

Report on varicocele and infertility: a committee opinion

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

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This document discusses the evaluation and management of varicoceles in the male partners of infertile couples, and presents the controversies and recommendations regarding this condition. This document replaces the ASRM Practice Committee document titled "Report on Varicocele and Infertility," last published in 2008, and was developed in conjunction with the Society for Male Reproduction and Urology (Fertil Steril 2008;90:S247–9). (Fertil Steril® 2014;102:1556–60. ©2014 by American Society for Reproductive Medicine.)

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Varicoceles, defined as abnormally dilated scrotal veins, are present in almost 15% of the normal male population and in approximately 40% of men presenting with infertility (1). Although the majority of men with varicoceles are fertile, varicocele remains the most common diagnosis seen in infertile men. The preponderance of experimental data from clinical and animal models demonstrates an adverse effect of varicoceles on spermatogenesis. Venous reflux and testicular temperature elevation appear to play important roles in varicocele-induced testicular dysfunction, although the exact pathophysiologic mechanisms involved are not yet completely understood. Despite the relationship between varicoceles and sperm production, irrefutable evidence for a clinical benefit of varicocele repair in improving fertility has been elusive. Therefore, the exact impact of varicoceles on male fertility is somewhat controversial.

DETECTION OF VARICOCELES

Evaluation of a male patient with infertility should include a careful medical and reproductive history, a physical examination, and at least two semen analyses. The physical examination should be performed with the patient in both the upright and recumbent positions. A palpable varicocele feels like a "bag of worms" and disappears or is very significantly reduced when the patient is recumbent. When a suspected varicocele is not clearly palpable, the scrotum should be examined while the patient performs a Valsalva maneuver in a standing position.

Only clinically palpable varicoceles have been clearly associated with infertility. Varicoceles are typically graded on a scale of 1 to 3, with grade 3 being present on visual inspection of the scrotum, grade 2 being easily palpable, and grade 1 only being palpable with Valsalva maneuver (2). These definitions are somewhat vague, as what may be easily palpable to one examiner

may not be for another. However, there is agreement that varicoceles palpable by most examiners are considered "clinically significant." Ancillary diagnostic measures, such as scrotal ultrasonography, thermography, Doppler examination, radionuclide scanning, and spermatic venography, should not be used for routine screening and detection of subclinical varicoceles in patients without a palpable abnormality. Scrotal ultrasonography is indicated for evaluation of an inconclusive physical examination of the scrotum. Although definitive evidence-based criteria are lacking, most investigators agree that multiple spermatic veins >2.5–3.0 mm in diameter (at rest and with Valsalva) tend to correlate with the presence of clinically significant varicoceles (3). Spermatic venography may be useful to demonstrate the anatomic position of refluxing spermatic veins that recur or persist after varicocele repair. Although early studies did not demonstrate a difference in outcome based on varicocele size, more recent data suggest that larger varicoceles may have a greater impact on semen parameters, and correction may result in greater improvement (4).

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INDICATIONS FOR TREATMENT OF A VARICOCELE

When the male partner of a couple attempting to conceive has a varicocele, treatment of the varicocele should be considered when most or all of the following conditions are met: [1] the varicocele is palpable on physical examination of the scrotum; [2] the couple has known infertility; [3] the female partner has normal fertility or a potentially treatable cause of infertility, and time to conception is not a concern; and [4] the male partner has abnormal semen parameters. Varicocele treatment is not indicated in patients with either normal semen quality, isolated teratozoospermia, or a subclinical varicocele (3).

An adult male who is not currently attempting to achieve conception but has a palpable varicocele, abnormal semen analyses and a desire for future fertility, and/or pain related to the varicocele is also a candidate for varicocele repair. Young adult males with clinical varicoceles who have normal semen parameters may be at risk for progressive testicular dysfunction and should be offered monitoring with semen analyses every 1 to 2 years to detect the earliest sign of reduced spermatogenesis. More recently, there is increased evidence that larger varicoceles may impact testosterone production, and some advocate repair in the setting of diminished testosterone levels (5).

