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VASECTOMY REVERSAL IN THE ERA OF INTRACYTOPLASMIC SPERM INJECTION (ICSI): INDICATIONS AND TECHNIQUE

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ABSTRACT

Vasectomy is an effective method of permanent contraception that has gained popularity in many countries during the last decade. Approximately one-half million men per year undergo this procedure in the United States. Between 2 to 6% percent of vasectomized men will request vasectomy reversal later in their lives. Microsurgical vasovasostomy and vasoepididymostomy are the primary surgical techniques used today for vasectomy reversal. These procedures are highly successful in the hands of experienced microsurgeons.

Success after vasectomy reversal depends on several factors including the length of the interval between the vasectomy and the reversal, the experience of the surgeon, and other pre-operative and intra-operative factors. Alternative surgical techniques for reconstruction, including the use of lasers and fibrin tissue glue, are currently under investigation. Also, with the recent advances in the field of in vitro fertilization (IVF) and the development of intracytoplasmic sperm injection (ICSI), some have advocated the use of this technique to treat all types of male infertility, regardless of etiology. Recent cost-effective analyses showed that microsurgical reconstruction is a more cost-effective approach for the treatment of obstructive azoospermia after a vasectomy thus, it remains as the treatment of choice for vasectomized men who wants to re-establish fertility.

Postoperative patency is generally achieved by six months after a vasovasostomy and by twelve months after a vasoepididymostomy. Patients should be followed for approximately six months to one year after reconstruction, depending on the procedure performed, before further treatment. Complications are similar to those related to scrotal surgery: scrotal hematoma, swelling and infection. Twelve percent of patients with initial patency after vasovasostomy and 25% with an initial patent anastomosis after vasoepididymostomy will develop a late obstruction within 14 months of the surgical reconstruction. Repeat reconstruction is a viable option in these cases. Since failures are common after repeat procedures, intraoperative and postoperative sperm cryopreservation is recommended.

In the current era of IVF advancements and ICSI, microsurgical vasectomy reversal remains the standard of care for patients who want to re-establish fertility after vasectomy.

Key words: infertility, vasectomy, reversal, surgery, ICSI
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INTRODUCTION

Vasectomy is an effective method of permanent contraception that has gained popularity in many countries during the last decade. It has been estimated than more than thirty million couples worldwide are using this form of birth control (1). Thirteen percent of all married couples in the United States rely on vasectomy for contraception (2) and approximately one-half million men per year undergo this procedure. However, the divorce rate in the United States has remained high and stable at approximately 50%. The high divorce rate is the major factor contributing to the fact that 2 to 6% of vasectomized men request vasectomy reversal (3). Vasectomy reversal is generally performed with the microsurgical technique and

involves reconstruction of the male reproductive tract in order to bypass the area of obstruction created during the vasectomy. This may be accomplished with a microsurgical vasovasostomy alone or may require vasoepididymostomy. The following article reviews the current indications, techniques, and outcomes of vasectomy reversal, as well as, the alternatives in the era of in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI).

INDICATIONS FOR VASECTOMY REVERSAL

Vasectomy represents the leading cause of infertility for men with ductal obstruction and the most common indication for vasectomy reversal is the treatment of infertility in this population. A large multicenter study by the Vasovasostomy Study Group (4) revealed that more than 2/3 of patients underwent vasectomy reversal because of divorce or remarriage. Other reasons include the death of a spouse or child, change in religious belief, change of opinion regarding family size, and the desire to regain masculinity or fertility for the future (5,6).

Another rare indication for vasectomy reversal is for the treatment of the postvasectomy pain syndrome, which has been reported to occur in as low as 3 to 8% and as high as 33% of patients after a vasectomy (7). The pathogenesis of this pain remains poorly understood. Although Myers et al (7) reported pain relief in 84% of patients after vasectomy reversal, the surgical management of this entity remains controversial and should be reserved as a last resort when all other forms of treatment have failed (6).

Patients with associated epididymal obstruction not caused by a previous vasectomy (i.e. congenital, infectious, inflammatory or traumatic) or with absence of fluid, sperm, or both in the testicular portion of the vas at the time of vasectomy reversal, will require a vasoepididymostomy (6).

