Received: 3 April 2024 | Accepted: 27 May 2024

DOI: 10.1002/rmb2.12589

Reproductive Medicine and Biology

WILEY

REVIEW

Role of varicocele repair in the era of assisted reproductive technologies: Lessons from 2000 cases of microsurgical varicocele repair

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Abstract

Backgrounds: In an era of advanced maternal age, there is less conclusive evidence regarding the treatment outcomes of varicocele repair for assisted reproductive technology (ART). Progress in basic research on varicocele is notable whereas there are many clinically relevant points to discuss.

Methods: Based on our experience with more than 2000 cases of microsurgical varicocele repair, we focused on the effectiveness of varicocele repair, pathophysiology, surgical approaches, contributions to ART, sperm DNA fragmentation, and varicocele-associated azoospermia in this review with the aim of identifying clearer directions for basic and clinical research on varicocele.

Results: Microsurgical low ligation for varicocele repair is expected to remain the gold standard for surgical therapy. Based on the findings from a number of systematic reviews and meta-analyses, negative opinions regarding the efficacy of microsurgical varicocele repair in male infertility treatment have become virtually nonexistent. However, the majority of evidence regarding surgical indications and effectiveness pertains to improvements in semen parameters or non-ART pregnancy rates.

Conclusions: Further understandings regarding to pathophysiology of varicocele will likely be gained through comprehensive genetic, transcriptomic, and epigenetic analyses using blood and testicular samples from humans and we hope to develop new diagnostic methods and pharmacotherapy.

KEYWORDS
assisted reproductive technology, male infertility, varicocele, varicocele repair

1 | INTRODUCTION

Varicoceles affect approximately 15% of fertile adult males[1] and are the most common cause of male infertility; they are diagnosed in 30%–40% of men with primary infertility and up to 80%–90% of men with secondary infertility.[2–5] According to nationwide research in Japan, varicocele accounts for 30.2% of male infertility cases, making it the most common identifiable cause.[6] By simple calculation, 7–8 million men are estimated to have varicocele in Japan. Therefore, it is necessary to provide accurate information regarding varicocele to general urologists and the public, regardless of whether men are infertile. Approximately 20% of men with varicocele are

infertile, and the remaining 80% of men are fertile.[7] The balance between intrinsic fertility capacity, including factors such as testicular volume and intratesticular antioxidant capacity, and the harmful effects of varicocele should determine men's fertility.[8]

Varicocele repair, also called varicocelectomy, is the best and most reliable surgical approach for correcting varicocele. The significance of varicocele repair has been discussed from various perspectives. For example, surgical techniques, improvements in semen analysis, the management of pain cases, and the management of pediatric cases have been discussed for a long time, and recently, their effectiveness in treating late-onset hypogonadism (LOH) syndrome has been a matter of debate. In the 1990s, when the number of assisted reproductive technology (ART) facilities was limited, accessibility to ART was restricted for patients. As a result, the expected result of varicocele repair is a non-ART pregnancy. However, even during the peak popularity of ART in the early 2000s, some in vitro fertilization (IVF) doctors suggested that male infertility treatment might be unnecessary. Consequently, ART and male infertility treatment were treated as opposing treatments. Unfortunately, due to the lack of striking improvements in ART success rates, reports have begun to emerge that encourage male infertility treatment; moreover, gynecologists have also begun to actively advocate for the necessity of male infertility treatment. Furthermore, since April 2022, infertility treatments, including ART, have been covered by insurance, reducing the financial burden on many infertile couples and increasing the availability of treatment. In this context, it is highly important to reconsider the importance of managing varicocele.

Based on our experience with microsurgical varicocele repair in more than 2000 patients and considering the historical background, in this work we review the significance of varicocele repair in the ART era and the evolution of microsurgical approaches, which are clinically important.