Adolescent males who have unilateral or bilateral varicoceles and objective evidence of reduced testicular size ipsilateral to the varicocele may also be considered candidates for varicocele repair (6–9). If objective evidence of reduced testis size is not present, then adolescents with varicoceles should be followed with annual objective measurements of testis size and/or semen analyses to detect the earliest sign of varicocele-related testicular injury. Varicocele repair may be offered on detection of testicular or semen abnormalities, as catch-up growth has been demonstrated as well as reversal of semen abnormalities; however, data are lacking regarding the impact on future fertility.

MANAGEMENT CONSIDERATIONS

Varicocele repair, intrauterine insemination (IUI), and in vitro fertilization/intracytoplasmic sperm injection (IVF-ICSI) are options for the management of couples with male factor infertility associated with a varicocele. The decision to proceed with any of these management options is influenced by a number of factors. Varicocele repair has the potential to reverse a pathological condition, as opposed to IUI or IVF-ICSI, which are treatments that circumvent abnormal semen parameters and are required for each attempt at pregnancy. Other factors to be considered include associated symptoms attributed to the varicocele, age, fertility potential of the female partner, and time available for conception as improvement in semen parameters after varicocele repair may take 3 to 6 months. The potential cost-effectiveness of varicocele repair compared with IVF with or without ICSI is another aspect that may influence treatment (10). In addition, factors that may help to predict improvement including size of varicocele, follicle-stimulating hormone level, and preoperative total motile sperm count should be taken into consideration

(11). Finally, failure to treat a varicocele may result in a progressive decline in semen parameters, which may further compromise future fertility (12–14).

Varicocele repair is not usually indicated when IVF or IVF-ICSI is otherwise required for the treatment of a female factor infertility, although some studies have also suggested a benefit (15, 16). However, there are certain circumstances in which treatment of a varicocele should be considered before assisted reproductive technology (ART), even when a significant female factor is present. Specifically, men with nonobstructive azoospermia have been shown to respond to varicocele repair, albeit in fairly low-quality observational studies. Several studies have suggested restoration of low numbers of sperm to the ejaculate in approximately 10% to 50% of men with nonobstructive azoospermia due to either hypospermatogenesis or late maturation arrest based on previous testicular biopsy (17, 18). In such cases, varicocele repair is associated with return of sperm to the ejaculate, thus potentially making it possible to perform IVF-ICSI without testicular sperm aspiration or extraction. These studies have also shown that men with Sertoli-cell only or early maturation arrest histology did not have sperm return to the ejaculate. It is important to remember that men previously found to be azoospermic may also have sperm found in the ejaculate with no intervention (5, 19). Therefore, testicular biopsy/testicular sperm extraction or varicocele repair may be offered to such men, although the value of varicolectomy in all patients with nonobstructive azoospermia remains controversial (20).

TREATMENT OF VARICOCELES

There are two approaches to varicocele repair: surgery and percutaneous embolization. Surgical repair of a varicocele may be accomplished by various open surgical methods, including retroperitoneal, inguinal, and subinguinal approaches, or by laparoscopy. Percutaneous embolization treatment of a varicocele is accomplished by percutaneous embolization of the refluxing internal spermatic vein(s). None of these methods has been proven superior to the others in its ability to improve fertility, although there are differences in recurrence rates (21).

Surgical Repair

All surgical procedures entail ligation and division of the spermatic veins (pampiniform plexus) in the spermatic cord, thus leading to venous drainage of the testis via collaterals from the vasal veins. Most experts perform inguinal or subinguinal surgical repair employing loupes or an operating microscope for optical magnification. Some practitioners use a retroperitoneal (high ligation) approach, which consists of a small abdominal incision. Laparoscopy has been used for varicocele repair, but this approach is less commonly performed and may carry additional risks not associated with open surgical approaches. Techniques using optical magnification maximize preservation of arterial and lymphatic vessels while reducing the risk of persistence or recurrence of varicocele (21, 22). High ligation approaches (retroperitoneal, laparoscopic) have higher rates of

recurrence (up to 15%) compared with low inguinal/subinguinal techniques (1% to 2%) and thus are considered to be inferior to the lower approaches (21, 22).

