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REVIEW

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Contemporary challenges and advanced technologies in the management of subfertile men with varicocele

Azizbek Shomarufov[1,2,*], Farkhad Akilov[1], Shukhrat Mukhtarov[2]

[1]Urology Department, Tashkent Medical Academy, 100109 Tashkent, Uzbekistan
[2]Surgical Department, Republican Specialized Scientific-Practical Medical Center of Urology, 100109 Tashkent, Uzbekistan

***Correspondence**
a.shomarufov@tma.uz
(Azizbek Shomarufov)

Abstract

Varicocele, closely linked to male fertility, requires urgent and focused research due to many unresolved questions. The absence of clear reference values distinguishing "normal" from "abnormal" semen parameters in the 6th World Health Organization (WHO) laboratory manual significantly complicates diagnosis and treatment. Additionally, the clinical relevance of total progressively motile sperm count (TMSC) remains unclear, leaving practitioners without critical guidance. The decision to perform varicocelectomy, particularly in cases of isolated teratozoospermia, is fraught with uncertainty. Furthermore, the best treatment strategy for those experiencing subfertility after varicocele surgery is still undetermined, adding another layer of complexity. These pressing issues, along with contentious debates surrounding isolated teratozoospermia treatment, highlight the need for large-scale multicenter randomized clinical trials. Such studies are essential to fully understand varicocele's impact on male fertility and to develop evidence-based management protocols.

Keywords

Varicocele; Varicocelectomy; Semen parameters; Subfertility

Desafíos contemporáneos y tecnologías avanzadas en el manejo de hombres subfértiles con varicocele

Resumen

El varicocele, estrechamente vinculado a la fertilidad masculina, requiere una investigación urgente y focalizada debido a muchas preguntas sin resolver. La ausencia de valores de referencia claros que distingan los parámetros del semen "normales" de los "anormales" en el sexto manual de laboratorio de la Organización Mundial de la Salud (OMS) complica significativamente el diagnóstico y el tratamiento. Además, la relevancia clínica del conteo total de espermatozoides móviles progresivamente (TMSC) sigue vaga, dejando a los profesionales sin una guía crítica. La decisión de realizar una varicocelectomía, especialmente en casos de teratozoospermia aislada, está llena de incertidumbre. Además, la mejor estrategia de tratamiento para aquellos que experimentan subfertilidad después de la cirugía de varicocele aún no se ha determinado, añadiendo otra capa de complejidad. Estas cuestiones urgentes, junto con los debates contenciosos en torno al tratamiento de la teratozoospermia aislada, subrayan la necesidad de ensayos clínicos aleatorizados multicéntricos a gran escala. Tales estudios son esenciales para comprender completamente el impacto del varicocele en la fertilidad masculina y para desarrollar protocolos de manejo basados en la evidencia.

Palabras Clave

Varicocele; Varicocelectomía; Parámetros del semen; Subfertilidad

1. Introduction

Varicocele is identified as the most common and treatable cause of male subfertility [1–3]. It is common in the general male population being present in up to 15% of healthy men. Additionally, 35% of men with primary infertility and 45–81% of men with secondary infertility have a varicocele [4, 5]. Although the mechanisms of the influence of varicocele on male fertility are still being discussed, in general, the results of studies demonstrate that varicocele has a negative impact on spermatogenesis and that varicocele correction improves sperm quality and increases real fertility [6–10]. Based on recent data, the European Association of Urology (EAU), the American Urological Association (AUA), and the American Society for Reproductive Medicine (ASRM) recommend surgery for infertile men with clinical varicocele and abnormal semen parameters [1, 11]. E. Persad *et al.* [6], S. Çayan *et al.* [12], and H. Ding *et al.* [13] in their meta-analyses showed that microsurgical varicocelectomy is the preferred surgical method in the treatment of clinical varicocele in infertile men in comparison with open (nonmicroscopic), laparoscopy and endovascular vein occlusion techniques. Simultaneously, varicocelectomy does not always lead to an improvement in sperm quality and fertility recovery: semen improvement after surgery usually occurs in 60–70% of cases and natural pregnancies occur in 25–40% of couples [14–18].