2 | VARICOCELE REPAIR HAS BEEN SHOWN TO BE EFFECTIVE FOR MALE INFERTILITY

The detrimental effect of varicocele on semen parameters has been known since 1965, when MacLeod reported a decrease in sperm concentration and motility.[9] In 1978, Johnsen compared testicular biopsies before and after 1 year of varicocele repair and reported significant improvement in seminiferous tubule appearance and germ cell content after surgery.[10] Most urologists believe that varicocele repair may have contributed to improvements in semen parameters and pregnancy outcomes for a long time, but a Cochrane review published in 2000 failed to show a significant improvement in pregnancy rates for patients undergoing varicocelectomy.[11] Revisiting the conclusion and problems in the Cochrane review, a number of retrospective studies and meta-analyses have proven the effectiveness of varicocele repair for semen parameters and pregnancy rates.[12,13] Agawral et al. reported that 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.[12] Baazeem et al. reported that sperm concentration increased by 12.32×10^6/mL (95% CI: 9.45–15.19, $p<0.00001$) and motility increased by 10.86% (95% CI 7.07–14.65, $p<0.0001$) after microsurgical varicocelectomy.[13] Interestingly, the same group that published the Cochrane review in 2000 subsequently published an update concluding that varicocele repair may be beneficial.[14] Ironically, in a recent Cochrane review, a significant difference was found in terms of pregnancy rates between treatment groups and controls for patients with abnormal semen parameters based on the results of 15 RCTs.[15] In this report, improvements in live birth rates were unclear from two RCTs, whereas concerning pregnancy rates, the analysis of 13 RCTs indicated that varicocele treatment improved pregnancy rates (OR: 1.55, 95% CI: 1.06–2.26). Furthermore, among patients with palpable varicoceles and poor semen parameters, the improvement rate was greater (OR: 1.94, 95% CI: 1.23–3.05). Birowo et al. analyzed 31 studies, including 14 RCTs, and reported a significant improvement in pregnancy rates (OR: 1.82, 95% CI: 1.37–2.41) and live birth rates (OR: 2.80, 95% CI: 1.67–4.72) after varicocele treatment.[16] In this context, the European Association of Urology (EAU) guidelines on sexual and reproductive health recommend varicocele repair in infertile men with abnormal semen parameters/DNA fragmentation indices and unexplained infertility,[1] and the American Urological Association (AUA)/American Society for Reproductive Medicine (ASRM) guidelines suggest that surgical varicocelectomy should be considered for men attempting to conceive who have palpable varicocele(s), infertility, and abnormal semen parameters (Moderate Recommendation; Evidence Level: Grade B).[17] The most recent meta-analysis reported robust evidence that varicocele repair has a positive effect on semen parameters in infertile men with clinical varicocele.[18]

The differences in the effectiveness of varicocele grade after varicocele repair are controversial. Most studies have indicated that men with palpable varicoceles, usually those with grade 2 or higher varicoceles, may benefit from treatment the most. A systematic review by Asafu-Adjei examined the effects of varicocele grade by analyzing 20 studies and reported improvements in sperm concentration and motility for all grades following varicocele repair.[19] Recently, Falla et al. reported that treatment of any-grade varicoceles may improve pregnancy rates and sperm concentrations in infertile adult men.[20] The lack of significant differences in pregnancy rate and live birth rate may be attributed to the presence of numerous confounders, including factors related to female infertility. The effects of varicocele repair on ART outcomes are discussed in the following section.

3 | PROGRESS IN UNDERSTANDING THE PATHOPHYSIOLOGY OF VARICOCELE

Varicocele is an abnormal enlargement of the pampiniform plexus in the scrotum, basically on the left, because of the anatomy of the spermatic veins, a network of testicular veins that helps in the heat

exchange mechanism of blood to maintain a testicular temperature lower than the body temperature. Classical studies have demonstrated that men with varicoceles have higher intrascrotal temperatures[21] and that these temperatures decrease following varicocele repair. In the presence of varicocele, scrotal hyperthermia affects testicular temperature and can dysregulate spermatogenesis, as the testis requires a lower temperature (2–3°C less than body temperature).[22,23] In particular, gonocytes and primary spermatocytes are vulnerable to high temperatures.[24] Unlike the central nervous system, the testis is sensitive to even minimal changes in blood pressure, and increases in venous pressure provoke compensatory vasoconstriction of intratesticular arterioles, leading to slight ischemia/hypoxia and thereby reducing the oxygen and nutrient supply to the testis.[25] The present evidence indicates that varicocele affects spermatogenesis via multiple distinct mechanisms, such as scrotal hyperthermia, hypoxia, the backflow of toxic metabolites, elevated oxidative stress, hormonal deregulation, and testicular hypoperfusion.[26]

