not guarantee restoration of fertility. Studies in a variety of animal species have shown adverse changes in testicular histology following vasectomy which may adversely affect future fertility. These changes include immune complex deposits, autoimmune orchitis, and apoptosis of germ cells (12-19). In men, histologic findings after vasectomy include degeneration of spermatids (20), thickened basement membranes (21-22) and increased phagocytosis by Sertoli cells (23). Results of morphometric analysis of testicular histology in vasectomized men revealed seminiferous tubular dilation, interstitial fibrosis, and reductions in the seminiferous cell population (24). The severity of the interstitial fibrosis inversely correlates with vasovasostomy success (25). Despite a unifying explanation, it is clear that vasectomy results in altered testicular histology and this may impair future fertility in select men who choose to undergo a reversal of their vasectomy.

3.2. Microsurgical vasovasostomy

3.2.1. Indications

Vasovasostomy restores fertility by direct reconnection of the vasal ends. It is most commonly utilized in men who have previously undergone elective sterilization with vasectomy, but can also be required when there has been a traumatic injury to the vas deferens such as from a hernia repair or other surgery. In men whose vasectomy is less than ten years old, vasovasostomy is usually the appropriate procedure. Obstruction at the level of the epididymis can occur in long-standing vasectomies due to secondary obstruction of an epididymal tubule. In these men vasovasostomy will not restore genital tract patency and they will need vaso-epididymostomy to bypass the epididymal obstruction. It is rare for men within 4 years of their vasectomy to have epididymal obstruction, but Fuchs and colleagues showed that 60 percent of men with vasectomies 15 years or older will have epididymal obstruction on at least one side (26). A linear regression algorithm using patient age and time since vasectomy as predictors of need for vaso-epididymostomy has been developed which assigns a score based on the equation (age X 0.31) + (obstructive interval X 0.94). (27) If the score was greater than 20, then a vaso-epididymostomy was predicted on at least one side. Model sensitivity was intentionally set at 100 percent so a urologist not skilled in vaso-epididymostomy could identify patients who might require an epididymal anastamosis and refer the patient to a microsurgeon skilled in this procedure.

At the time of planned vasovasostomy, the fluid from the proximal vas deferens is analyzed and ultimately dictates if vasovasostomy is appropriate. If sperm are seen then epididymal patency is proven and vasovasostomy can proceed. If no sperm are seen, but the fluid is thin or milky, vasovasostomy is still appropriate as a large percentage of patients will ultimately have return of sperm to the ejaculate. If there is no fluid or the fluid is thick and pasty, then epididymal obstruction is present and the surgeon should proceed to vaso-epididymostomy (28).

Vasovasostomy may be required for individuals with vasal obstruction for reasons other than prior vasectomy. Non-vasectomy vasal injury usually results from hernia repairs during infancy or early childhood. There have also been reports of vasal obstruction secondary to the use of mesh in adult herniorrhaphies (29). Injuries may go unnoticed if unilateral but patients may present with infertility if there is bilateral injury or the testis contralateral to the injured side is hypofunctioning for other reasons. Diagnosis is confirmed by a vasogram, where radiologic contrast is injected distally in the vas deferens to reveal the site of obstruction.

3.2.2. Traditional microsurgical technique

Microsurgical vasovasostomy, direct reconnection of the vasal ends, is the most common microsurgical procedure for male infertility. The procedure may be done under local or general anesthesia. A small incision is made vertically in the scrotal skin overlying the prior vasectomy site and the vas deferens is delivered into the operative field. At this point under optical magnification using the microscope, the vas deferens is dissected from surrounding tissues. The intervening segment of scar from the prior vasectomy is removed to leave a fresh lumen on each side for anastomosis. Fluid from the proximal end of the vas deferens is then examined under a light microscope in the operating room for presence of sperm. If a vasovasostomy is to be performed, then the two ends of the vas deferens will be anastomosed in an end to end fashion. Though there are multiple techniques to do this, traditionally an inner layer of 10-0 Nylon sutures are used to approximate the mucosa of the vas and an outer layer of 9-0 Nylon sutures are used for connecting the seromuscular layers. (Figure 1)