Although vasectomy reversal has a high degree of success, vasectomy should be considered a permanent form of contraception. Therefore, individuals requesting a vasectomy should be appropriately counseled. Characteristics associated with increased risk of requesting a vasectomy reversal are age younger than 30 years, few or no children, religion that condemns sterilization and interest in surgical reversal or sperm banking at the time of vasectomy (8). A recent retrospective analysis by Potts et al. (5) also revealed that a younger age at time of vasectomy (less than 30 years old) was significantly associated with increased incidence of vasectomy reversal. Unfortunately, we are unable to reliably identify patients likely to request a reversal in the future. This is an area that needs further investigation.

PROGNOSTIC FACTORS TO PREDICT SUCCESS OF VASECTOMY REVERSAL

Duration of Obstructive Interval

Silber noted that there was an inverse relationship between the duration of the obstructive interval (time since the vasectomy until attempted reconstruction) and the patency and pregnancy rates (9). This was subsequently confirmed in a large multicenter study published by the Vasovasostomy Study Group (4). When the obstructive interval was less than three years, patency and pregnancy rates of 97% and 76% were achieved. From four to eight years, the patency and pregnancy rates were 88% and 53%, respectively. From nine to fourteen years, the patency and pregnancy rates were 79% and 44%. Finally, when reconstruction was performed more than 15 years after vasectomy rates of 71% and 30%, respectively, were achieved.

Intraoperative Observations

In the same study, the characteristics of the fluid in the testicular portion of the vas at the time of vasovasostomy have been shown to be of prognostic value. When clear fluid with motile intravasal sperm was observed, 94% of patients had a return of sperm to the ejaculate compared with only 60% of those patients with no sperm in the vasal fluid. Even in the absence of sperm, the physical characteristics of the fluid in the testicular portion of the vas correlated with the likelihood of success. If the fluid was watery, the authors demonstrated an 80% patency and 45% pregnancy rate after vasovasostomy. Thick,

white, or "toothpastelike" fluid in the proximal vas indicated a poor prognosis (4). In the latter case a vasoepididymostomy would then be indicated. The absence of any fluid in the proximal vas at the time of reversal has generally been accepted as an indication for a vasoepididymostomy. However, recently, Sharlip (10) reported return of sperm in the ejaculate after vasovasostomy in 80% of males without fluid in the vas at the time of vasectomy reversal. Until further studies reveal similar findings, these results should be viewed with caution.

A sperm granuloma, which results from leakage of sperm at the vasectomy site, allows the release of pressure from the epididymis thus decreasing the risk of epididymal tubule rupture, subsequent scarring and the development of proximal epididymal obstruction. Although the presence of a sperm granuloma has been associated with better outcome (6), the Vasovasostomy Study Group found no beneficial effect (4) and consequently the prognostic significance of this factor remains unclear. The lack of clear reproducible criteria for sperm granuloma adds to further confusion regarding its potential beneficial impact.

The site of the anastomosis during a vasoepididymostomy has been correlated to the postoperative pregnancy rate. Silber (11) reported a 72% pregnancy rate for patent vasoepididymostomy performed at the level of the corpus epididymis as opposed to only 43% for anastomosis done at the level of the caput epididymis. Schlegel & Goldstein (12) found a similar trend, although it did not reach statistical significance.

Preoperative Observations

Witt et al. (13) determined that the length of the proximal vasal remnant, when measured preoperatively, accurately predicted the presence of sperm in the vasal fluid. They showed that 94% of patients with a vasal remnant greater than 2.7 cm had whole sperm in the vasal fluid. Conversely, 85% of patients with a vasal remnant shorter than 2.7 cm had no sperm in the vasal fluid. This observation is difficult to employ in the preoperative setting. However, a man with a long palpable vasal segment without epididymal nodularity and less than 5 years of obstruction, is likely to have sperm in the proximal vas. Another area of controversy is the presence of antisperm antibodies after vasectomy. Some studies showed decreased fertility potential and pregnancy rates with the presence of increase titers of sperm antibodies in serum (14-16). Others reveal conflicting results regarding the effects of IgG versus IgA antisperm antibodies on fertility (6). Approximately 50% of post-vasectomy patients have measurable titers of serum antisperm antibodies, but the majority is fertile after vasectomy reversal (17). Due to the ongoing controversy and the proven fertility of many patients in the presence of antisperm antibodies, we do not recommend the determination of antisperm antibodies status before vasectomy reversal (6). Antisperm antibodies may be measured after reversal when persistent asthenospermia or sperm agglutination is observed in patients with good sperm counts. When this occurs, patients are counseled to proceed with in vitro fertilization as this has been demonstrated to be successful in the presence of antisperm antibodies (18).

