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Review Article

Effect of Varicocelectomy on Male Infertility

Kang Su Cho, Ju Tae Seo[1]

Department of Urology, Gangnam Severance Hospital, Urological Science Institute, Yonsei University College of Medicine, Seoul, [1]Department of Urology, Cheil General Hospital & Women's Healthcare Center, Catholic Kwandong University College of Medicine, Seoul, Korea

Varicocele is the most common cause of male infertility and is generally correctable or at least improvable by various surgical and radiologic techniques. Therefore, it seems simple and reasonable that varicocele should be treated in infertile men with varicocele. However, the role of varicocele repair for the treatment of subfertile men has been questioned during the past decades. Although varicocele repair can induce improvement of semen quality, the obvious benefit of spontaneous pregnancy has not been shown through several meta-analyses. Recently, a well-designed randomized clinical trial was introduced, and, subsequently, a novel meta-analysis was published. The results of these studies advocate that varicocele repair be regarded as a standard treatment modality in infertile men with clinical varicocele and abnormal semen parameters, which is also supported by current clinical guidelines. Microsurgical varicocelectomy has been regarded as the gold standard compared to other surgical techniques and radiological management in terms of the recurrence rate and the pregnancy rate. However, none of the methods has been proven through well-designed clinical trials to be superior to the others in the ability to improve fertility. Accordingly, high-quality data from well-designed studies are needed to resolve unanswered questions and update current knowledge. Upcoming trials should be designed to define the best technique and also to define how to select the best candidates who will benefit from varicocele repair.

Keywords: *Infertility; Pregnancy; Treatment outcome; Varicocele*

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Corresponding Author:
Ju Tae Seo
Department of Urology, Cheil General Hospital & Women's Healthcare Center, Catholic Kwandong University College of Medicine, 17 Seoae-ro 1-gil, Jung-gu, Seoul 100-380, Korea
TEL: +82-2-2000-7585
FAX: +82-2-2000-7787
E-mail: jtandro@cgh.co.kr

INTRODUCTION

Varicocele can be detected in at least 35% of infertile men and is generally correctable or at least improvable [1,2]. Subsequent pregnancy rates are estimated by pooled analysis to be 38.4% after varicocele repair [3]. Varicocele repair includes a variety of surgical options, including retroperitoneal, inguinal, subinguinal, and scrotal approaches, and percutaneous techniques such as embolization and sclerotherapy [4-6].

However, the role of varicocele repair for the treatment of subfertile men has been questioned during the past decades [7]. Although varicocele repair can induce improvement of semen quality, the obvious benefit of spontaneous pregnancy has not been shown through several meta-analyses. The Cochrane Collaboration conducted a meta-analysis of studies published since 2001 to assess the effects of varicocele repair on pregnancy [8]. They showed consistently that there is no beneficial effect of varicocele treatment on a couple's chance of conception [9-11]. Thereafter, the role of varicocele repair as a means of infertility treatment was at stake. Actually, the National Institute for Health and Clinical Excellence's clinical guideline on fertility declared in 2004 that varicocele repair should not be offered as a form of infertility treatment because it does not improve pregnancy rates.

Recently, a well-designed randomized clinical trial (RCT) was introduced in 2011 and, subsequently, a novel meta-analysis was provided in 2012 [12-14]. These studies could be important evidence that varicocele repair in men from couples with otherwise unexplained subfertility may improve pregnancy outcome [13]. At present, varicocele re-

pair is regarded in influential clinical guidelines as a standard treatment modality in infertile men with clinical varicocele and abnormal semen parameters. Herein, we review the current status of varicocelectomy and embolization, with a particular focus on their effect on male infertility.

INDICATIONS FOR VARICOCELE REPAIR

Not all varicocele is worthwhile to treat as we already know. Generally accepted indications for the treatment of varicocele are men with infertility and scrotal pain or discomfort [15]. Recently, some urologists have advocated varicocele repair for men with hypogonadism because of the progressive negative effect of varicocele on Leydig cell function. However, much controversy remains, and varicocele repair cannot be considered as a standard of care at this time [15,16].