Among various pathophysiologies, intratesticular oxidative stress is one of the major causes of impaired spermatogenesis and is clinically important because oxidative stress is one of the major factors that causes sperm DNA fragmentation and spermatogenesis. An increasing number of studies have suggested an association between the presence of varicocele and increased oxidative stress by demonstrating increased levels of reactive oxygen species (ROS), nitric oxide (NO), and lipid peroxidation products in infertile men with varicocele at the testicular/seminal/spermatozoa level.[27] The potential site of ROS production in men with varicocele is considered to be the testis, epididymis, and dilated pampiniform plexus, but presumably, the testis is the major site of ROS production because of active cell proliferation and metabolic activity of germ cells and hypoxic stress in the testicular microenvironment. NO is essentially a vasodilator, and increased expression of endothelial nitric oxide synthase (eNOS) is observed in testicular endothelial cells to compensate for hypoxic conditions,[28] and the expression of vascular endothelial growth factor (VRGF) is increased.[29] However, human studies have reported NO-mediated testicular damage.[30] Activated macrophages are considered to originate from NO and lead to increased NO production, which then promotes cell damage.[31]

ROS production in testes with varicocele also influences Leydig cell steroidogenesis, which decreases intratesticular and serum testosterone levels and affects spermatogenesis.[32] To respond to oxidative stress, increased expression of the antioxidant hemoxygenase-1 (HO-1) in Leydig cells has been observed in human biopsy samples.[33] According to a meta-analysis regarding the effectiveness of oral antioxidants in men with varicocele, oral supplementation significantly increased sperm concentration, sperm motility, and semen volume.[34] It is believed that, in the era before the involvement of oxidative stress was highlighted, in many clinical trials utilizing various vitamins and similar compounds, their mechanism of action may have been effective in suppressing oxidative stress. Further research focusing on the pathophysiology of oxidative stress is expected to lead to the development of nonsurgical treatments such as antioxidants.

4 | SURGICAL APPROACHES

For a long time, a number of publications, including meta-analyses and systematic reviews, have focused on the superiority of varicocele repair, microsurgical low ligation, laparoscopic high ligation, and embolization of spermatic veins. Controversies are inevitable if surgical microscopy is not widespread in the world, especially in the 1990s. A meta-analysis reported by Cayan et al. revealed significant differences in spontaneous pregnancy rates, recurrence rates, and hydrocele rates between microsurgical repair and Palomo high ligation, macroscopic inguinal, laparoscopic, or radiographic embolization.[35] The pregnancy rate was the highest with the microscopic inguinal or subinguinal approach (41.2%, $p < 001$) and the lowest rates of recurrence (1.1%, $p < 001$) and postoperative hydrocele (0.4%, $p < 001$). Similarly, Ding et al., in their meta-analyses, showed that microsurgical varicocelectomy with the preservation of the testicular artery and lymphatic vessels was the preferred surgical approach in infertile men in comparison with open surgery, laparoscopy, and radiographic embolization.[36] A subsequent meta-analysis reported by Wang et al. confirmed these findings, indicating that the microsurgical inguinal and subinguinal approaches were associated with the highest rate of pregnancy and the lowest rate of complications.[37] A meta-analysis by Yuan et al. compared various surgical techniques, and seven RCTs were analyzed. Compared to open surgery, microsurgical procedures were reported to result in a significantly greater pregnancy rate (RR: 1.37, 95% CI: 1.12–1.69).[38] Furthermore, the complication rate was lower (OR: 0.21, 95% CI: 0.12–0.37), and the recurrence rate was also lower (OR: 0.11, 95% CI: 0.06–0.21), indicating superior outcomes for microsurgical procedures compared with open surgery. In a meta-analysis conducted by Wang et al. comparing microsurgery and laparoscopic surgery, 23 RCTs were analyzed.[39] Compared with laparoscopic surgery, microsurgery significantly improved the sperm concentration (RR: 3.00, 95% CI: 1.23–4.76) and was associated with lower rates of complications (RR: 0.40, 95% CI: 0.21–0.75) and recurrence (RR: 0.35, 95% CI: 0.22–0.55). Reflecting these findings, the current situation in Japan shows that over 80% of varicocele repairs are performed using the microsurgical approach.[6] As shown in Figure 1, our experience with 2000 recent cases also revealed a recurrence rate of 0.3% and a rate of testicular atrophy of 0% (Figure 1). In the review reported by Cayan et al., overall recurrence rates were 1.05% in the microsurgical varicocelectomy techniques, which was significantly the lowest among Palomo, laparoscopic, radiologic embolization, and macroscopic inguinal (Ivanissevich) techniques and testicular atrophy occurs at a negligible frequency.[35] Compared to microsurgical seminal reconstruction, microsurgical varicocele repair has a steeper learning curve (Figure 1) and should be performed by many general urologists. The complexity associated with the microsurgical subinguinal approach has become a significant barrier for many microsurgical beginners. As is evident from the anatomical structure of the spermatic cord to the testis, the vascular system becomes more intricate as it approaches the testis, with both arteries and veins increasing in number, making surgery more challenging.[40] However,