Percutaneous Embolization Treatment

Percutaneous embolization of varicoceles uses either metal coils or sclerosants (e.g., as pure alcohol) to obstruct the dilated spermatic veins. These are accessed percutaneously under fluoroscopic guidance. Percutaneous embolization requires a physician with experience in interventional radiologic techniques. This technique may be associated with less pain than occurs after the standard inguinal surgical approach. Moreover, in some patients, interventional access to the internal spermatic veins cannot be achieved because of technical problems (up to 20%). Recurrence rates are higher than microscopic approaches and are similar to high ligation surgical approaches (15%). The results of percutaneous embolization are variable and depend on the experience and skill of the interventional radiologist performing the procedure.

Complications

The potential complications of surgical varicocele repair occur infrequently and are usually mild. Overall, complications may occur in 1% to 5%, based on the approach used (23). All approaches to varicocele surgery are associated with a small risk of wound infection, hydrocele, persistence or recurrence of varicocele, and, rarely, testicular atrophy. Potential additional complications from an inguinal incision for varicocele repair include scrotal numbness and prolonged pain, although these are somewhat rare.

RESULTS OF VARICOCELE TREATMENT

Surgical treatment successfully eliminates over 90% of varicoceles, with some series reporting over 99% success (20). Improvement in semen parameters after varicocele repair is somewhat difficult to measure, as there is no standard definition for what constitutes significant improvement. Furthermore, improvement needs to be interpreted in the context of the presurgical and postsurgical parameters. Most studies have reported that semen quality improves in a majority of patients after varicocele repair, as defined by a comparison of pretreatment and posttreatment semen parameters. In a meta-analysis of studies that examined infertile men who underwent varicocele repair, sperm concentration increased by a mean of 12 million sperm/mL with a mean 11% increase in motility and variable effects on sperm morphology (23). In addition to the improvement in semen parameters, varicocele repair may allow a couple with severely impaired semen parameters to have less invasive treatment. Men with severe oligospermia who would otherwise require IVF-ICSI to conceive may have adequate improvement in semen analysis to allow IUI instead of IVF-ICSI, and those with oligospermia may have sufficient improvement in semen parameters to allow natural conception in some cases (24). Time to improvement is typically 3 to 6 months, which corresponds to one to two spermatogenic cycles. This period of time may be a concern for the female partner with age-related infertility or decreased ovarian reserve.

There are several randomized, controlled published studies examining the impact of varicocele repair on pregnancy rates for men with palpable varicoceles, abnormal semen parameters, and normal female evaluation (25, 26) (Table 1). Two of the studies showed an improved pregnancy rate after varicocele repair compared with controls. The first study observed a statistically significant improvement in fertility following varicocele repair (25). This study, a randomized, controlled study of infertile men with varicoceles, observed a natural conception rate of 60% in treated patients compared with 10% in untreated patients. The untreated patients then underwent repair and had a natural conception rate of 66% (44% in the first year and 22% in the second year). Although the second study observed no greater likelihood of pregnancy after varicocele repair, it did demonstrate significant improvement in testis volume and semen parameters compared with those in untreated controls (27). The most recent study examined 145 couples who were randomized to varicocelectomy (study) versus observation (control). The control group had a natural conception rate of 13.9%, while the study group had a rate of 32.9% with an odds ratio (OR) 3.04 (95% confidence interval [CI], 1.33–6.95). The baseline characteristics of both groups were statistically similar. No crossover was done (27).

A number of meta-analyses have been performed to analyze the existing data on varicocele repair and pregnancy rates. One recent report included randomized, controlled trials and observational studies of infertile men with clinical varicoceles and abnormal semen analyses (28). The spontaneous pregnancy rate in the treated group (33%) was statistically significantly higher than in the untreated group (15.5%). The calculated OR of spontaneous pregnancy after varicocele repair was 2.87 (95% CI, 1.33–6.20; $P=.007$). The most recent Cochrane review, which included the two studies mentioned here, concluded that treatment of a varicocele in men from couples with otherwise unexplained subfertility may improve a couple's chance of pregnancy (29). This supersedes previous versions of Cochrane reviews which did not demonstrate this effect; however, it should be noted that even this most recent Cochrane review commented on the low quality of the studies reviewed.