Varicocele repair is not necessarily recommended for all infertile men with varicocele, and currently existing guidelines suggest some considerations for selecting candidates for surgical or radiological treatments. The Male Infertility Best Practice Policy Committee of the American Urological Association and the Practice Committee of the American Society for Reproductive Medicine described the indication for treatment of varicocele as follows [17]. When the male partner of a couple attempting to conceive has a varicocele, treatment of the varicocele should be considered when 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 (4) the male partner has abnormal semen parameters or abnormal results on sperm function tests. Varicocele treatment for infertility is not indicated in patients with either normal semen quality or a subclinical varicocele. European Urological Association guidelines released in 2012 and 2013 are similar to the aforementioned guidelines and make three representative recommendations [18]. First, varicocele treatment is recommended for adolescents with progressive failure of testicular development documented by serial clinical examination (recommendation grade B). Second, no evidence indicates benefit from varicocele treatment in infertile men who have normal semen analysis or in men with subclinical varicocele. In this situation, varicocele treatment cannot be recommended (recommendation grade A). Third, varicocele repair should be considered in case of a clinical varicocele, oligospermia, infertility duration of >2 years, and otherwise unexplained infertility in the couple (recommendation grade A).

TREATMENT OPTIONS FOR VARICOCELE

The basis of varicocele treatment is blockade of the internal spermatic venous drainage of the testicle while preserving the internal spermatic artery, the vasal and deferential vessels, and the spermatic cord lymphatics [15]. Various techniques have been introduced and practiced for varicocele repair. These techniques can largely be classified into two categories: surgical and radiological approaches. Each of these approaches can also be subdivided into a number of techniques, which generally aim for a higher success rate and lower complication rate. Surgical techniques can be classified variously on the basis of different criteria. There are conventional open, microsurgical, and laparoscopic methods applied by means of surgical instruments. Meanwhile, there are retroperitoneal, inguinal, subinguinal, and scrotal approaches according to the level of access. Radiological treatment has been used as an alternative for surgical repair with the merits of less invasiveness and better opportunity to control the small collaterals that may not be detected during surgery. The representative modalities of radiological intervention are retrograde embolization or sclerotherapy and antegrade sclerotherapy. The aforementioned modalities for varicocele repair are next reviewed in brief.

1. Open retroperitoneal, inguinal, or scrotal varicocelectomy

Palomo initially described the retroperitoneal approach with a title of "radical cure of varicocele," which aimed for ligation of the internal spermatic vein superior to the internal ring. The skin incision is made at the level of the internal ring medial of the anterior superior iliac spine, and dissection is carried out through the external and internal oblique fascia and muscles. The advantage of this technique is that it is easy because only two to three veins are usually encountered at that level before extensively branching; a significant disadvantage of this approach is that it is impossible to access the external spermatic veins, which are also known to be alternative routes of varicoceles [19]. The inguinal approach was initially described by Ivanissevich [20]. In this approach, exposure and incision of the external oblique aponeurosis is needed, and the approach also enables the control of internal spermatic veins and external cremasteric vessels. In conventional retroperineal and inguinal approaches, it is difficult to identify and preserve the spermatic artery and lymphatics, which is associated with a high incidence of postoperative hydrocele formation. In the past, the scrotal approach had been used, but it is no longer considered a viable option because of the higher risk of injury to the spermatic arteries and resultant testicular atrophy [21].

2. Microsurgical inguinal or subinguinal varicocelectomy

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 a decrease in the rate of recurrence and complications [4]. During microsurgical varicocelectomy, delivery of the testicle provides direct visual access to all avenues of testicular venous drainage, and this reportedly results in a significantly decreased varicocele recurrence rate [22].

3. Laparoscopic varicocelectomy

As many urologists become familiar with laparoscopic procedures, laparoscopic varicocelectomy has become another treatment option [23]. Outcome studies have shown that there is less postoperative pain and faster return to normal activities following laparoscopic surgery and that it is safe and efficacious when performed by experienced surgeons. However, the laparoscopic approach is almost the same as the retroperitoneal approach, so there is the inevitable demerit that external spermatic vessels cannot be controlled. Accordingly, patients may be at higher risk of varicocele persistence or recurrence [24].