3.2.3. New developments in vasal re-anastomosis

Less traditional, but more innovative strategies to re-connect the vas deferens have also been employed. In an effort to minimize suture placement, which can be technically challenging under the microscope, research is underway to use tissue adhesives or welding techniques. Multiple animal studies using fibrin glue, a biologic sealant made from human or animal clotting factors, have demonstrated patency rates equivalent to traditional microsurgical techniques (30-35). Ho and associates were the first to demonstrate success with fibrin glue vasovasostomy in humans. They used three transluminal sutures with fibrin glue to complete the anastomosis in 42 patients. Patency and pregnancy rates were equivalent to traditional standards with shorter operative times (36).

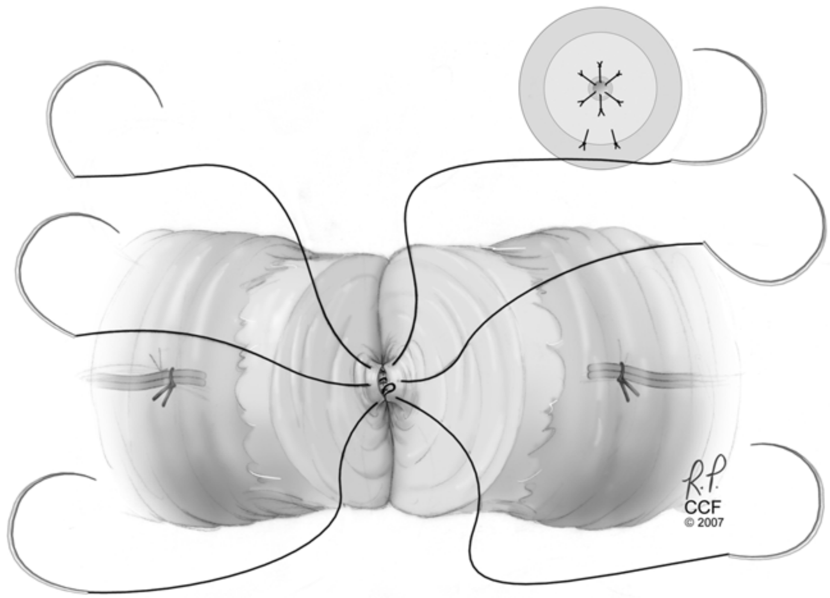

Figure 1. Magnified view of the inner mucosal layer of the traditional 2 layer microsurgical technique. The back wall sutures have been placed and tied, while the anterior sutures have been placed and are ready to be tied.

Robotic-assisted surgery is becoming more prevalent and it is not surprising that this cutting-edge technology has been applied to microsurgery. One of the reasons microsurgery is so challenging is a surgeon's natural tremor is magnified under the operating microscope. Robotic surgical technology offers an innovative solution to this problem. The da Vinci Surgical System (Intuitive Surgical, Mountain View, California) is a system where the surgeon is seated at a remote console located in the operating room and the robot is positioned over the patient and responds to input from the surgeon (Figure 2). Motion downscaling software allows the surgeon to use both dominant and non-dominant hands without discernable tremor. Excellent patency rates have been noted using robotic assistance for microsurgical vasectomy reversals in the rat model (37) and in *ex-vivo* vasovasostomies with human vas deferens (38). Though operative times were initially longer in some series, with experience they were approaching that of traditional technique. Patency rates were similar for both traditional microsuture and robotic-assisted procedures.