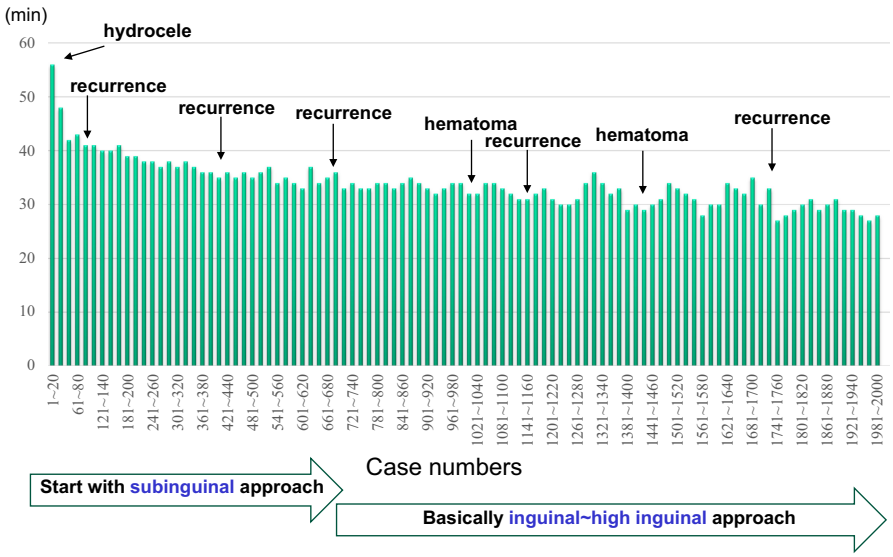

FIGURE 1 Varicocele cases, operation time, and complications.

in the inguinal canal, the number of vessels decreases, making microsurgical steps easier and rendering the microsurgical subinguinal approach a beginner-friendly procedure. The numbers of preserved arteries and ligated veins were significantly greater, and the artery size was significantly smaller for the subinguinal approach (1.6 arteries, 11.5 veins, and 1.1 mm, respectively) than for the high inguinal approach (1.2 arteries, 7.3 veins and 1.3 mm).[41] In this series of 2000 cases, the average number of preserved lymphatic vessels is 4.6 vessels (1 to 8 vessels). Even if only one to two lymphatic vessels are preserved within the spermatic cord, we did not experience hydrocele if we preserve even a part of external spermatic fascia. Lymphatic vessels can be readily identified primarily around the testicular artery without the use of indigocarmine, as they appear as transparent ducts. In microsurgical varicocele repair, performing microsurgical steps quickly and safely is crucial for achieving shortened surgical times and positive postoperative outcomes. Therefore, an approach at the level of the inguinal ring is appropriate because it allows for precise manipulation and visualization of the spermatic cord structures. Although recurrence from the external spermatic vein is a concern, the rate was 1.3% in adults[42] and 0% in adolescents.[41] In our series of 2000 patients, including those in these series, there were six patients (0.3%). The gubernacular vein is not ligated in cases of testicular torsion, suggesting that there is no involvement of the external spermatic vein or gubernacular vein in the inguinal to high inguinal approach. There are publications attempting to identify lymphatic vessels while conserving them by regional injection of indocyanine green into the testis and scrotum. The number of lymphatic vessels within the spermatic cord and within the external spermatic fascia are inversely correlated.[43] In our experience, even when lymphatic vessels cannot be preserved within the spermatic cord, scrotal hydrocele due to preservation of the external spermatic fascia has not been encountered. The recurrence of varicocele occurs at a certain frequency regardless of experience, suggesting the existence of anatomical issues such as gubernacular vein abnormalities (Figure 1). It is important to note that scrotal hematoma occurred in approximately the 1000th and 1400th patients (Figure 1), indicating the need for meticulous attention throughout the procedure, from adequate hemostasis within the spermatic cord to subcutaneous suturing, despite these being basic aspects.

