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Review Article

Current Issues in Varicocele Management: a Review

Woo Suk Choi, Soo Woong Kim

Department of Urology, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Korea

The most common cause of male infertility is varicocele, and varicocele is the most common correctable cause of male factor infertility. In this article we reviewed the concept of varicocele in terms of its diagnosis, method of treatment, indications for treatment, treatment outcomes, and prognostic factors. Physical examination is an essential diagnostic tool in the evaluation of a patient with a varicocele. However, as it depends on subjective findings, standardization of the physical examination method is needed. Various methods for treatment of varicocele exist, including open surgical, laparoscopic, microscopic surgical, and radiologic treatment such as embolization. Among these treatment approaches, microscopic inguinal or subinguinal varicocelectomy has superior outcomes, with a low complication rate. The influence of the treatment of varicocele on fertility is still a controversial issue and a difficult question to address, because there are limitations to performing a randomized control study, and previous studies had a heterogeneity of subjects and high dropout rate. However, there is robust evidence that varicocelectomy improves semen parameters as a surrogate marker of the potential for fertility. To date, general indications for treatment of varicocele are limited in patients with proven infertility, clinical palpable varicocele, and abnormal semen characteristics. Recently, it was shown that some symptoms other than infertility could be an indication for varicocelectomy because these symptoms are frequently related to deterioration of semen parameters. Varicocele in the adolescent presents a more difficult decision regarding whether to treat. A testicular size discrepancy of more than 20% is helpful for treatment decisions. Various prognostic factors were noted in several studies without, however, a consistent consensus.

Key Words: Varicocele; Infertility, male; Varicocelectomy

INTRODUCTION

Varicocele is a collection of abnormally dilated, tortuous spermatic veins.[1] Most varicoceles are left-sided, and the left-sided predominance is explained by turbulent venous flow related to the right angle insertion of the left testicular vein into the left renal vein.[2] The prevalence of varicocele is reported as high as 10～15% in the general population, 30～35% in men with primary infertility, and 69～81% in men with secondary infertility.[2-4] The varicocele has clinical importance because it is the most common cause of male infertility and could be correctable.[5] However, the impact of varicocele on male fertility and the benefits of varicocele treatment are controversial. In this study, we reviewed the varicocele in terms of diagnosis, evaluation, treatment, influence of treatment on fer-

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Correspondence to: Soo Woong Kim
Department of Urology, Seoul National University Hospital, 101 Daehak-ro, Jongno-gu, Seoul 110-744, Korea.
Tel: +82-2-2072-2426, Fax: +82-2-762-4665, E-mail: swkim@snu.ac.kr

tility and semen parameters, and prognostic factors.

DIAGNOSIS AND EVALUATION

1. Physical examination and grading system

Physical examination is an essential diagnostic tool in evaluation of a patient with a varicocele.[6] Based on a physical examination, varicoceles are graded according to the system of Dubin and Amelar as follows: grade 3, visible and palpable at rest; grade 2, palpable at rest, but not visible; grade 1, palpable during Valsalva maneuver but not otherwise; and subclinical varicoceles, not palpable or visible at rest or during Valsalva maneuver but demonstrable by special tests not detectable on clinical examination (Doppler ultrasound studies).[7,8] However, the diagnosis and the grading of varicoceles by physical examination is limited by significant inter-observer and intra-observer discrepancies, even when the physical examination is performed by experienced andrologists.[9,10] To resolve this problem, Stahl and Schlegel[11] proposed standardization of varicocele evaluation. According to Stahl's suggestion, physical examination for varicocele should be performed after the scrotum has been warmed to achieve relaxation of the cremasteric and dartos muscles. Scrotal examination should be performed first with the patient in the supine position, and then the examination should be repeated with the patient in the standing position, both prior to and during the Valsalva maneuver.