The latest EAU/AUA guidelines recommend varicocele repair for non-azoospermic infertile men with palpable varicocele and abnormal semen parameters, but the specific criteria remain unclear [11, 19]. Recent evidence suggests that total progressively motile sperm count (TMSC) and other indicators can help predict the success of varicocelectomy [20, 21]. However, the clinical value of these parameters and postoperative management strategies needs further clarification through large-scale clinical trials.

In this review, an analysis of the controversial issues regarding the current evidence on varicocele management in men with clinical varicocele and compromised reproductive function is provided.

2. Evidence acquisition and analysis

A comprehensive review of literature published from 1965 to 2024, sourcing data from PubMed, Scopus, Cochrane Library and Google Scholar, was conducted. Our focus was on research evaluating the efficacy of varicocele repair in subfertile men. We employed keywords such as “varicocele”, “varicocele repair”, “varicocelectomy”, “reproductive function”, “fertility”, “male infertility”, “subfertility”, “semen” and “sperm” in our search. The search criteria were limited to studies involving human subjects that investigated reproductive function in men with varicocele. The effectiveness of varicocelectomy was assessed 3–12 months post-surgery by examining changes in semen parameters and the rates of natural pregnancies and pregnancies achieved through assisted reproductive technologies (ART).

3. EAU/AUA guidelines and the 6th ed. of WHO manual for human semen analysis

The latest EAU and AUA guidelines, in conjunction with the ASRM, advocate for varicocele repair in non-azoospermic infertile men with palpable varicocele (grades I, II and III) and “abnormal” semen parameters [1, 11]. However, the specific criteria for defining these “abnormal” semen parameters remain unspecified in the guidelines.

The recent 6th edition of the WHO Manual for Human Semen Analysis aims to enhance the reliability of semen analysis by providing detailed instructions on laboratory procedures. Notably, while this edition includes reference limits, it emphasizes that these limits should not be construed as definitive thresholds separating fertile and infertile men. Instead, the manual explains the contextual use of these limits and underscores the complexity of interpreting semen parameters [22]. Thus, although varicocelectomy is advised for infertile men presenting with palpable varicocele and abnormal semen parameters as per the EAU/AUA guidelines, the precise sperm parameter(s) employed to ascertain the necessity for varicocele repair and to assess its effectiveness remain unspecified.

4. Recent role of the total progressively motile sperm count (TMSC)

A recent in-depth analysis of available evidence suggests that TMSC, combined with sperm concentration, could serve as important indicators of semen improvement and pregnancy outcomes following varicocele repair. Specifically, scrotal Doppler ultrasound (DUS) parameters, sperm DNA fragmentation index (DFI), and bilateral varicocelectomy have emerged as dependable predictors of success in terms of semen improvement with microsurgical varicocelectomy. Nevertheless, there remains inadequate evidence regarding predictors of efficacy for this technique concerning pregnancy and live birth occurrences [21].

Considering these discoveries, the inquiry arises regarding the allocation of subfertile men to either the surgical or observational cohort based on semen quality. Current evidence suggests that TMSC might offer superior insights into male fertility status compared to conventional semen parameters [23–25]. However, determining the boundary defining normal TMSC (or other semen parameters) where varicocele repair is unnecessary and abnormal TMSC persists as a challenge.

Another study conducted by Shomarufov *et al.* [20] uncovered an intriguing finding: among patients with initially high TMSC, semen quality might decline after undergoing varicocele repair. In their investigation encompassing 93 subfertile men diagnosed with clinical varicocele, deterioration in semen parameters was noted three months post-varicocelectomy in 27% of individuals with initially high TMSC, correlating with low pregnancy rates. Conversely, individuals with relatively low TMSC experienced notable enhancements in semen parameters and pregnancy rates. In addition, another study conducted by Greenberg *et al.* [26] revealed that TMSC decreased after varicocelectomy in men with initially larger left testis size and clinical grade III varicoceles.

These observations underscore the complexity of decision-making regarding varicocele repair in subfertile men and highlight the need for further research to elucidate optimal management strategies based on semen quality and other clinical parameters.