4. Retrograde embolization or sclerotherapy

Radiological occlusion of varicocele is an alternative treatment option. The major benefit of this technique is the lesser invasiveness and the ability to control the small collateral veins which may not be detected during the operation. However, the high cost and high failure rate are known to be disadvantages [3]. There are various techniques for radiological occlusion of varicocele, largely either sclerotherapy or an embolization technique that can be applied after retrograde venography is taken. It is still uncertain which is better. Some radiologists advocate sclerotherapy as a standard technique, but others prefer the embolization technique [25].

5. Antegrade sclerotherapy

Antegrade sclerotherapy is an alternative option of the radiological modalities. Tauber and Johnson [26] first reported antegrade sclerotherapy via the scrotal approach. Later, groin or subinguinal access was introduced for a better success rate [25].

SUCCESS RATE OF VARICOCELE REPAIR ACCORDING TO VARIOUS TECHNIQUES

Various surgical and radiological techniques and their modifications have been introduced. Quite a number of studies have been reported, and they revealed somewhat conflicting outcomes, such as for success rates and complication rates. Therefore, in this situation, an individual study cannot suggest representative treatment outcomes and conclude which treatment option is the best way to manage men with varicocele. Pooled data analysis and meta-analysis can provide better guidance to physicians and patients when selecting a treatment method. Diegidio et al. [3] reported such a pooled data analysis. The recurrence rate is the lowest for the microsurgical subinguinal technique (2.07%; range, 1.4%–14.8%); other techniques seem to have higher recurrence rates than the microsurgical subinguinal technique. The recurrence rate was 9.47% (range, 0.7%–15.2%) for the microsurgical inguinal technique, 12.5% (range, 7.3%–15.5%) for the Palomo technique, 4.29% (range, 1.9%–9.3%) for radiological embolization, 15.65% (range, 3.57%–17.5%) for the conventional inguinal technique, and 11.11% (range, 4.0%–26.5%) for the laparoscopic operation. Ding et al. [24] performed a meta-analysis to compare various techniques of open nonmicrosurgical, laparoscopic, and microsurgical varicocelectomy procedures to describe the best method for treating varicocele in infertile men. They summarized that the incidences of recurrent varicocele were significantly lower after microsurgery than after open (odds ratio [OR], 0.13; 95% confidence interval [CI], 0.07–0.25; $p < 0.001$) or laparoscopic (OR, 0.12; 95% CI, 0.06–0.32; $p < 0.001$) varicocelectomy. Meanwhile, there remain critical concerns that recurrence rates after radiological embolization might be much higher than the reported data, likely as the result of recanalization through the coils [27].

IMPACT OF VARICOCELE REPAIR ON SEMEN QUALITY

Although there have been controversies concerning whether varicocele repair can improve the pregnancy rate, most studies consistently revealed that varicocele repair had a positive influence on semen parameters.

Agarwal et al. [28] performed a meta-analysis to determine the efficacy of surgical varicocelectomy (high ligation or inguinal microsurgery) in improving semen parameters from 17 studies including both RCTs and observational studies. The study population was infertile men with clinically palpable unilateral or bilateral varicocele and at least one abnormal semen parameter. The results showed that the sperm concentration increased by 9.71×10^6/mL (95% CI, 7.34–12.08, $p < 0.00001$) and motility increased by 9.92% (95% CI, 4.90–14.95, $p < 0.0001$) after microsurgical varicocelectomy. Similarly, the sperm concentration increased by 12.03×10^6/mL (95% CI, 5.71–18.35; p=0.0002) and motility increased by 11.72% (95% CI, 4.33–19.12; p=0.002) after high ligation varicocelectomy. The improvement in World Health Organization sperm morphology was 3.16% (95% CI, 0.72 to 5.60; $p < 0.01$) after both microsurgery and high ligation varicocelectomy.