2. Doppler ultrasound

Assessment of varicocele with Doppler ultrasound is more objective and reproducible, but it is not recommended as a routine practice[6] because of lack of consensus on how to assess varicoceles with Doppler ultrasound, despite its high sensitivity (97%) and specificity (94%).[12] Furthermore, subclinical varicocele that is commonly diagnosed by ultrasonography is still not robust evidence of the necessity for treatment. In fact, subclinical varicoceles are common lesions, occurring in 35～62% of healthy and fertile men.[13-15] Doppler ultrasound is useful and indicated only when physical examination is indeterminate, such as when the scrotum is small, the patient is obese, or the patient has a history of prior scrotal surgery.[6]

3. Hormonal assay and other laboratory tests

Endocrine evaluation, including measurement of serum testosterone (T) and follicle stimulating hormone (FSH) levels, should be performed in men with varicoceles when the semen analysis is abnormal or there are clinical signs or symptoms of endocrinopathy.[6] Some clinicians recommend routine measurement of serum T in all patients with palpable varicoceles on the premise that varicocele is associated with lower serum T levels in subfertile men and that microsurgical repair of varicoceles can significantly increase serum T.[16]

In addition, sperm DNA integrity testing is another diagnostic test that may be useful in selected patients with varicoceles. In a recent prospective study, varicocele was associated with sperm DNA damage, and microsurgical varicocelectomy improves sperm DNA integrity.[17]

TREATMENT OF VARICOCELE

1. Open scrotal varicocelectomy

The first open surgical approach to treat patients with varicocele was performed in the early 1900s. At that time, an open scrotal approach involving mass ligation and excision of the plexus of dilated veins was employed. However, surgery via a scrotal approach was not widespread due to the difficulty of preserving the arterial supply of the testis because the pampiniform plexus of veins encoils the testicular artery at the level of the scrotum. Therefore, scrotal operations are to be avoided because testicular atrophy and further impairment of spermatogenesis and fertility occurred infrequently.[18]

2. Open inguinal varicocelectomy

In 1949, retroperitoneal high ligation of the testicular artery and vein above the internal inguinal ring (the Palomo technique) was introduced.[19] The advantage of Palomo technique is that it is easy for the surgeon because ligation is performed at a high level where only 2～3 veins are usually found. However, at the high level, the surgeon cannot assess the collateral veins that branch out of the bundle inferior to the operating field. Therefore, this technique has a higher incidence of recurrence.[20] There are several modified techniques such as high ligation of the

veins while sparing the artery (Bernardi technique),[21] but these operations have also higher recurrence rates.

3. Microsurgical inguinal or subinguinal varicocelectomy

A macroscopic inguinal approach (Ivanissevich technique)[22] ligates the cremasteric and internal spermatic veins as they travel within the inguinal canal as structures of the spermatic cord. The inguinal approach has the benefit that the surgeon can ligate the collateral veins including the external spermatic veins. To spare the arteries and lymphatics, modifications of this technique (modified inguinal or modified Ivanissevich) have been developed that use injection of dye into the lymphatics.

An operating microscope may be used to assist in dissection. The inguinal and subinguinal microsurgical techniques are innovative techniques that allow the ligation of all of the veins except the vasal vein while sparing the testicular artery and lymphatics, resulting in the decrease of the recurrence rate and complications.[23,24] The recurrence rate of microsurgical varicocelectomy is reported to be as low as 1～2%, lower than that of the open approach.[24-26] It is noticeable that the scrotal hydrocele, the most common complication of varicocelectomy, ranging from 3% to 33%,[26] hardly occurs after the microsurgical operation because lymphatics can be observed and saved easily under a magnified visual field.[23-25] The subinguinal approach does not incise the external oblique aponeurosis, reducing pain for the patient, but at the expense of the increased number of veins that must be ligated.[27]