The utility of microsurgical low ligation in varicocelectomies is evident. However, for general urologists, access to microsurgical training opportunities is often limited. Compared with more common procedures, such as endourological, laparoscopic, and robotic surgeries, microsurgical varicocelectomies require unique skills. Due to the specialized nature of microsurgery, opportunities for comprehensive training may be limited in some medical settings. Access to experienced mentors, specialized courses, and hands-on training programs is crucial for developing the expertise necessary for performing microsurgical procedures effectively. The microsurgical high inguinal approach may help microsurgical beginners overcome this educational hurdle. As robotics systems are becoming standard in urology practice, the introduction of robotic systems for microsurgical varicocele repair, vasovasostomy, and microsurgical denervation of the spermatic cord has been reported.[44] The potential advantages of incorporating robotic platforms in microsurgery include the following: the elimination of surgeon tremors and improved stability, improved motion scalability, better surgeon ergonomics, multi-input visual interphases, enhanced magnification, and the ability to manipulate three surgical instruments and cameras simultaneously. Indeed, there are limited reports available at present regarding the utility of robotic-assisted surgery in microsurgery, and further validation is necessary to ascertain its effectiveness and benefits. In Japan, it is believed that the introduction and maintenance of advanced medical technology incur high costs, and we do not feel the need to use a robotic system for microsurgical varicocele repair that can be completed within 30–40 min.

5 | CONTRIBUTION TO ART OUTCOMES

With the current trend of delayed marriages, there is an increasing demand for swift infertility treatments. Consequently, some

gynecologists are averse to performing varicocele surgeries, which take more than 3 months to yield results. Interestingly, in a recent Cochrane review, a significant difference was found in terms of pregnancy rates for treatment of male infertility arms versus controls irrespective of semen examination,[15] indicating that improvements have been observed not only in typical parameters such as concentration and motility but also in aspects not typically assessed, such as sperm quality. In the past, male infertility treatment, including varicocele repair, was perceived as being diametrically opposed to ART, aiming for non-ART pregnancies. However, in addition to such step-down (upgrading) approaches, it is increasingly common for treatments to focus on improving sperm quality for ART.

In the 1980s, Ashkenazi et al.[45] examined the effect of varicocele repair on successful IVF and embryo transfer. They evaluated 22 infertile couples with varicocele for whom IVF failed. Male partners underwent varicocele repair before a subsequent IVF attempt, and postoperatively, the embryos showed statistically significant improvements in fertilization, cleavage, and pregnancy rates. Esteves et al.[46] examined 242 infertile men with varicoceles undergoing ART. Prior to ART, 80 men underwent microsurgical varicocele repair; the other 162 men remained untreated at the time of ART. Pregnancy and live birth rates favored varicocele repair, with an odds ratio (OR) of 1.82 (95% CI: 1.06–3.15) for pregnancy and an OR of 1.87 (95% CI: 1.08–3.25) for live births, followed by improvements in sperm concentration and motility. More recently, Kirby et al.[47] reported a detailed meta-analysis addressing the impact on pregnancy and live birth rates for men who underwent varicocele repair before intrauterine insemination (IUI) and ART and demonstrated improved outcomes for both IUI and IVF after varicocele repair. They also showed that men requiring testicular sperm extraction benefited from varicocele repair. Esteves et al. also performed a meta-analysis including four studies comprising 438 IVF cycles with prior varicocele repair and 432 IVF cycles without varicocele repair and found that there was a significant increase in the pregnancy rate (OR 1.59, 95% CI 1.19–2.12) and live birth rate (OR 2.17, 95% CI 1.55–3.06) with prior varicocele repair compared with no surgery.[48] In the next section, we explain why varicocele repair is effective for the success of ART treatments, that is, what exactly sperm quality improvement entails.