3.2.4. Outcomes

Data regarding results of vasovasostomy is readily available, but critical comparison can be challenging due to confounding variables such as female factor infertility and variable algorithms for deciding on vasovasostomy versus vaso-epididymostomy. It is clear that microsurgical techniques produce superior results over vasovasostomy performed without optical magnification (Table 1). The presence of sperm in the ejaculate post vasovasostomy can be as high as 94 percent when sperm are seen in the vasal fluid intra-operatively (39). When examining success in terms of pregnancy rates, the age of the female remains a critical factor. Pregnancy rates of 64 percent for women under age 30 were reported with a progressive decline to 28 percent for women over 40 years old (40). Though technically more challenging, inguinal reconstructions (such as for repair of obstruction after hernia repair) have similar patency and pregnancy rates to scrotal vasovasostomy done to reverse vasectomy (41).

3.3. Vasoepididymostomy

3.3.1. Indications

In general, vasoepididymostomy is indicated when azoospermia is a result of epididymal obstruction. In clinical practice, the scenario is often noted during a planned vasectomy reversal. If fluid is absent from the proximal vas deferens or if the fluid is thick and pasty without any sperm, then there is epididymal obstruction and the surgeon should proceed to vasoepididymostomy. The other, less common, indication for vasoepididymostomy is patients with primary obstructive azoospermia (no prior vasectomy) and is undergoing testis biopsy and vasography. If the distal vas deferens is patent and spermatogenesis is confirmed on testis biopsy, the obstruction is usually at the level of the epididymis and a vasoepididymostomy is indicated

3.3.2. Technique

Vasoepididymostomy is a technically more challenging procedure than vasovasostomy as it requires anastomosing the delicate epididymal tubule to the distal end of the vas deferens. Unlike vasovasostomy which can be performed with loupe magnification, vasoepididymostomy requires high degrees of magnification necessitating the use of the surgical microscope. Multiple techniques have been described, but in general the epididymal tunic is first opened as the initial step. It is important to perform the anastomosis at a point in the epididymis where sperm is seen in the fluid but as distal as possible because the sperm are more mature in this

Table 1. Vasovasostomy Series

Author	Year	Microsurgery	Patients (#)	Patency (%)	Pregnancy (%)
Derrick(53)[1]	1973	No	1600	38	19
Silber(54)	1977	Yes	126	90	76
Lee(55)	1980	No Yes	41 26	90 96	46 54
Soonawala(56)	1984	No Yes	194 339	81 89	44 63
Belker(28)	1991	Yes	1247	86	52
Kabalin(57)	1991	No	111	79	36
Fox(58)	1994	Yes	103	84	48

[1]survey of practicing urologists

Table 2. Vasoepididymostomy Outcomes

Author	Year	# Patients	Anastomosis	Patency(%)	Pregnancy(%)
Dubin(59)	1985	46	End-to-End	39	13
Silber(60)	1989	139	End-to-End	78	56
Dewire(61)	1995	137	End-to-Side	79	50
Berger(62)	1998	12	Intussusception	92	Not reported
Marmar(63)	2000	9	Intussusception	78	22
Chan(64)	2005	68	Intussusception	84	40
Schiff(65) [1]	2005	153	End-to-End End-to-Side 3-Suture Intuss 2-Suture Intuss	73 74 84 80	20 40 46 44

[1]$p<0.05$ comparing patency rates between intussusception techniques and end-to-end or end-to-side vasoepididymostomies. No statistically significant differences in pregnancy rates between techniques.