Most trials have observed improved semen parameters and fertility after varicocele treatment, and only a few have concluded that varicocele treatment has little or no effect on fertility. However, most published studies regarding fertility outcomes after varicocele repair have had a low number of patients, were not randomized, and lacked consideration of female factors, and/or controls. In addition many studies have not limited their analysis to men with clinical varicoceles, abnormal semen parameters, and normal and age-restricted female partners. Despite these limitations, varicocele treatment should be considered an option for appropriately selected infertile couples.

FOLLOW-UP EVALUATION

Patients should be evaluated after varicocele treatment for persistence or recurrence of the varicocele. If the varicocele

TABLE 1

Summary of data from three randomized, controlled trials involving treatment of varicoceles in infertile men.

Study	Type of study	No. of total patients	Clinical grade of varicocele	Inclusion criteria of semen parameters (10 ⁹ /mL)	Semen parameter improvement with intervention	Pregnancy rate	Comments
Madgar et al., 1995 (25)	Randomized, crossover control trial	45 C: n = 20 T: n = 25	2, 3	>5–20	Yes	C: 2/20 (10%) T: 15/25 (60%)	Significant dropout and exclusion rate (>75%)
Nieschlag et al., 1998 (26)	Randomized, controlled trial	125 C: n = 63 T: n = 62	1–3	0–<20	Yes	C: 16/63 (25.4%) T: 18/62 (29%)	Significant dropout rate (38%) Treatment group included embolization and surgical ligation No significant difference in pregnancy rates between treatment and control Regardless of treatment modality, females who achieved pregnancy were younger (P<.05)
Abdel-Meguid et al., 2011 (27)	Randomized control trial	145 C: n = 72 T: n = 73	1–3	>8–<20	Yes	C: 10/72 (13.9%) T: 24/73 (32.9%)	Low dropout rate (1%) Treatment group underwent microsurgical subinguinal ligation Pregnancy rates higher in treatment arm

Note: C = control, T = treatment.

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persists or recurs, internal spermatic venography may be performed to identify the site of persistent venous reflux and be followed by either surgical ligation or percutaneous embolization of the refluxing veins. Semen analyses should be performed at approximately 3-month intervals during the first year after varicocele treatment or until pregnancy is achieved. Intrauterine insemination and ART should be considered for couples with persistent infertility despite an anatomically successful varicocele repair.

SUMMARY

- The diagnosis of varicoceles is based primarily on physical examination.
- Imaging studies are not indicated for the standard evaluation unless physical examination is inconclusive.
- Only clinically palpable varicoceles have been clearly associated with infertility.
- Adolescents and young men not actively trying to conceive who have a varicocele and objective evidence of reduced ipsilateral testicular size may be offered varicocele repair.
- Treatment options include surgical approaches or percutaneous embolization techniques.
- Low microsurgical approaches (inguinal/subinguinal) have been demonstrated to have lower recurrence and complication rates than high non-microsurgical approaches (retroperitoneal and laparoscopic).
- Varicocele repair is associated with a low risk of complications.
- Although data are limited and of lower quality, most studies show improvement in semen parameters and fertility after repair of varicocele.
- Time to improvement in semen parameters is approximately 3 to 6 months.

CONCLUSIONS

- Treatment of a clinically palpable varicocele may be offered to the male partner of an infertile couple when there is evidence of abnormal semen parameters and minimal/no identified female factor, including consideration of age and ovarian reserve.
- In vitro fertilization with or without ICSI may be considered the primary treatment option when such treatment is required to treat a female factor, regardless of the presence of varicocele and abnormal semen parameters.
- The treating physician's experience and expertise, including evaluation of both partners, together with the options available, should determine the approach to varicocele treatment.

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approved standard of practice or to dictate an exclusive course of treatment. Other plans of management may be appropriate, taking into account the needs of the individual patient, available resources, and institutional or clinical practice limitations. The Practice Committee and the Board of Directors of the American Society for Reproductive Medicine and the Board of the Society for Male Reproduction and Urology have approved this report.

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