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REVIEW ARTICLE

Role of varicocele repair for male infertility in the era of assisted reproductive technologies

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Abstract Varicocele is an abnormal condition characterized by dilatation of the pampiniform plexus veins draining the testis and is present in 15 % of men. Varicoceles have an adverse effect on spermatogenesis and are the most common cause of male infertility. Approximately 35 % of infertile men and more than 70 % of men with secondary infertility were reported to have varicoceles. Although data on methods of varicocele repair are accumulating, there remains controversy regarding the indications and techniques for varicocele repair. In addition, the role of varicocele repair in this era of assisted reproductive technologies continues to be debated. In this study, we performed a comprehensive PubMed search in order to review the current status of varicocele repair for male infertility. We reviewed English-language studies published from 1992 through 2013. After reviewing the articles, we identified a recent meta-analysis of four randomized controlled trials, which found that varicocele repair for oligozoospermic men was associated with better pregnancy rates as compared with observation. Our review of prospective studies showed that all semen parameters, including sperm concentration, motility, and progressive motility, were significantly improved after varicocele repair. We also summarize the findings of recent studies reporting beneficial effects of varicocele repair, i.e., decreased oxidative stress and sperm DNA fragmentation after varicocele repair and superior cost effectiveness versus in vitro fertilization/intracytoplasmic sperm injection alone, which may be important in the era of assisted reproductive technologies. Varicocele repair is a widespread, well-established procedure that can improve semen parameters in men with infertility. The effect of such treatment on the pregnancy rate is unclear because evidence is limited due to difficulties in recruiting patients for studies. Among the repair techniques, microsurgical repair using a subinguinal approach is potentially the best practice, although this procedure requires training in microsurgery. All these topics require further research in studies with sufficient patient enrollment and follow-up.

Keywords Cost-effectiveness · Male infertility · Oxidative stress · Sperm · Varicocele

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Introduction

A number of assisted reproductive technologies (ART) are now widely available, and male-factor infertility in couples has become more treatable due to the use of in vitro fertilization/intracytoplasmic sperm injection (IVF/ICSI). In this context, although infertile couples may include men with a varicocele, IVF/ICSI as primary treatment for male-factor infertility has greatly increased and can potentially decrease direct medical intervention for infertile men when they seek treatment from a urologist specializing in male infertility. Such series of treatment strategy might increase the risk of unnecessary interventions for the female partner, which could lead to potentially serious complications of ART, such as multiple pregnancies and ovarian hyperstimulation syndrome. In addition, repeat IVF/ICSI can be a considerable economic burden for infertile couples. However, using the internet, patients now have greater access to information on feasible treatment options for male infertility. This knowledge might motivate infertile couples to visit a male infertility clinic. In such cases, physicians and patients must choose the most appropriate treatment from the variety of treatments available for male-factor infertility.

Unfortunately, there is no consensus as to whether varicocele repair improves pregnancy rate. Additionally, there remains controversy regarding the procedures that are most appropriate for treating varicoceles in male infertility patients. In this review, we conducted a Medline/PubMed search to investigate the current status of varicocele repair. This comprehensive search comprised English-language articles published from 1992 through 2013 and utilized the keywords "varicocele", "varicocele repair", "infertility", "male infertility", "pregnancy rate", "semen parameter", and "sperm". We also include the findings of a recent meta-analysis of studies on varicocele repair. In this review, we discuss the current status of varicocele repair for infertile men and focus on surgical methods and the effects on pregnancy rate and semen parameters. Moreover, we assess the findings of recent studies that report several new aspects of varicocele repair in the ART era (namely, varicocele repair for nonobstructive azoospermia, improved outcomes of IVF/ICSI). Lastly, we analyzed the cost-effectiveness of varicocele repair during infertility treatment in this era of ART. Although the government provides some subsidies for female infertility, the costs of ARTs are a burden for patients, especially young couples.

Pathophysiology of varicoceles

Varicocele is the most common detectable cause of male infertility and results in progressive deterioration of testicular function. A World Health Organization (WHO) observational study of 9,034 men found that 25.6 % of men with abnormal results on semen analysis had varicoceles and that, in these men, ipsilateral testicle volume was significantly lower than contralateral testicle volume. This differential in testicular volume is not present in men with infertility who do not have varicoceles [1]. Varicoceles often develop on the left side, as the left testicular vein is longer than the right testicular vein and enters the left renal vein at a right angle. Additionally, the so-called "nutcracker phenomenon" has been observed in cases of compression of the left renal vein between the descending aorta and the superior mesenteric artery. This leads to increased pressure on the renal vein followed by increased pressure on the left testicular vein.