Baazeem et al. [14] reported a similar meta-analysis that consisted of only RCTs, but they included several studies for radiological embolization as well as surgical varicocele repair. Sperm concentration (22 studies), total motility (17 studies), and progressive motility (5 studies) before and after repair of clinical varicocele were analyzed. The random-effects model combined improvement in sperm concentration was 12.32×10^6/mL (95% CI, 9.45–15.19; $p < 0.0001$). The random-effects model combined improvements in sperm total and progressive motility were 10.86% (95% CI, 7.07–14.65; $p < 0.0001$) and 9.69% (95% CI, 4.86–14.52; p=0.003), respectively. These results indicate that varicocelectomy is associated with a significant increase in sperm concentration as well as total and progressive motility. Another meta-analysis by Schauer et al. [29] investigated the impact of three surgical techniques (high ligation, inguinal varicocelectomy, and the subinguinal approach) for varicocelectomy on sperm parameters (count and motility) and suggested that varicocelectomy leads to

significant improvements in sperm count and motility regardless of surgical technique. In addition, varicocele is associated with sperm DNA damage, and this sperm pathology may be secondary to varicocele-mediated oxidative stress. Several studies showed that varicocelectomy can reverse this sperm DNA damage [30]. Meanwhile, meta-analysis of the effect of radiological intervention on semen quality has not yet been reported.

IMPACT OF VARICOCELE REPAIR ON THE SPONTANEOUS PREGNANCY RATE

In 2009, Cayan et al. [31] analyzed the pregnancy rate after varicocele repair to define the best technique based on outcomes from 36 studies. They concluded that the microsurgical varicocelectomy technique has higher spontaneous pregnancy rates and lower postoperative recurrence than conventional varicocelectomy techniques and radiologic embolization in infertile men. Similarly, Diegidio et al. [3] reviewed over 5,000 patient-pooled data from 33 studies in 2011. The overall pregnancy rate was shown to be 38.37% (954/2,486) by use of simple addition and division. The pregnancy rate was highest for the microsurgical subinguinal technique (44.75%) and the microsurgical inguinal technique (41.78%). Other techniques seem to have a lower pregnancy rate compared with the microsurgical technique. For example, the pregnancy rate with the Palomo technique was 34.21%, 31.93% for radiological embolization, 30.06% for the conventional inguinal technique, and 27.53% for the laparoscopic technique.

The Cochrane Collaboration has performed meta-analyses to evaluate the effects of varicocele repair on pregnancy since 2001 [8]. They showed consistently that there is no beneficial effect of varicocele treatment on a couple's chance of conception [9-11]. Earlier meta-analyses by the Cochrane collaboration simply concluded that there is no evidence that treatment of varicocele in men from couples with otherwise unexplained subfertility improves the couple's chance of conception [9]. However, this finding has been criticized by several investigators, because some RCTs included men with subclinical varicoceles or normal semen analyses, and others had significant dropout rates after randomization [32,33]. Baazeem et al. [14] reported a new meta-analysis in which 380 couples (192 randomized to treatment and 188 randomized to observation) were included from four RCTs 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 Q-statistic p-value was 0.024, indicating the heterogeneity of their studies (chi-square=14.60 with 3 degrees of freedom). Therefore, they performed a random-effects model due to severe heterogeneity, and the OR using this model indicated that the differences in the effects of varicocelectomy compared to observation were not statistically significant (OR, 2.23; 95% CI, 0.86–5.78; p=0.091). Notably, the latest meta-analysis conducted by the Cochrane collaboration suggested that treatment of varicocele in men from couples with otherwise unexplained subfertility may improve a couple's chance of pregnancy, but the authors maintained that the findings were inconclusive, because the quality of the available evidence is very low [13].