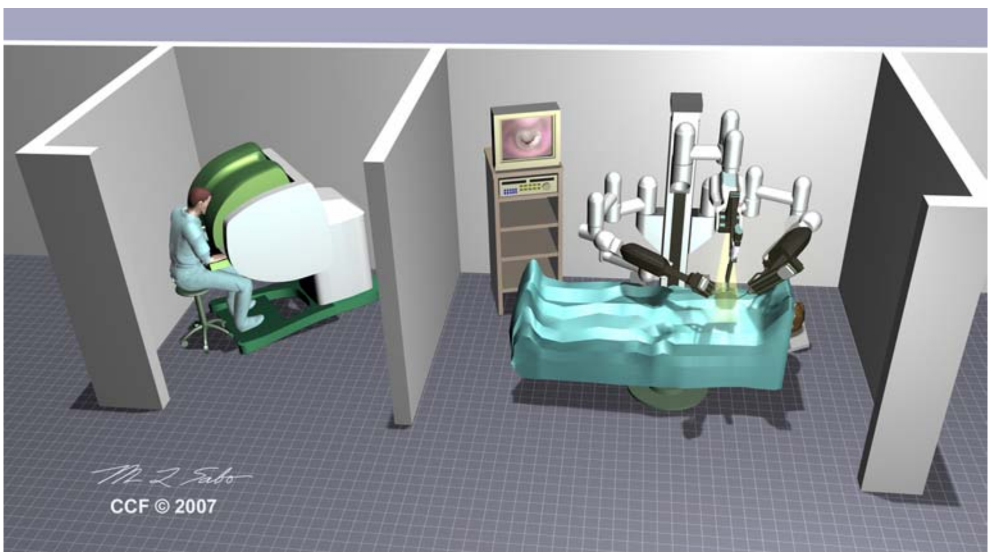

Figure 2. Schematic of robotic assisted surgery. The surgeon is seated at a remote console from the operating table.

area. Using 10-0 nylon suture the epididymal tubule is then anastomosed to the distal end of the vas either in an end-to-side fashion or using an intussusception technique (Figure 3) A second layer of 9-0 suture is used to secure the serosa of the vas to the epididymal tunic.

3.3.3. Outcomes

Vasoepididymostomy is technically more difficult than vasovasostomy and not surprisingly has lower success rates. It also takes longer to see results from a vasoepididymostomy. Though vasovasostomy may result in sperm in the ejaculate within weeks of surgery, vasoepididymostomy patients may wait three to six months from the time of their procedure before sperm appear in the ejaculate. Some cases take even longer and therefore vasoepididymostomies are not labeled as failures until after one year has elapsed without sperm in the ejaculate (42-43). Table 2 reviews contemporary outcomes of vasoepididymostomy.

3.4. Microsurgical testicular sperm extraction

3.4.1. Indications

Unlike the procedures discussed previously, microsurgical testicular sperm extraction is indicated in