Several clinical and animal studies have examined varicocele pathophysiology and the adverse effects of varicoceles on testicular function [2–4]. Although there have been numerous studies, the pathophysiological effects of varicoceles on human spermatogenesis and male fertility remain unclear. As previously described, an important adverse effect of varicoceles on testicular function is testicular hyperthermia, which is caused by reflux of warm abdominal blood flow down the internal spermatic veins and cremasteric veins through the incompetent valves [5, 6]. This effect is bilateral, even if the varicocele is present only on the left side. Using sensitive needle thermistors to measure intratesticular and bilateral scrotal surface temperatures directly and simultaneously, Goldstein and Eld [7] found bilateral elevation of scrotal surface temperature, even in men with unilateral varicoceles.

Increased oxidative stress was reported to be an important cause of testicular dysfunction in men with varicoceles [8–13]. Reactive oxygen species (ROS), such as hydrogen peroxide and unstable free radicals with an unpaired electron in their outer orbits, are essential for normal fertilization, capitation, hyperactivation, motility, and acrosome reaction [14, 15]. Oxidative stress results from an imbalance between ROS generation and cellular antioxidant defenses. A number of studies reported that overproduction of ROS or decreased antioxidant production leads to excessive oxidative stress in seminal plasma, which can hamper spermatogenesis [13, 16]. Antioxidant protection is crucial for spermatozoa, since these cells are relatively deficient in ROS-scavenging enzymes, due to limited volume and restricted distribution of cytosolic space [16]. Several studies and reviews highlighted the potential of varicocelectomy to reduce seminal oxidative stress and sperm DNA damage [17–19]. Chen et al. [18] reported that the incidence of a 4,977-bp deletion in mitochondrial DNA in sperm and 8-OHdG level in sperm DNA decreased, and that seminal plasma protein thiols and ascorbic acid significantly increased, in all 30 patients who had undergone varicocele repair, which suggests that surgery is an effective treatment for subfertile men.

In contrast, in a study of ROS levels in fertile men with and without clinical varicoceles, Cocuzza et al. [20] found no difference in ROS levels between these groups, and ROS levels were not correlated with varicocele grade or testis volume. Their study population was limited to fertile men, and the authors explained that such a population may have more efficient defense mechanisms to protect themselves against varicocele. Future studies should evaluate both the role of oxidative stress in infertile men with varicoceles and the difference in ROS scavenging between fertile and infertile men with varicoceles.

As described above, oxidative stress ultimately affects genomic and mitochondrial DNA in spermatozoa, causing fragmentation and base degradation, which alter the molecular and genetic mechanisms responsible for spermatogenesis [21–23]. Zini et al. [24] observed improvement in sperm DNA integrity after varicocele repair, which suggests that varicocelectomy improves spermatogenesis and sperm function and provides another mechanism for the reported improvement in pregnancy rates after treatment. Bertolla et al. [25] studied DNA integrity in adolescents with and without varicoceles. They found that although the results of semen analysis did not differ between the groups, adolescents with varicoceles had more nuclear DNA fragmentation in sperm, indicating that evaluation of DNA fragmentation could be important in selecting treatment options for adolescents. Smit et al. [23] reported that DNA fragmentation was significantly decreased after varicocele repair and that a low value on an index of DNA fragmentation was associated with higher rates of spontaneous pregnancy and pregnancy after ART.

Hormonal imbalance is another causative factor in the deterioration of spermatogenesis in varicocele patients. Patients with varicoceles have a higher prevalence of venous reflux, which increases reflux of metabolic products such as catecholamines from the kidney and adrenal gland. It has been suggested that reflux of adrenal steroids is related to decreased spermatogenesis in men with varicoceles, via chronic testicular vasoconstriction, and is eventually toxic to testicular function. However, this hypothesis was not confirmed in an animal model [26, 27]. Therefore, further investigation is required.