Experience

Finally, the microsurgical experience of the surgeon may be the most important factor predictive of the success of vasectomy reversal. Nagler & Belker demonstrated that surgeons who performed microscopic vasovasostomy without practice had a 53% patency rate as opposed to an 89% patency rate for those surgeons with previous laboratory microsurgical training. Laboratory and clinical practice are mandatory to obtain good outcomes (6).

ALTERNATIVE SURGICAL TECHNIQUES FOR RECONSTRUCTION

Due to the time-consuming and challenging nature of microsurgical vasectomy reversal, many surgeons have developed new techniques in an attempt to decrease the operative time and technical difficulties associated with these procedures. These developments include laser-assisted vasovasostomy and vasoepididymostomy, where both neodymium:

yttrium-aluminium-garnet and CO2 lasers are used to perform the anastomosis (laser welding) (19,20). Laser tissue soldering has also been used to perform the anastomosis. In this technique a protein solder composed of albumin, sodium hyaluronate, and indocyanine green dye, is activated by a specific wavelength of laser energy (21). Another new technique is the use of fibrin tissue glue as a replacement for suture anastomosis (22). Although some of these new techniques have reported patency rates up to 90% (21), they remain investigational and until more studies are performed their clinical use is only anecdotal.

ALTERNATIVES TO RECONSTRUCTION: SPERM ACQUISITION WITH IN VITRO FERTILIZATION

In recent years major improvements have been made in the treatment of infertility. In vitro fertilization, although very successful in the treatment of certain types of infertility, has not been an effective modality for male factor infertility because of the poor fertilization rates achieved with abnormal semen analyses. It was not until the development of intracytoplasmic sperm injection (ICSI), the ability to inject a single sperm into the ooplasm of an ovum, that in vitro fertilization became a viable option for the treatment of male infertility. The first pregnancies from these procedures were reported by Palermo et al in 1992 (23). Due to the success of this technique utilizing sperm acquired from essentially all sites within the male reproductive system, its use has been suggested to treat all types of male infertility regardless of etiology, including obstructive azoospermia after a vasectomy.

Recently, Pavlovich & Schlegel (2) performed a cost-effectiveness analysis between vasectomy reversal and sperm retrieval with ICSI. They showed that the cost-per-delivery after vasectomy reversal was U$25,475 and after sperm retrieval with ICSI U$72,521 and concluded that vasectomy reversal should be the recommended initial treatment for men requesting correction of ductal obstruction after vasectomy. In a similar analysis, Kolettis & Thomas (24) compared microsurgical vasoepididymostomy with microsurgical sperm aspiration with ICSI for the treatment of epididymal obstruction secondary to vasectomy. The pregnancy rate, delivery rate and cost-per-newborn were 44%, 36% and U$31,099, respectively for vasoepididymostomy and 56%, 29% and U$ 51,024 for microsurgical sperm aspiration with ICSI (See Table-1). They concluded that microsurgical vasoepididymostomy is at least as successful as and more cost-effective than microsurgical sperm aspiration and ICSI. The authors of these two studies also recommended sperm aspiration and cryopreservation at the time of the surgical reconstruction that could potentially be used for ICSI in the event of persistent azoospermia after failed reversal.

Table 1 *- Cost per newborn*

Authors	VR	ICSI
Pavlovich & Schlegel (ref. 2)	U$ 25,475	U$ 72,521
Kolettis & Thomas (ref. 24)	U$ 31,099	U$ 51,024
Donovan et al. (ref. 42)	U$ 14,892	U$ 35,570

VR: Vasectomy reversal (includes microsurgical vasovasostomy, vasoepididymostomy, or a combination of both).
ICSI: Sperm retrieval plus in vitro fertilization with Intracytoplasmic Sperm Injection.