6 | VARICOCELE REPAIR AND SPERM DNA FRAGMENTATION

In recent years, the integrity of sperm DNA has emerged as a crucial factor influencing fertilization and embryo development. Elevated levels of sperm DNA fragmentation (SDF) are more prevalent among infertile men than among fertile men and have been linked to reduced pregnancy rates in timed intercourse, poorer outcomes in ART procedures, and decreased rates of fertilization, live births and increased rates of miscarriages when compared to men with normal SDF levels.[49–54] Numerous risk factors contributing to SDF have been identified, including smoking, chemotherapy, advanced paternal age, and chronic illness. Clinical varicoceles have also been implicated in elevated SDF. Varicoceles are widely recognized as a significant factor contributing to sperm DNA damage. Although the exact mechanism by which varicoceles induce DNA damage remains somewhat unclear, it is thought to occur via increases in ROS and reductions in antioxidant capacity. It is presumed that venous stasis induces oxidative stress and causes membrane lipid peroxidation and then breaks in the DNA strands of developing spermatogonia and spermatozoa per se.[27,50,55,56] In humans, increased expression of 4-hydroxy-2-nonenal (4-HNE)-modified proteins, which reflects stable lipid peroxidation, is observed in the testes of infertile men with varicocele.[57]

Because of its ease of evaluation, SDF is one of most commonly evaluated factors among sperm qualities. The potential clinical role of evaluating SDF is its ability to aid in the selection of patients who could benefit from varicocele treatment[58]; however, high SDF coupled with normal sperm parameters has yet to be considered an indication of varicocele repair due to limited studies.[16] In fact, accumulating evidence suggests that SDF may be reduced through varicocele repair. In 2011, Zini et al. conducted a review encompassing 12 studies involving 511 patients, wherein varicocele repair consistently correlated with reductions in SDF.[59] Subsequently, a meta-analysis by Wang et al. in the following year revealed an average improvement of 3.37% (95% CI: 2.65–4.09) in DNA fragmentation after varicocelectomy.[52] These findings are supported by recent randomized controlled trials. For instance, Sun et al. reported a decrease in the DNA fragmentation index from 21.6% to 11.8% and from 23.0% to 12.1% 1 year after unilateral and bilateral varicocele repair, respectively.[60] Similarly, Zaazaa improved from 34.6% to 28.3% following subinguinal varicocele repair.[61] Regarding pregnancy, researchers have evaluated the effects of varicocele repair on infertile men who present with clinical varicocele and elevated sperm DNA fragmentation, and they reported a notable difference in pregnancy rates. Among the 45 men who underwent surgical correction of varicocele, a 62% pregnancy rate was observed, whereas among the 40 men who did not undergo varicocelectomy, the pregnancy rate was 30%. However, several modifiable risk factors affect SDF. Among the above risk factors, varicocele, impaired glucose tolerance, testicular tumors, smoking status, pollution status, and paternal age greater than 50 years were associated with the highest SDF.[62]

As described above, varicocele repair has been shown to decrease SDF, contributing not only to non-ART pregnancies but also potentially enhancing outcomes in ART. Recent advancements in sperm selection techniques, such as the use of sperm separators such as ZyMot®, have allowed for the preparation of sperm with lower SDF. Although there is no solid evidence yet regarding the efficacy of these devices in achieving pregnancy and birth, there is a risk that their use could replace surgical interventions. Importantly, sperm quality encompasses more than just SDF. DNA fragmentation is merely the ultimate product of cellular damage, and it is speculated that impairments in sperm quality occur at earlier stages. Alongside pursuing non-ART pregnancies via varicocele repair, we

must comprehensively assess the impact of varicocele repair on sperm per se, semen quality, ejaculatory function, and endocrinological changes. Further investigation is necessary to determine what improvements are being made and by what mechanisms they contribute to infertility treatment.

7 | VARICOCELE-ASSOCIATED NONOBSTRUCTIVE AZOOSPERMIA (VAA)

In 1952, Tulloch reported the first instance of a spontaneous pregnancy following surgical repair of a varicocele in a couple of patients diagnosed with nonobstructive azoospermia (NOA).[63] Matthews and Goldstein reported the induction of spermatogenesis and subsequent pregnancy following microsurgical varicocele repair in men diagnosed with NOA. Remarkably, more than 50% of these men exhibited motile sperm in the ejaculate, which was deemed suitable for ART procedures. According to a recent review, the percentage of males with motile spermatozoa in their ejaculates varies widely, ranging from 5% to 69%.[64]