4. Laparoscopic varicocelectomy

Laparoscopy was also employed in the treatment of varicocele. Laparoscopic high ligation can achieve the preservation of the testicular artery and to some degree, the lymphatics.[28] However, it is not used frequently because of the need for general anesthesia, the need for an experienced laparoscopic surgeon, its invasiveness, and its higher complication rate.[28]

5. Embolization

As an alternative treatment modality, the embolization and sclerosing techniques of the radiological approach are also an option to consider. This approach is less invasive, and provides the opportunity to embolize the small collateral veins that may not be detected during surgery.[18] However, due to its high cost and high failure rate, this approach is recognized as an option for when the surgical approach has not been successful.[29,30]

THE INFLUENCE OF VARICOCELECTOMY ON MALE INFERTILITY

Whether correction of a varicocele in infertile men could improve fertility has been an ongoing matter of debate since varicocelectomy was introduced. With the principles of evidence-based medicine, several systematic analyses have aimed to prove the effectiveness of varicocele treatment in improving male fertility. However, these studies have not drawn a consistent conclusion due to the

Table 1. Results of studies evaluating the influence of varicocelectomy on the alleviation of male infertility

Study	Year	Type	Subjects	Results	Pregnancy rate	Statistics
Evers et al[31]	2001	Meta-analysis	5 RCT	No significant	66/314 (21.0%) (T) vs. 56/293 (19.1%) (C)	OR=1.15 (95%CI, 0.73～1.83)
Ficarra et al[32]	2006	Meta-analysis	3 RCT	Significant	39/107 (36.4%) (T) vs. 24/120 (20%) (C)	p=0.009
Marmar et al[33]	2007	Meta-analysis	5 studies (2 randomized, 3 observational)	Significant	132/396 (33.3%) (T) vs. 27/174 (15.5%) (C)	OR=2.87 (95%CI, 1.33～6.20)
Baazeem et al[1]	2011	Meta-analysis	4 RCT	Not significant	62/192 (32.3%) (T) vs. 34/188 (18.1%) (C) 954/2486 (38.37%) (T)	OR=2.23 (95%CI, 0.86～5.78)
Diegidio et al[20]	2011	Review, simple addition	33 studies	Cost-effective	No control	NA

RCT: randomized controlled trial, T: treatment group, C: control group, OR: odds ratio, CI: confidence interval, NA: not assessed.

heterogeneity of subjects, diversity of treatment methods, and high dropout rates (Table 1).

In 2001, a Cochrane review of the effect of varicocelectomy or embolization in subfertile men concluded that insufficient evidence exists that treatment of varicocele in men from couples with otherwise unexplained subfertility improves the couple's chance of achieving spontaneous pregnancy.[31] However, this analysis included many studies that reported the result of varicocelectomy in men with subclinical varicocele. To solve this problem, Ficarra et al[32] performed a meta-analysis again with studies included in the initial Cochrane review. In this meta-analysis, five randomized controlled studies that reported results in patients with normal semen analysis or subclinical varicocele were excluded. Three remaining studies revealed a significantly higher pregnancy rate in the treatment group than in the controls. However, the authors of the study noted that the pooling of only three studies cannot result in a good quality meta-analysis. Another meta-analysis that included five studies (two randomized, three observational) that reported the pregnancy rate after varicocelectomy among men with only palpable lesions and at least one abnormal semen parameter, concluded that varicocelectomy has beneficial effects on fertility status with an odds ratio (OR) of 2.87 (95% confidence interval [CI], 1.33～6.20).[33] Recently, Baazeem et al[1] reported a new meta-analysis. Included were 380 couples (192 randomized to treatment and 188 to observation) from four randomized controlled studies that reported pregnancy outcomes after repair of clinical varicocele in oligospermic men. The OR resulting from a fixed-effects model was in favor of therapy (OR=2.10, 95%CI=1.31～3.38; p=0.002). However, the OR using the random effects model indicated that the difference in the effect of varicocelectomy compared to observation was not statistically significant (OR=2.23, 95% CI=0.86～5.78, p=0.091).