The previous data confirms that primary microsurgical reconstruction remains the treatment of choice for post-vasectomy men who wants to re-establish fertility. However, these studies do highlight the fact that patients have alternative therapies from which to choose.

SURGICAL TECHNIQUE

The surgical technique to perform a vasovasostomy has advanced from a macrosurgical one-layer to a microsurgical two-layer anastomosis. Most studies using this latter approach have confirmed the superiority of microsurgical technique compared with the macrosurgical and loupe-magnified techniques (6). We believe that this represents the standard of care. However, microscopic vasovasostomy requires some level of expertise in

microsurgical technique by the operating surgeon in order to obtain high success rates. A detailed description of these techniques is beyond the scope of this review. We will only highlight some basic principles for a successful repair.

Vasovasostomy can be performed under local, regional or general anesthesia. A small vertical incision in the scrotum may be used to exteriorize the vasal ends if the site of vasectomy is easily identified. If this is not possible, then a longer vertical scrotal incision angled towards the external inguinal ring may be used to deliver the testis with an intact tunica vaginalis. This incision can be extended superiorly into the external inguinal ring, if needed, to reach a high vasectomy site or if a large vasal gap is encountered (6). Both ends of the vas are mobilized and then sharply incised to create a perpendicular cut. The perivasal vasculature should be preserved if possible to avoid injury to the vasal artery to minimize the potential for subsequent testicular atrophy (3). A small angiocatheter is used to aspirate any fluid that may efflux from the proximal (testicular end) vas and this is analyzed under the microscope for the presence of sperm. If sperm is visualized, a vasovasostomy is performed. If no sperm is found, this end can be barbotaged with 0.1 ml of saline while the convulated vas is milked. If no sperm is found after multiple samples are examined, a vasoepididymostomy should be performed (see above) if this is within the technical capability of the surgeon.

The patency of the distal or abdominal vas should be confirmed before proceeding with the microsurgical anastomosis. A 24-gauge angiocatheter is inserted into this end of the vas and 5 ml of dilute methylene blue is injected. The bladder is then catheterized. The return of blue-stained urine confirms the patency of the distal reproductive tract. On the contralateral side, patency can be confirmed by instilling saline. If obstruction is present, fluid cannot be instilled and a formal radiologic vasography must be performed (6).

Two microsurgical methods of anastomosis can be used for a vasovasostomy: the two-layer technique and the modified one-layer technique. The two-layer technique offers great precision in approximating the lumen of each end of the vas deferens and can be useful when there is a significant difference in the size of the vasal lumen on both ends (6). The modified one-layer technique described by Sharlip & Belker (25,26) can be useful for patients in whom the muscularis of the testicular side is thin due to luminal dilatation making difficult to differentiate the mucosa from the muscularis. In this scenario a two-layer anastomosis can be difficult to achieve. Although many authors prefer the two-layer technique as compared to the one layer technique, its superiority has not been clearly established (27)

Based on the Vasovasostomy Study Group (4), the mean patency and pregnancy rates for vasovasostomy were 86% and 52%, respectively, for 1247 men studied over a nine year period. A recent surgical aid called “micro-dot technique” was reported by Goldstein (28). This maneuver helps the surgeon execute the anastomosis by mapping the planned suture points with microdots placed using a microtip marking pen. This aid does not change the overall technique but may be of assistance to some surgeons and enable precise suture placement during a two-layer repair. He reported patency and pregnancy rates of 99.5% and 64%, respectively (29).

Microsurgical vasoepididymostomy can be performed using mainly two methods of anastomosis: end-to-end, single tubule anastomosis, also known as Silber technique (30) and end-to-side, single tubule anastomosis, initially described by Fogedestam et al. (31) and Wagenknecht (32) and later popularized by Thomas (33). The former has been used for distal obstruction and when the vas deferens is short. The outer diameter of the epididymis is similar to that of the vas at this level making this procedure similar to a vasovasostomy of the convulated vas (3). The end-to-side anastomosis has been used when there is marked dilatation of the epididymis and the obstruction is on the epididymal head (proximal obstruction) and there is no compromise of the vasal length. This approach does not disturb the epididymal blood supply, is minimally traumatic to the epididymis and relatively bloodless.