Treatment indications and varicocele management

Clinical varicoceles are classified into three grades: grade 1, palpable only during the Valsalva maneuver; grade 2, palpable distension while the patient is standing; and grade 3, visible distension. In 2008, the Practice Committee of the American Society for Reproductive Medicine recommended that varicocele repair 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 proven infertility, (3) the female partner has normal fertility or a potentially treatable cause of infertility, and (4) the male partner has abnormal semen characteristics or abnormal results on sperm function tests. Similarly, the 2013 European Association of Urology (EAU) guideline, as well as the 2012 EAU guideline [28], recommends that varicocele repair should be considered in cases of clinical varicocele, oligospermia, duration of infertility >2 years, and otherwise unexplained infertility in a couple, which is classified as evidence level A. There is no evidence of benefit from varicocele treatment in infertile men with normal results on semen analysis or in men with subclinical varicoceles. These findings do not conform to evidence level A, and varicocele treatment, thus, cannot be recommended for such men. In summary, on the basis of EAU recommendations, physical examination of varicoceles is strongly recommended when an infertile male with abnormal semen characteristics visits an infertility clinic. When examination of varicoceles is not possible, early consultation with a urologist specializing in male infertility should be considered best practice.

Despite the existence of guidelines, diagnosis and surgical treatment of varicoceles are not straightforward [29]. A subclinical varicocele is defined as a "varicocele from the pampiniform plexus which cannot be diagnosed solely by physical examination but can be shown on adjunctive diagnostic methods such as color Doppler ultrasound" [30]. However, diagnosis of clinical varicoceles, which are detected by visual inspection or palpation, is not straightforward because ascertainment is subjective and the findings can be equivocal. The WHO reported that physical examination had a sensitivity of only about 50 % in detecting varicoceles [1]. In addition, the lower sensitivity and lower specificity of physical examination than other modalities such as thermography and color Doppler ultrasound was reported [31–33]. Jarow et al. [34] used ultrasound to examine vein diameters. Men who had spermatic veins with a diameter >3.0 mm had significantly better semen characteristics after varicocele repair than did men with veins <3.0 mm in diameter. Some studies suggested that a cut off value of 1 mm for maximum dilated vein diameter was predictive of improvement in semen characteristics after varicocele repair; other studies suggested a cut off of 5 mm. The most widely accepted criterion is presence of multiple veins with a diameter >3.0–3.5 mm in conjunction with reversal of flow on color Doppler ultrasound [35]. In a recent study, Pilatz et al. [36] found that clinical varicoceles can be predicted with high accuracy (sensitivity >80 %, specificity >80 %) based only on the diameter of testicular veins, using cut off values of 2.45 mm (at rest) and 2.95 mm (during the Valsalva maneuver) in the supine position. An implication of that study is that Doppler evaluation is not necessary to assess clinical varicoceles, because a B-scan of vein diameters predicts clinical varicoceles with high accuracy. However, attempting to diagnose subclinical varicoceles based only on vein diameters results in a high number of false positives and negatives (sensitivity and specificity, both <70 %), which suggests that color Doppler ultrasound is useful in detecting subclinical varicoceles.

In addition to concerns regarding sensitivity, there are several other obstacles to varicocele diagnosis. The scrotal skin of Asians might be thicker than that of whites, which could mask varicoceles. In addition, obesity, history of scrotal surgery, concomitant hydrocele, unsuitable room temperature, and tonicity of the cremaster muscle can interfere with the diagnosis of clinical varicoceles. These factors might introduce bias to the findings of physical examinations, resulting in huge variances in the diagnosis of clinical varicocele. Thus, we encourage further attempts to both improve the diagnostic techniques for clinical varicoceles and refine the diagnostic criteria by combining physical examination and objective measurement, such as the use of ultrasound.

There are a number of unresolved issues in the management and treatment of varicoceles in adolescents [37–44]. Since 80 % of adult males with varicoceles will be fertile, surgical treatment for adolescent varicoceles is indicated only for carefully selected patients. The 2013 EAU guideline recommends varicocele treatment for adolescents with progressive failure of testicular development, as documented by serial clinical examinations [45]. However, surgical repair should not be limited to severe varicoceles. The differential in testicular volume is the most important indicator of the need for surgical intervention. Although this point is frequently debated, a study from Children's Hospital Boston, by Diamond et al., reported that a sonographically derived testicular volume differential >10 % between the normal and affected testes was associated with significant decreases in sperm concentration and total motile sperm count. Moreover, when the differential was >20 %, decreases in sperm concentration and total motile sperm were greater [46]. Therefore, the authors of that study recommended annual physical examinations with scrotal ultrasonography to monitor differential in testicular volume for adolescents with clinical varicoceles and equal testicular volume but no symptoms. Once adolescent males reach Tanner stage V, data from semen analysis are an important additional indicator of the need for surgical intervention [39].