Besides the meta-analysis, several well-designed studies reported positive effects of treatment in patients with varicocele on fertility. Diegidio et al[20] reviewed 33 studies and calculated the overall pregnancy rate to be 38.37% (954/2486) by using simple addition and division. In the review, they compared cost-effectiveness and concluded that varicocelectomy is a cost effective treatment modality for infertility. Subgroup analysis showed that pregnancy rates were highest with the microsurgical subinguinal technique. Recently one randomized controlled study with a nearly ideal study design provided level 1b evidence of the superiority of varicocelectomy over observation.[34] One hundred and fifty patients who experienced infertility for more than one year, had palpable varicoceles, and had at least one impaired semen parameter were randomized to a treatment group (n=75) or observation group (n=75) and were followed for spontaneous pregnancy. Only five patients dropped out during the 12 months after surgery. The result showed a significantly higher pregnancy rate in the treatment arm (32.9% in varicocelectomy vs. 13.9% in observation, OR=3.0.4; 95%CI=1.33～6.95).

In conclusion, recent analysis cannot provide a conclusive result on the issue because of the small number of studies and the heterogeneity of subjects. To clarify these controversial and inconsistent results, more randomized controlled studies are needed. However, several difficulties, such as ethical problems and high dropout rates, limit performing randomized controlled studies to evaluate the objective effect of varicocelectomy on the spontaneous pregnancy rate.

THE INFLUENCE OF VARICOCELECTOMY ON THE IMPROVEMENT OF SEMEN PARAMETERS

In contrast to the effect on the pregnancy rate, studies consistently show the influence of varicocelectomy on the improvement of semen parameters (Table 2). A meta-analysis including infertile men with palpable varicocele and abnormal semen who underwent surgical varicocelectomy (high ligation or inguinal microsurgery) was reported by Agarwal et al[35] They demonstrated that the sperm concentration increased by 9.71×10^6/ml (95%CI=7.34～12.08, $p<0.00001$), motility increased by 9.92% (95%CI=4.90～14.95, p=0.0001), and World Health Organization sperm morphology increased by 3.16% (95%CI=0.72～5.60, p=0.01) after microsurgical varicocelectomy. Similar improvement in semen parameters was observed after high ligation varicocelectomy. A study that evaluated the clinical outcomes of 118 infertile couples with isolated asthenospermia reported a significant in-

Table 2. Results of studies evaluating the influence of varicocelectomy on the improvement of semen parameters

Study	Year	Type	Subjects	Concentration	Sperm motility	Morphology
Agarwal et al[35]	2007	Meta-analysis	17 studies	Microsurgical D=+9.71×10^6/ml (95%CI, 7.34~12.08, p=0.00001) High ligation D=+12.03×10^6/ml (95% CI, 5.71~18.35, p=0.0002)	Microsurgical D=+9.92% (95%CI, 4.90~14.95, p=0.0001) High ligation D=+11.72% (95%CI, 4.33~19.12, p=0.002)	Microsurgical or high ligation D=+3.16% (95%CI, 0.72~5.60, p=0.01)
Baazeem et al[1]	2011	Meta-analysis	22 RCT (concentration) 17 RCT (motility)	D=+12.32×10^6/ml (95%CI=9.45~15.19, p<0.0001)	D=+9.69% (95%CI=4.86~14.52, p=0.003).	NA
Boman et al[36]	2008	Retrospective case control study	118 couples with isolated athenospermia	D=+9.4×10^6/ml p=0.027	D=+9.8% p=0.0002	D=+4.5% p>0.05
Choi et al[37]	2009	Retrospective study	133 patients who had impaired semen parameters	Normalization 27/64 (42.2%)	Normalization 31/105 (29.5%)	Normalization 39/68 (57.4%)
Abdel-Meguid et al[34]	2011	RCT	150 infertile men with impaired semen parameters	Varicocelectomy D=+14.1×10^6/ml, 95%CI, 12.9~15.4 Control D=−0.22×10^6/ml, 95%CI, −0.54~0.1 *p<0.0001	Varicocelectomy D=+15.75% 95%CI, 14.1~17.4 Control D=−0.25% 95%CI, −0.71~0.21 *p<0.0001	Varicocelectomy D=+7.89% 95%CI, 6.5~9.3 Control D=+0.21% 95%CI, 0.003~0.413 *p<0.0001