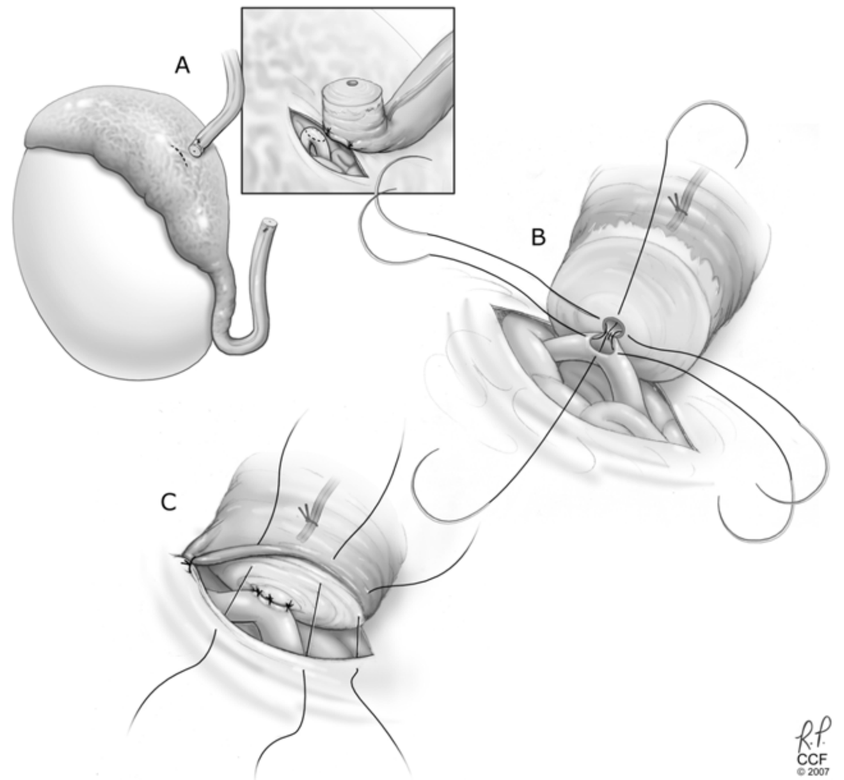

Figure 3. Magnified view of vasoepididymostomy- A. The distal end of the vas deferens is brought to the epididymis. B. Sutures are placed for the end-to-side anastamosis of the vas deferens to a single epididymal tubule. C. Completion of the second layer, suturing the seromuscular layer of the vas deferens to the epididymal tunic.

men who have obstructive as well as non-obstructive causes of azoospermia. These men either cannot be made fertile by a reconstructive procedure or choose to undergo sperm harvest instead of complex reconstructive procedures. Typically, the harvested sperm is frozen, or cryopreserved. The sperm is later thawed for use in with a specialized type of *in-vitro* fertilization called intracytoplasmic sperm injection (ICSI). ICSI involves micromanipulation where a single sperm is injected into a respective egg. After a period of incubation, the embryos are transferred back into the female partner.

3.4.2. Technique

Microsurgical testicular sperm extraction is a novel technique to extract sperm for patients who clinically have azoospermia (44). Prior to this procedure sperm harvest was performed without the use of an operating microscope by taking multiple random specimens of testicular tissue to find sperm. In microsurgical testicular sperm extraction, the testis is opened with an incision about 2/3 of the circumference of the testis. The seminiferous tubules are then systematically examined under the operating microscope to identify tubules that appear fuller and more opaque than the remainder. These are felt to be the tubules that harbor isolated areas of spermatogenesis. These tubules are carefully removed and examined for presence of sperm, which can be cryopreserved if found. These sperm can subsequently be used for in-vitro fertilization.

3.4.3. Outcomes

In his original paper, Schlegel reported finding sperm in 45 percent of men using traditional open biopsy techniques, but this number increased to 63 percent using his microdissection technique (44). In a subsequent study, microdissection technique was confirmed to yield higher sperm harvest success than the traditional group (45). Additionally, because a much smaller volume of testis tissue is removed, microdissection has fewer deleterious effects on the remaining testis tissue. (46).

4. PERSPECTIVES

Complete evaluation of microsurgical treatment for male infertility is impossible without placing its use in context with current assisted reproductive technologies. Successful *in-vitro* fertilization with intracytoplasmic sperm injection (IVF-ICSI), which allows injection of a single sperm into a single egg and requires very few sperm in total, was reported by Palermo in 1992 (47). Because this technique requires very few sperm from the male partner, some have recommended it for all causes of infertility, regardless of etiology. However, there are inherent risks associated with ovulation induction, including ovarian hyperstimulation which, though rare, can be fatal (48-49). There is added risk and additional cost from multiple births since 40 percent or more of *in-vitro* fertilization pregnancies are multiple gestations of twins, triplets or higher (50). Also, microsurgical reconstruction is much more cost-effective when compared to IVF-ICSI for patients with obstructive azoospermia (51-52). All factors argue for the prudent use of assisted reproduction with repair of genital tact obstruction where possible.

In cases of non-obstructive azoospermia, assisted reproduction, in conjunction with microsurgical testicular sperm extraction has enabled men who could not otherwise father children to become a genetic parent. Since so few sperm are required for IVF-ICSI, men who could not otherwise have children can do so if only a few hundred motile sperm can be found on microscopic testicular sperm extraction.

Novel developments in microsurgical techniques and equipment have opened exciting new areas in the treatment of male infertility. Surgical outcomes are still dependent on surgeon experience and technique, but further refinement and new technologies are sure to continue to improve outcomes for these patients.

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Key Words: Male Infertility, Microsurgery, Azoospermia, Vasectomy Reversal, Review

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