In patients with hypospermatogenesis, the restoration of spermatogenesis results in the reappearance of sperm in the ejaculate. Conversely, individuals exhibiting a histopathological pattern of maturation arrest (at the primary spermatocyte stage) or Sertoli cell-only syndrome (SCO) did not exhibit any significant alteration in semen analysis following varicocele repair.[65] Similarly, Majzoub et al. reported that 72.7% of patients who exhibited hypospermatogenesis and 27.3% of patients with SCO regained sperm in the ejaculate after varicocele repair.[66] Weedin et al. documented the emergence of motile sperm in semen samples collected postvaricocele repair in 91 of 233 men, accounting for 39.1% of the cohort. The authors highlighted the occurrence of 14 spontaneous pregnancies (6%) and 10 pregnancies facilitated by IVF.[67] A meta-analysis, which compared the outcomes of varicocelectomy in men with nonobstructive azoospermia (NOA) based on diagnostic testicular biopsy profiles, revealed a greater likelihood of successful induction of spermatogenesis in men with NOA with maturation arrest or hypospermatogenesis than in those with Sertoli cell-only syndrome (SCO).[48] The percentages of males who exhibited spermatozoa in their semen samples following varicocele repair were 35.3% in the subgroup of NOA men with maturation arrest and 56.2% in the subgroup of NOA men with hypospermatogenesis; these percentages were notably greater than those observed in individuals with SCO (9.7%).[48] The difference in the SRR (sperm retrieval rate) depends on the patient's background, including the presence of conditions such as hypospermatogenesis or late maturation arrest. A comparative assessment of 23 003 genes among subpopulations of NOA males, specifically those with maturation arrest, either positive or negative for spermatozoa in semen samples, revealed a subset of genes that were upregulated and others that were downregulated in men exhibiting sperm recovery postvaricocelectomy. The expression of proliferating cell nuclear antigen was notably greater in males who responded positively to varicocelectomy than in those who showed a negative response.[68]

In reports focusing on the sperm retrieval rate (SSR) of micro-TESE, Haydardedeoglu et al. reported that the SRR was greater in the group of NOA men who underwent varicocele repair (60.81% and 38.46%, $p=0.01$, respectively).[69] Zampieri et al. also reported a significantly greater SRR (57.8%) in men treated with varicocelectomy than in men not treated with varicocelectomy (27%). In a recent study by Jensen, it was established that testicular histology could be valuable in identifying NOA males who are most likely to benefit from the appearance of spermatozoa after varicocele repair. Thirteen studies evaluated spermatogenesis postvaricocele repair, with an average rate of 27.3%.[70] The average SRR across five studies for NOA men undergoing micro-TESE after varicocele repair was 48.9%, compared to 32.1% for untreated cohort groups.[70] The average spontaneous pregnancy rate was 5.24%.[70] Among patients who underwent intracytoplasmic sperm injection (ICSI) after varicocele repair, the average pregnancy rate was 65.2%, whereas the pregnancy rate for untreated cohort groups following ICSI averaged 39.5%.[70] However, Schlegel et al.[71] and Althakafi et al.[72] proposed that varicocele repair may not be a significant predictor of success in NOA men undergoing micro-TESE; the presumably high SSR in men who did not undergo varicocele repair may be one reason for this.

Considering the high frequency of varicoceles, it is conceivable that varicoceles coexist in a significant proportion of men evaluated for infertility, of whom 10%–20% are azoospermic.[73] In other words, if varicocele plays a significant role in each patient's spermatogenic dysfunction, there is a likelihood of sperm appearing in the ejaculate after surgery and in the SSR after micro-TESE. Conversely, if varicocele involvement is minimal, expectations regarding the efficacy of varicocele repair may be diminished. Varicocele-associated azoospermia (VAA) varies in terms of the degree of varicocele involvement for each patient, with a greater degree of involvement typically correlating with higher expectations of varicocele effectiveness. According to our experience at Yamaguchi University involving 131 patients with varicocele-associated NOA, the presence of postoperative ejaculated sperm was indicated based on the findings of diagnostic testicular biopsy performed during surgery (Figure 2). Among patients with hypospermatogenesis and late maturation arrest, ejaculated sperm was observed in 45% and 20% of patients postoperatively, respectively. In contrast, in cases of early maturation arrest and SCO, the percentages were 6% and 0%, respectively. This finding suggests that varicocele plays a significant role in the pathophysiology of NOA, particularly in cases of relatively mild spermatogenic dysfunction, such as late maturation arrest and hypospermatogenesis, which could be considered a narrow definition of VAA (Figure 2). The only parameter to predict the effectiveness of varicocele repair is testicular histology, but this procedure is invasive. Simultaneous diagnostic testicular biopsy at the time of varicocele repair may help guide patients if sperm appearance is likely. It is crucial to carefully select appropriate indications for this approach.[74] Further investigations into the implications of hormonal evaluation and gene expression may help clarify which patients have the best prognosis after varicocele repair.