RCT: randomized controlled study, D: mean differences, CI: confidence interval.
*p value between treatment and control.

crease in sperm motility by 9.8% (p=0.0002).[36] In the study, the concentration of sperm that was not impaired preoperatively also increased further from 29.6×10^6/ml preoperatively to 39.0×10^6/ml. The most recent meta-analysis also demonstrated improvement of semen parameters after treatment of varicocele.[1] Using a random effects model on 22 studies, the calculated mean difference between preoperative and postoperative sperm concentration was +12.32×10^6/ml (95%CI=9.45~15.19, p<0.0001). Using the same method on 17 studies, the mean improvement in sperm motility was 9.69% (95%CI=4.86~14.52, p=0.003). In this meta-analysis, the improvement in sperm morphology was not compared. Our previous data on Korean patients also found improvement of semen parameters.[37] Included in the study were 133 varicocele patients who had at least one abnormal semen parameter preoperatively. Sperm concentration, motility, and morphology were normalized in 42.2%, 29.5%, and 57.4% of the patients, respectively.

Improvement of semen parameters was also observed in varicocele patients with causes other than infertility such as such as testicular pain, discomfort, or scrotal mass. Cho et al[38] reported that more than 60% of patients who underwent microsurgical subinguinal varicocelectomy for causes other than infertility had at least one abnormal semen parameter on preoperative semen analysis. In that study, 76.0% of patients showed improvement in at least one semen parameter after the surgery.

These objective improvements in semen parameters might support the idea that varicocelectomy could increase the spontaneous pregnancy rate. This is because semen parameters are surrogate markers of the chance for pregnancy. The recent data on the criteria for normal semen parameters suggested that there are no definite cutoff points for semen parameters to distinguish between fertile and infertile males, but fertility should be regarded as a

continuum because higher semen parameters reflect a higher chance of pregnancy.[39]

INDICATION FOR TREATMENT OF VARICOCELECTOMY

1. General indication for varicocelectomy

Generally accepted indications for varicocelectomy are as follows: 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; 4) the male partner has abnormal semen quality or abnormal results from sperm function tests.[6] Treatment of the varicocele should be considered when all of the above conditions are met.

2. Subclinical varicocele

Varicocele treatment for infertility is not indicated in patients with either normal semen quality or a subclinical varicocele.[6] To date, there is not enough evidence to justify treatment of subclinical varicocele. Cina et al[15] reported that they could not observe any significant associations between Doppler ultrasound parameters (venous diameter, retrograde flow) and semen analysis parameters among healthy men with normal semen analyses. Caşkurlu et al[40] examined 100 infertile patients without clinical varicocele, 100 infertile patients with clinical varicocele, and 50 fertile men without clinical varicocele, and concluded that venous diameters should not be used as diagnostic criteria for subclinical varicocele because the highest mean diameters of the veins did not differ significantly across the groups. Due to the lack of a well-controlled comparative analysis, the effect of subclinical varicocele on fertility and semen parameters cannot be conclusively stated at present.