The aforementioned meta-analyses have included data from surgical repair and percutaneous embolization. Although these procedures have been performed to prevent venous reflux into the scrotum, a fundamental difference exists in that the veins are neither ligated nor divided during percutaneous embolization, which is unlikely with a surgical repair [27]. There remain critical concerns that recurrence rates after percutaneous embolization might be much higher than the reported data, likely due to recannulization through the coils. In 2007, Marmar et al. [32] reported the first meta-analysis for evaluating the value of surgical varicocelectomy as a treatment for male subfertility, at least partly in response to the Cochrane review, and they performed another meta-analysis that included five studies (two randomized, three observational) reporting pregnancy rates after varicocelectomy among men with only palpable lesions and at least one abnormal semen parameter. They concluded that varicocelectomy has beneficial effects on fertility status with an OR of 2.87 [32]. However, they included three observational studies as well as two RCTs, which could be an inherent weakness of their analysis. Recently, Kim et al. [34] also performed a meta-analysis with only three RCTs for surgical varicocele repair, which included patients with clinical varicocele and abnormal semen parameters. In that meta-analysis, the fixed-effects pooled OR was significant (OR, 4.15; 95% CI, 2.31–7.45), favoring varicocelectomy. Some researchers investigated the treatment effect of surgical varicocele repair versus percutaneous embolization through prospective RCTs, and their results demonstrated that both treatment modalities seemed to be equivalent in terms of pregnancy rate [35,36]. Nevertheless, there is an important drawback of percutaneous embolization in the management of subfertile patients with varicocele in the era of evidence-based medicine. Unfortunately, no available meta-analysis has yet investigated the effect of radiological intervention on the pregnancy rate. Previously published meta-analyses regarding the effect of varicocelectomy on the pregnancy rate are summarized in Table 1.

IMPACT ON ASSISTED REPRODUCTIVE TECHNIQUE

In general, varicocele repair should not be considered as the primary treatment for couples when *in vitro* fertilization (IVF) is needed for treatment of a female factor [17]. However, varicocele repair can be considered before IVF/intracytoplasmic sperm injection (ICSI) even when there is a female factor present. Varicocele repair can provide a chance to obtain viable sperm in the ejaculate in some men with nonobstructive azoospermia due to either hypospermatogenesis or late maturation arrest, although the

Table 1. Summary of published meta-analyses regarding the effect of varicocelectomy on the pregnancy rate

Source	Year	Studies included	Treatments	Pregnancy rate (Treat vs. control)	Statistical results, OR (95% CI, p-value)	Comment
Evers et al. [8]	2001	5 RCTs	Surgical or radiological	58/226 vs. 47/204	1.15 (0.73–1.83)	Patients with subclinical varicocele or normal SA were also included
Evers et al. [9-11]	2004, 2008, 2009	8 RCTs	Surgical or radiological	66/314 vs. 56/293	1.10 (0.73–1.68, p=0.06)	Patients with subclinical varicocele or normal SA were also included
		3 RCTs	Surgical or radiological	38/120 vs. 24/117	1.75 (0.97–3.14, p=0.06)	Only patients with clinical varicocele and abnormal SA were included
Ficarra et al. [33]	2006	3 RCTs	Surgical or radiological	39/107 vs. 24/120	36.4% vs. 20% (p=0.009)	Only patients with clinical varicocele and abnormal SA were included
Marmar et al. [32]	2007	2 RCTs and 3 observational studies	Surgical	131/396 vs. 27/174	2.87 (1.33–6.20, p=0.007)	Only patients with clinical varicocele and abnormal SA were included
Baazeem et al. [14]	2011	4 RCTs	Surgical or radiological	62/192 vs. 34/188	2.23 (0.86–5.78, p=0.091)	Only patients with clinical varicocele and abnormal SA were included
Kroese et al. [13]	2012	5 RCTs	Surgical or radiological	81/255 vs. 40/250	2.39 (1.56–3.66, p=0.00006)	Only patients with clinical varicocele and abnormal SA were included
Kim et al. [34]	2013	3 RCTs	Surgical	58/160 vs. 18/152	4.15 (2.31–7.45, p < 0.001)	Only patients with clinical varicocele and abnormal SA were included

RCT, randomized clinical trial; OR, odds ratio; CI, confidence interval; SA, semen analysis.

number of sperm in ejaculate is low [37-39]. In this situation, varicocele repair can allow IVF/ICSI without testicular sperm aspiration or extraction, and this suggests that varicocele repair provides meaningful improvement not only to obviate the need for assisted reproductive technique (ART), but also to down-stage or shift the level of ART against male factor infertility [40].