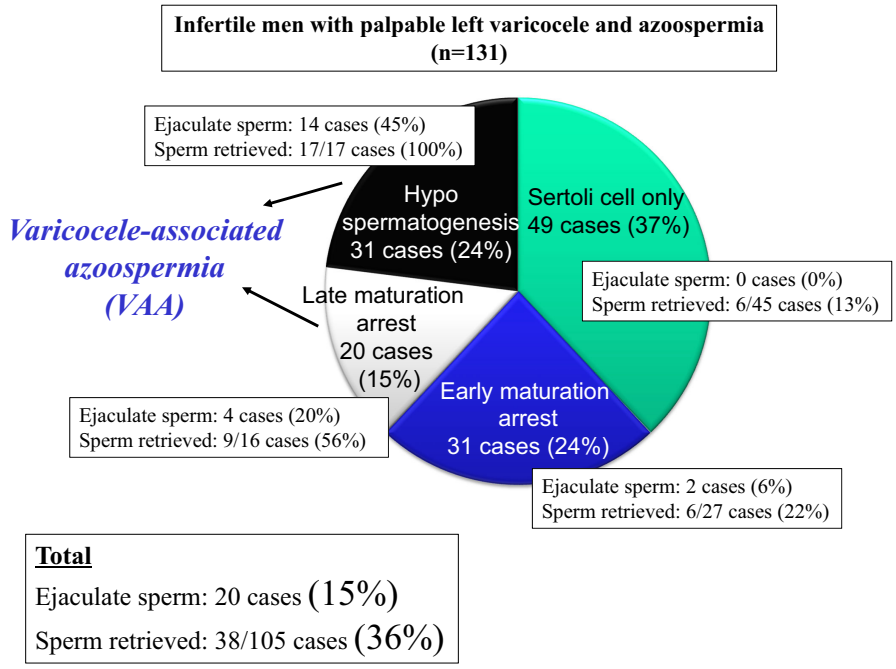

FIGURE 2 Varicocele-associated azoospermia is a condition if ejaculated sperms are observed after varicocele repair. In other words, varicocele plays a major role in the pathophysiology. Not all patients with Sertoli cell only and early maturation arrest identified during testicular biopsy at the time of varicocele repair underwent micro-TESE.

There is debate regarding whether varicocele repair should precede micro-TESE in cases of VAA. In cases of advanced maternal age, observation of the varicocele repair response may lead to worsening female factors, ultimately risking a decrease in live birth rates. However, proponents against varicocelectomies argue that the excellent SRR in the non-varicocelectomy group has been demonstrated. Although the difference in the quality of micro-TESE is unclear, it has been shown that varicocele repair can at least improve the SRR to the level observed in those who oppose varicocele repair. Micro-TESE has a significant impact on patients both psychologically and economically, and its outcomes, namely, sperm retrieval rates, should be maximized accordingly. Many patients seek surgery in hopes of the possibility of sperm retrieval, as long as the occurrence of ejaculated sperm is not zero. Shared decision-making based solely on percentages is not feasible in such cases. In Japan, microsurgical varicocele repair is also covered by insurance, and simultaneous diagnostic testicular biopsy can predict the expected ejaculated sperm and SRR in micro-TESE, serving as a helpful guide for patients. Accumulating clinical trial data on VAA suggest that the significance of varicocele repair for VAA should be reconsidered.

8 | CONCLUSION

There are numerous basic and clinical studies on varicocele, but based on our experience with more than 2000 cases of varicocele repair conducted over the past approximately 20 years, we discuss particularly clinically significant points. Regarding pathophysiology, further understanding will likely be gained through comprehensive genetic, transcriptomic, and epigenetic analyses using blood and testicular samples from humans in the future. Based on these findings, we hope to develop new diagnostic methods and pharmacotherapy. Microsurgical low ligation for varicocele repair is expected to remain the gold standard for surgical therapy for some time, and it is essential to actively train surgeons in this technique.

For varicocele, the most common cause of male infertility, further efforts must be made in both basic and clinical research.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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How to cite this article: Shiraishi K. Role of varicocele repair in the era of assisted reproductive technologies: Lessons from 2000 cases of microsurgical varicocele repair. Reprod Med Biol. 2024;23:e12589. https://doi.org/10.1002/rmb2.12589