Approaches to varicocele repair

Several techniques are used for varicocele repair, including surgery and embolization, and a number of studies have compared the following surgical techniques: (1) the Palomo technique—retroperitoneal high ligation of the testicular artery and vein above the inguinal ring, (2) the Bernardi technique—high ligation of the vein, sparing the artery, (3) the Ivanissevich technique—ligation of the cremasteric and internal spermatic veins within the inguinal canal, (4) inguinal microsurgical technique—low ligation of the internal and external spermatic vein within the inguinal canal (a surgical microscope is used so as to preserve the artery and lymphatics), (5) subinguinal microsurgical technique—low ligation of the internal and external spermatic vein in the level from the external inguinal ring (the artery and lymphatics are preserved by using a surgical microscope), (6) laparoscopic high ligation technique, and (7) interventional therapy using embolization under radiographic guidance. Among these techniques, most recent reviews concluded that microsurgical varicocele repair has clear advantages over the other techniques, namely, better pregnancy outcomes, lower complication rates, and lower recurrence rates, although this technique requires specific training in microsurgery [31, 47–49]. Similarly, in a recent review article [50], Diegidio et al., manifested that microsurgical subinguinal technique yields the best outcomes, in terms of pregnancy rate, recurrence rate, and rate of hydrocele formation. In contrast, high ligation and the inguinal and laparoscopic approaches were associated with recurrence rates of 10 % or higher and a rate of hydrocele formation of 5–10 %, as compared with values of 2 and 0.7 % for the microsurgical subinguinal approach (Table 1). In addition, several studies reported that invasiveness and costs associated with surgery were greater for laparoscopic surgery under general anesthesia than for subinguinal microsurgical repair with local anesthesia, because of the use of aeroperitoneum for laparoscopic surgery [49, 50].

Effectiveness of varicocele repair in treating male infertility

Pregnancy rate

Previous studies of pregnancy rates after varicocele repair were likely to have methodological flaws, since those studies were contaminated by men with subclinical varicoceles and normal semen characteristics. A Cochrane review published in 2001 [51] and a review article [52] by Evers et al., reported that varicocele repair by surgery or embolization had little effect on pregnancy rates. These studies have been criticized, however, because of the problems in study design mentioned above and the inherent bias attributable to the authors' specialties and affiliations. In 2009, Marmar [53] summarized the findings of a meta-analysis of RCTs. That analysis revealed a statistically significant improvement in semen characteristics and natural pregnancy rates after surgical varicocelectomy. The study maintained that varicocele repair could be an important treatment option for infertile men presenting with palpable varicoceles and at least one low measurement in semen testing. In contrast, a recent meta-analysis and systemic review found insufficient evidence for an increase in spontaneous pregnancy rate after varicocele repair [47]. In that meta-analysis, the authors excluded studies contaminated with men with normal semen characteristics and/or subclinical varicoceles; four recent RCTs reporting pregnancy rates were ultimately selected. The study used a random effects model to calculate the combined odds ratio (OR) for improvement of pregnancy rate and semen characteristics associated with varicocele repair. In total, 380 couples were analyzed,

Table 1 Rates of pregnancy, recurrence, and hydrocele formation stratified by approach used for varicocele repair

Surgical technique	No. of studies analyzed	Pregnancy rate, % (range)	Recurrence rate, % (range)	Hydrocele formation, % (range)
High ligation	4	34.21 (33.5–36)	12.5 (7.3–15.5)	7.58 (4.6–9.0)
Inguinal approach	6	30.06 (20–31.5)	15.65 (3.57–17.5)	7.47 (4.3–17.5)
Subinguinal approach	1	26.09 (26.09)	3.57 (3.57)	0
Microsurgical inguinal	6	41.78 (40.8–42.8)	9.47 (0.7–15.2)	0.29 (0.0–0.7)
Microsurgical subinguinal	13	44.75 (33.8–51.5)	2.07 (1.4–14.8)	0.72 (0.3–1.6)
Laparoscopic	9	27.53 (13.1–40)	11.11 (4.0–26.5)	7.57 (1.7–12.7)
Radiological embolization	7	31.93 (12.2–40)	4.29 (1.9–9.3)	N/A[a]