Meanwhile, varicocele repair seems not to have any benefit in terms of pregnancy rate in couples who undergo ICSI. Pasqualotto et al. [41] retrospectively analyzed 248 patients who had varicocele or underwent a previous varicocelectomy and were treated with ICSI. The fertilization rate was higher in men who underwent varicocelectomy than in men not treated (73.2% vs. 64.9%, p=0.0377), but there were no significant differences between the two groups in terms of the pregnancy rates (31.1% vs. 30.9%, p=0.9806), implantation rates (22.1% vs. 17.3%, p=0.5882), or miscarriage rates (21.7% vs. 23.9%, p=0.8401) between groups 1 and 2. Although a varicocelectomy should always be performed before ART is pursued, this surgery does not increase pregnancy rates or decrease miscarriage rates following ICSI. Recently, Mansour Ghanaie et al. [42] reported a recent RCT comparing couples in which male partners underwent varicocele repair versus couples who underwent expectant therapy. They showed that varicocelectomy increases the pregnancy rate by 44.1% vs. 19.1% (p=0.003) and decreases the spontaneous first trimester miscarriage rate significantly (12.3% vs. 69.2%, p=0.001).

COST-EFFECTIVENESS OF VARIOCELE REPAIR VERSUS ART

Cost-effectiveness is also a very important factor for selecting a treatment method, especially when there are multiple modalities with comparable efficacy and safety for a certain disease. In 1997, Schlegel reported cost estimates per delivery to evaluate the cost-effectiveness of ART by use of IVF with ICSI as a primary treatment for varicocele-associated infertility [43]. The cost per delivery with ICSI was found to be 89,091 United States dollars (USD) (95% CI, 78,720–99,462), whereas the cost per delivery after varicocelectomy was only 26,268 USD (95% CI, 19,138–44,656). This suggests that specific treatment of varicocele-associated male factor infertility with surgical varicocelectomy is more cost-effective than primary treatment with ART. Meng et al. [44] also compared the cost-effectiveness of varicocelectomy versus ART. In men with total motile sperm counts less than 10 million, surgical repair was more efficacious than ART when a surgeon could achieve a pregnancy rate of greater than 14%. In patients with total motile sperm counts greater than 10 million, however, an individual center should be able to ensure at least a 45% pregnancy rate to be more cost-effective than ART. This information may not be directly applicable to all situations, because there are inevitably considerable differences in various health care systems according to each country. In Korea, Kim [45] suggested that the cost per delivery with

ICSI was approximately 16,382,448 Korea won (KRW) (14,893 USD), and the cost per delivery after varicocelectomy was 11,587,675 KRW (10,534 USD). However, under the National Health Insurance System, the patient's copayment after varicocelectomy was 5,258,106 KRW (4,780 USD), but that with ICSI was 14,977,969 KRW (13,616 USD). Therefore, he also advocated varicocelectomy as an infertility treatment compared to ART in terms of cost-effectiveness.

CONCLUSIONS

There has been significant controversy over the role of varicocele repair in relation to male infertility during the past two decades. At present, pooled data analysis from several clinical trials and meta-analysis using these data suggest that varicocele repair should be regarded as the first-line therapeutic option in men with clinical varicocele and abnormal semen parameters from couples with otherwise unexplained subfertility. Although meta-analysis of RCTs is recognized as a high level of evidence, lessons from current meta-analysis have some limitations; the numbers of RCTs and the patients enrolled in each RCT were relatively small. In addition, different techniques were applied in each RCT, so there were inevitable limitations due to their methodological heterogeneity. Microsurgical varicocelectomy has been regarded as the gold standard compared to other surgical techniques and radiological management in terms of the recurrence rate and pregnancy rate. However, none of the methods has been proven to be superior to the others in the ability to improve fertility in well-designed head-to-head clinical trials. Accordingly, high-quality data from large, well-designed RCTs are needed to resolve these unanswered questions and update our current knowledge. Upcoming RCTs should be designed to define the best technique and should also aim for how to select the best candidates who will certainly benefit from varicocele repair.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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