The epididymis is examined under the microscope to identify the presumed area of obstruction. Once a dilated tubule is identified and open, fluid is aspirated with an angiocatheter and examined for

the presence of sperm. If no sperm is found, the tubule is closed and the procedure repeated more proximally. Once sperm are recognized, a sample should be taken for cryopreservation. The application of methylene blue to the cut surface of the vas enhances the visibility of the mucosa, which does not stain. This can also be done over the cut surface of the epididymis to clearly outline the cut edges of the epididymal tubules.

Microsurgical vasoepididymostomy is the most technically demanding procedure in urologic microsurgery. Its success is directly related to the experience of the surgeon and it should be performed only by well-trained microsurgeons. The reported patency rates after a vasoepididymostomy range from 50% to 80%. Goldstein has reported patency and pregnancy rates of 70% and 43%, respectively (3). Thomas has reported a patency rate of 66% and a pregnancy rate of 42%, with the end-to-side anastomotic technique. Recently, Berger (34) introduced a modification of the end-to-side technique called "triangulation vasoepididymostomy". In this technique, three sutures are place into the epididymal tubule prior to opening the tubule. After the sutures are placed, a tubulotomy is made. The epididymal fluid is examined, and if sperm are observed, an anasotomosis is performed. Each of the two ends of each suture is then passed from inside out within the vasal lumen. This results in invagination of the epididymal tubule into the vasal lumen, creating a watertight 6-stitch anastomosis using only three sutures. This technique requires less operative time, is less technically demanding and uses fewer sutures. Berger reported a patency rate of 92%.

The success of all these procedures is based on several surgical principles (See Table-2)

Table 2 - *Surgical principles of vasectomy reversal (3)*

1) Accurate mucosa to mucosa approximation
2) Leak proof anastomosis
3) Tension-free anastomosis
4) Use of healthy mucosa and muscularis
5) Preservation of asequate blood supply
6) Use of good atraumatic anastomotic technique

Complications

Complications are similar to those of scrotal surgery: scrotal hematoma, swelling and infection. Testicular atrophy can result if there is injury to the internal spermatic artery and the vasal collateral blood supply. Late complications of vasovasostomy include sperm granuloma (seen in 5% of cases), stricture and obstruction of the anastomotic site. Twelve percent of patients with initial patency after vasovasostomy and 25% with an initial patent anastomosis after vasoepididymostomy will develop a late obstruction within 14 months of the surgical reconstruction (35). Immediate or primary failure after reversal may indicate unrecognized epididymal obstruction, whereas late failure is likely the result of anastomotic compromise secondary to ischemia, poor mucosal apposition or sperm granuloma (6).

Post-op management/Follow-up

Patency after a vasovasostomy is usually demonstrated by six months from surgery. Similarly, the mean interval to observation of motile sperm after vasoepididymostomy has been 5.9 months (35). Ninety four percent of patients, who eventually will have sperm in the ejaculate after vasectomy reversal, achieve this within 1 year of reconstruction. For this reason, no attempt at surgical re-intervention for persistent azoospermia after vasoepididymostomy should be done until that time, and patients should be followed expectantly for about one year. This does not represent a strict guideline since each case needs to be individualized for other intervening factors such as associated diseases, age of the partner, etc., which could mandate an earlier intervention.

VARICOCELE AND VASOVASOSTOMY

The impact of a varicocele on the spermatogenesis of previously vasectomized men cannot be estimated. Some authors do not recommend performance of a varicocelectomy in conjunction with vasectomy reversal due to an increase risk of testicular atrophy or varicocele recurrence (3). They rec-

ommend an observation period of at least 6 months after vasectomy reversal in an attempt to improve collateral circulation across the anastomotic line. Others have performed varicocelectomy in conjunction with vasectomy reversal obtaining similar patency and pregnancy rates when compared with patients who underwent vasovasostomy alone (36). We do not recommend performance of simultaneous varicocelectomy and vasectomy reversal because the increased risk of testicular compromise and the unclear benefits of varicocelectomy on a previously fertile population.

FAILURE AND RE-INTERVENTION

Persistent infertility after vasectomy reversal can be classified as:

Immediate Technical Failure

Failure after initial reversal may be due to unrecognized epididymal obstruction at the time of vasectomy reversal (37).