3. Varicocelectomy for causes other than infertility

One other indication for treatment is a varicocele associated with testicular pain.[18] Varicocele-associated pain is typically thought to be a dull ache or 'scrotal heaviness'.[41] Some studies suggested that varicocelectomy could relieve this testicular pain.[42,43] However, almost all testicular pain is very subjective, often described as 'dull' or 'throbbing', such that the effect of varicocele on pain has rarely been assessed objectively. Therefore, nearly every study recommends conservative measures prior to consideration of varicocelectomy. However, we should remember that the majority of varicocele patients who complain of testicular pain have had abnormal semen parameters, and most semen parameters showed significant improvement after microsurgical varicocelectomy.[38]

4. Indication for treatment of adolescent varicocele

In pediatric urology, the indication for the treatment of adolescent varicocele remains highly controversial. The prevalence of adolescent varicocele is reported to be between 9% and 26%.[44] Varicoceles are rarely seen in boys under the age of 10 years (3% in the Children's Hospital Boston database) and begin to increase at age 12, resulting in a 15% prevalence at 19 years.[45]

Because 80% of adult males with varicocele will be fertile, a selective approach to surgical management of adolescent varicocele has been advocated. Although a high ligation or laparoscopic approach is more common in the treatment of adolescent varicoceles, microsurgical subinguinal varicocelectomy in children is also currently used and is not more difficult than in adults.[46] To decide whether to treat or not, the grade of varicocele and testicular disproportion has been the predominant indicator for surgical intervention for adolescent varicocele, historically. However, a high grade of varicocele alone is currently not an indication for surgical correction.[47] A recent study noted no difference in semen parameters between Grade II and Grade III varicocele.[45] On the other hand, the testicular volume discrepancy is still a useful criterion for selection of patients to treat. A recent study from the Children's Hospital Boston of Tanner stage V adolescents with varicocele reported that 59% of boys with greater than a 20% volume differential had an abnormal total motile sperm count, a significantly higher rate than boys with volume differentials of 10～20% (11%).[48] Following these results, Diamond et al[45] recommended correction of a varicocele in an adolescent patient if there is a persistent size discrepancy greater than 20%.

PROGNOSTIC FACTORS

Although somewhat controversial, several prognostic

factors that predict outcomes after treatment of varicocele and could help selection of patients for surgery have been reported. Kondo et al[49] evaluated the age, testicular volume, varicocele grade, serum FSH, luteinizing hormone, T, sperm concentration and motility of 97 oligospermic patients who underwent microsurgical inguinal varicocele repair. They reported that low serum FSH and high T were significant factors predicting the improvement of semen characteristics. Our previous study on 133 Korean patients with abnormal semen parameters who underwent microsurgical subinguinal varicocelectomy identified some prognostic factors that could predict normalization of semen parameters.[37] In the analysis, besides the operative semen parameters, absence of testicular size discrepancy was an independent prognostic factor for normalization of sperm concentration, and lower age and higher grade of varicocele was related to normalization of sperm motility. On the other hand, in a recent study, no predictive factor was noted in the seminal fluid in a retrospective study of 202 patients.[50]

CONCLUSIONS

Diagnosis and treatment of varicocele is meaningful for infertile males with impaired semen parameters. Varicocele should be diagnosed by standardized physical examination. For the treatment of varicocele, open surgical, laparoscopic, microscopic surgical, and radiologic treatment are all possible options. However, microscopic inguinal or subinguinal varicocelectomy showed the highest pregnancy rates and the lowest recurrence and complication rates. Therefore, microsurgical inguinal or subinguinal varicocelectomy is accepted as a standard treatment by experienced clinicians. The evidence for the influence of varicocelectomy on fertility is not robust due to the relatively small number of well-designed studies. On the other hand, consistent findings that varicocelectomy improves semen parameters suggest that varicocelectomy could increase the possibility for spontaneous pregnancy. Generally, treatment of varicocele is recommended for patients only with proven infertility, clinical palpable varicocele, and abnormal semen parameters. However, some symptoms other than infertility such as testicular pain or scrotal mass could be an indication for varicocelectomy because these symptoms are frequently related to deterioration of semen parameters. In adolescents, treatment should be performed in selected patients who have risk factors such as testicular volume discrepancy.

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