[a] N/A (not available): hydroceles are not typically seen with embolization procedures

including 192 randomized to treatment and 188 to observation. The OR for improvement of spontaneous pregnancy rate associated with varicocele repair was 2.23 [95 % confidence interval (CI) 0.86–5.78; $P = 0.091$], which was not statistically significant. In their discussion of the results, the authors conceded the study limitations with respect to heterogeneity of patient characteristics, diagnostic criteria, treatment methods, and outcomes of these RCTs, which might have limited the ability of the analysis to yield correct answers to the study question.

Semen parameters

A number of studies reported that varicocele repair improves semen parameters such as sperm concentration, sperm motility, and progressive sperm motility [54–58]. The recent meta-analysis and review from Baazeem et al. [47] summarized the effectiveness of varicocele repair in improving semen parameters. In that analysis, the authors selected 22 prospective studies of men with abnormal semen parameters and clinical varicoceles, and observed sperm concentration before and after surgery. The mean improvement in sperm concentration for the 22 studies was 12.3 million sperm/mL (95 % CI 7.07–14.65; $P < 0.001$). Similarly, after varicocele repair, improvement in sperm total motility in 17 prospective studies and progressive sperm motility in 5 prospective studies was 10.86 % (95 % CI 7.07–14.65; $P < 0.001$) and 9.69 % (95 % CI 4.86–14.52; $P = 0.003$), respectively, which were statistically significant increases. In summary, current evidence indicates that varicocele repair improves semen parameters; however, evidence regarding spontaneous pregnancy rates is equivocal.

New role of varicocele repair in the ART era

Varicocele repair for couples who undergo IVF/ICSI

The evidence strongly suggests that varicocele repair improves semen parameters by reversing sperm DNA damage, which could ultimately improve IVF/ICSI outcomes. The mean intervals from surgery to improvement in semen parameters and to spontaneous pregnancy were reported to be approximately 5 and 7 months, respectively [59]. However, a recent study at Kobe University reported earlier improvement in sperm DNA integrity after microsurgical repair of varicoceles [60]. In that study, sperm DNA integrity significantly improved (to a level similar to that of a healthy control group) at 3 months after surgery.

Esteves et al. [61] studied 242 men with infertility and evaluated clinical outcomes of ICSI in patients with abnormal semen parameters, including oligozoospermia, asthenozoospermia, and teratozoospermia, stratified by clinical varicocele treatment status (treated vs untreated). The mean time from surgery to sperm injection was 6.2 and 4.2 months, respectively. Total number of motile sperm (6.7×10^6 vs 15.4×10^6, $P < 0.001$) and normal 2PN fertilization rate (78 vs 66 %, $P = 0.04$) were significantly higher in treated men than in untreated men. Notably, as compared with untreated men, the probability of achieving clinical pregnancy in couples with treated men increased by 1.82 fold, and the rate of live births increased by 1.87 fold; the rate of miscarriage rate decreased by 0.43 fold. All differences were statistically significant.

Pasqualotto et al. [62] evaluated the impact of varicocele repair after ICSI on 248 patients and found that the procedure did not increase pregnancy rates or decrease miscarriage rates after ICSI. The fertilization rate was higher in men who had undergone varicocele repair (73.2 %) than in those who had not (64.9 %; $P = 0.038$); however, there were no differences between groups in pregnancy rate (31.1 vs 30.9 %; $P = 0.981$), implantation rate (22.1 vs 17.3 %; $P = 0.588$), or miscarriage rate (21.7 vs 23.9 %; $P = 0.840$). However, the mean sperm concentrations in the two groups were 30.8×10^6 and 24.1×10^6, respectively. These values are higher than those in other reports, which suggests the possibility of bias in the results of that study.