Late Technical Failure

Is caused by compromise of the anastomosis and complete vasal re-obstruction. The incidence of late obstruction occurring within 14 months of the initial surgical reconstruction has been reported to be 12% percent after vasovasostomy and 25% after vasoepididymostomy (35).

Persistent Infertility

Persistent infertility after technically successful vasectomy reversal could be due to recurrent partial vasal obstruction, epididymal dysfunction, antisperm antibodies or a female factor.

With appropriate and careful counseling, these patients may benefit from a second attempt of vasal reconstruction.

Recently, other causes of persistent infertility after vasectomy reversal have been investigated. One area of current research is the effect of reactive oxygen species (ROS). Oxidative stress has been shown to produce sperm dysfunction (38,39). Shapiro et al. (40), demonstrated that seminal cells produced higher amounts of ROS in men after vasovasostomy than in fertile nonvasectomized controls. They also showed that after vasectomy reversal, men have significantly impaired sperm characteristics, especially motility, when compared with fertile controls, and conclude that the elevated level of ROS and their detrimental effect over sperm could be the cause of impaired fertility in these men. In another study, Kolettis et al. (41) also found a significant difference in seminal ROS levels between normal donors and vasectomy reversal patients, with higher levels on the latter group. But when fertile and infertile vasectomy reversal patients were compared, there was no significant difference between the ROS levels in these two groups, suggesting that there is a possible relationship between oxidative stress and vasectomy reversal, but not between oxidative stress and fertility in this population of men. The effect of ROS on the vasectomy reversal patient remains under investigation and at the present it has no proven role in the clinical management of these patients.

If repeat vasal reconstruction is planned, it is very important that the surgeon reviews the previous operative report in an attempt to determine the possible cause of failure. If the previous report describes the presence of sperm in the vasal fluid obtained from the testicular end at the time of vasovasostomy, obstruction most likely is the result of technical failure. If no sperm was seen at that time, then the reason for failure could be epididymal obstruction. If no information can be obtained from the previous operative result, one should assume that a vasoepididymostomy would be required. Vasoepididymostomy is almost three times more common after initial than late failure (37).

The Vasovasostomy Study Group (4) reported that repeat bilateral vasovasostomy resulted in patency and pregnancy rates of 84% and 53%, respectively. For those requiring vasoepididymostomy after failed vasovasostomy, those numbers were 43% and 15%, respectively. Similarly Matthew et al. (37) reported overall patency and pregnancy rates of 67% and 30%, respectively. This

numbers drop to 47% and 15%, respectively, for those undergoing vasoepididymostomy. Donovan et al. (42) reported patency and pregnancy rates after repeat vasectomy reversal of 78% and 44%, respectively, and they demonstrated that this approach was more cost-effective than ICSI/IVF for the treatment of infertility caused by vasal obstruction. The cost-per-delivery was 2.4 times higher for ICSI/IVF when compared to repeat vasectomy reversal (42) (See Table 1). More recently, Hernandez & Sabanegh (43) reported 79% patency and 31% pregnancy rates overall for patients who underwent repeat microsurgical reconstruction after failed vasectomy reversal. This group also determined that previous conception with the current partner was predictive of future conception with 80% of the former group initiating a pregnancy versus only 17% of remarried couples.

As with all reconstruction procedures, we recommend cryopreservation of sperm intraoperatively and postoperatively.

CONCLUSIONS

In the current era of IVF advancements and ICSI, microsurgical vasectomy reversal remains the standard of care for patients who want to re-establish fertility after vasectomy. These techniques when performed by experienced microsurgeons have proven to provide a cost-effective treatment option for patients with obstructive azoospermia after vasectomy. Patients should be followed for approximately one year after reconstruction before further treatment is performed. Newer techniques are currently under investigation in an attempt to decrease procedure time and lessen the technical demands of microsurgery. If they prove to be successful and reliable over time, they could further enhance the cost-effectiveness of reconstruction as compared to assisted reproductive technologies Proper counseling, including offering sperm cryopreservation for possible IVF in the future, should be offered to each patient. Finally, other factors, which may contribute to infertility, such as, the age of the partner, should not be overlooked when treating and counseling these patients and their couples.

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