There have been several reports and discussions regarding varicocele repair for men with nonobstructive azoospermia [63–69]. In a review by Schlegel et al. [63], the rate of return of sperm to ejaculate ranged widely, from 21 to 56 %, while pregnancy rate was relatively low, from 0 to 15 %. In 2004, Schlegel et al. [70] reported data on 31 patients with clinical varicoceles and nonobstructive azoospermia who had undergone varicocele repair: 7 of the 31 (22 %) men had sperm on at least one semen analysis postoperatively. However, without testicular sperm extraction (TESE), only 3 of the 31 (9.6 %) men after varicocele repair had sufficient motile sperm in ejaculate for ICSI. After varicocele repair, men with clinical varicoceles associated with nonobstructive azoospermia rarely have sufficient sperm in ejaculate to avoid TESE. The authors concluded that the benefit of varicocelectomy in men with nonobstructive azoospermia may be less than previously reported.

A recent study by Inci et al. [71] showed that varicocele repair had significant effectiveness for men with clinical varicoceles and nonobstructive azoospermia who had undergone micro-TESE/ICSI, at a mean time after surgery of 23.6 months. They studied 96 men with complete nonobstructive azoospermia and a history of clinical unilateral or bilateral varicocele. In an analysis of treated and untreated men, the sperm retrieval rate (53 vs 30 %) was significantly higher in the treated group, although the clinical pregnancy rate (31.4 vs 22.2 %) did not significantly differ. These results suggest that varicocele repair may be an option for infertile men who are undergoing ICSI.

Overall, evidence of an advantage for varicocele repair in conjunction with ART is weak, especially for varicocele repair in men with nonobstructive azoospermia, as this technology is relatively new. It should be noted, however, that there was a clear difference in patients with nonobstructive azoospermia who underwent varicocele repair, depending on whether sperm utilized for ICSI was from ejaculate or retrieved by TESE, as this affected outcomes such as sperm retrieval rate, pregnancy, and miscarriage rate. Research in this area is progressing rapidly, and future studies should clearly identify the role of varicocele treatment for men with clinical varicoceles who undergo IVF/ICSI.

Cost-effectiveness of varicocele repair with ART

Most of the several cost-effectiveness analyses of couples with infertility undergoing ART found that varicocele repair was more cost-effective than primary treatment with assisted reproduction alone, if the male has a clinical varicocele. Schlegel et al. [72] compared costs with varicocele-associated male-factor infertility. The cost per delivery with ICSI was $89,091, whereas the cost per delivery after varicocelectomy was only $26,268, which implies that surgical varicocele repair is more cost-effective than primary treatment with assisted reproduction. Penson et al. [73] calculated both the average cost and cost per live birth for the following four treatments: (1) observation, (2) varicocele repair with IVF, (3) intrauterine insemination with IVF, and (4) immediate IVF. Varicocele repair with IVF was the most cost-effective, after observation. Lee et al. [74] conducted a decision analysis limited to patients with clinical varicoceles and nonobstructive azoospermia and found that, when indirect costs were considered, microsurgical TESE was more cost-effective than varicocelectomy for treatment of varicocele-associated nonobstructive azoospermia, although further research is warranted.

Conclusion

Physical and ultrasound examinations for varicoceles are strongly recommended when an infertile male with abnormal semen characteristics visits an infertility clinic, as most evidence indicates that varicocele repair improves semen characteristics. Alternatively, early consultation with a urologist specializing in male infertility should be considered. Among the several techniques available for varicocele repair, inguinal/subinguinal microsurgical techniques are potentially the best in terms of effectiveness, complication rate, and recurrence rate. With respect to cost-effectiveness, microsurgical varicocele repair under local anesthesia was the most cost-effective treatment option; laparoscopic varicocele repair required expensive surgical materials and general anesthesia. In addition, varicocele repair for infertile men with abnormal semen characteristics allowed couples to reduce medical expenses related to childbirth by reducing the number of repeat IVF/ICSI cycles. In summary, despite the necessity for specific training in microsurgery, microsurgical varicocele repair, whether inguinal or subinguinal, is the most promising treatment option and is expected to become the gold standard for treating infertility in men with varicoceles. Evidence on varicocele repair is rapidly accumulating, and future research should evaluate current and new diagnostic methods, management plans, and repair techniques in studies with unified reporting methods and sufficient patient enrollment.

Conflict of interest Masaki Kimura and Koichi Nagao declare that they have no conflict of interest.

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