5. Varicocelectomy in patients with Isolated teratozoospermia

Teratozoospermia, also known as teratospermia, is a condition characterized by a high percentage of sperm with abnormal morphology in a semen sample. According to the World Health Organization (WHO) manual, a semen sample is considered teratozoospermic if less than 4% of sperm exhibit normal morphology based on Tygerberg strict criteria. These abnormalities can include defects in the head, midpiece or tail of the sperm, impacting its ability to fertilize an egg and thus reducing fertility. However, the recent WHO 2021 manual do not classify any semen sample as "teratozoospermic". The manual merely outlines the distribution of results from a mixed reference population [22]. This fact, in turn, contributes to the ambiguity surrounding the indications for varicocele repair.

Isolated teratozoospermia may also be considered for varicocele treatment according to the EAU/AUA Guidelines. However, recent studies present highly debatable results. For example, J. Choe *et al.* [27] showed that varicocelectomy may be beneficial for only 20% of subfertile men with clinical varicocele and isolated teratozoospermia. Also, B. Cakiroglu *et al.* [28] in their study showed no improvement in sperm morphology after varicocele treatment (morphology changed from 3.6 ± 1.6 to 3.7 ± 1.4, $p = 0.4$). Simultaneously, some studies approve varicocelectomy efficacy in infertile men with teratozoospermia. Recent retrospective study of A. Fathi *et al.* [29] demonstrated of varicocele surgery superiority over antioxidants treatment only in subfertile patients with isolated teratozoospermia in terms of sperm morphology improvement and natural pregnancy rates.

6. Postoperative management of subfertile men after varicocelectomy

Another question is how to manage patients who remain subfertile within 6–12 months after varicocele repair and what criteria should be considered in decision-making.

6.1 Prediction of varicocelectomy efficacy

According to some authors, using special prediction tools or nomograms may help specialists in decision-making regarding the management of couples who remain infertile after varicocele repair [20, 30–33]. M. Samplaski *et al.* [30] study showed that using special designed nomograms may assist specialist to predict the results of varicocele repair, and also to inform patients about the chances for varicocelectomy success [30, 34]. According to Shomarufov *et al.* [20], if a patient experiences "clinically significant improvement" (CSI), *i.e.*, an increase in TMSC of more than 12.5 million, this couple may wait for natural conception within 12 months. If it is less than this number, a couple may require intrauterine insemination (IUI) or even *in-vitro* fertilization (IVF) for conception. The authors also suggested a special tool (formula) to count the natural pregnancy chances after varicocelectomy.

Some studies demonstrate that clinicians can use TMSC as a tool for assigning infertile men for different management groups: active surveillance or natural conception group, IUI group and IVF group. According to M. Samplaski *et al.* [35] men with TMSC more than 9 million may be the candidates for natural conception, with TMSC between 5–9 million for IUI, and men with less than 5 million progressively motile sperm are the best candidates for IVF [35]. S. Cayan *et al.* [36] in their study suggested the same TMSC for IVF group (0–1.5 million for Intracytoplasmic Sperm Injection (ICSI) and 1.5–5 million for IVF), 5–20 million TMSC for IUI group and more than 20 million TMSC for natural pregnancy group [36].

Table 1 demonstrates the suggested postoperative care for subfertile patients after varicocele repair.

6.2 Antioxidant therapy after varicocele repair

Additionally, alternative support treatments such as nutritional or antioxidant therapy are used in the treatment of male subfertility after varicocele repair. According to a recent Cochrane Review by Smits *et al.* [37] and other authors, antioxidant supplementation in subfertile males may improve semen quality and live birth rates in infertile couples [37, 38]. Another meta-analysis provided by J. Wang *et al.* [39] concluded that compared with the placebo, the antioxidant therapy after varicocelectomy can improve the sperm parameters and reduce follicle stimulating hormone (FSH) levels. Study performed by P. Tsounapi *et al.* [40] suggest that micronutrient supplementation combined with avanafil administration or avanafil alone may increase significantly sperm motility.

Those evidences show that it may be reasonable to use additional antioxidant therapy in selected patients who experienced significant or any improvement in their semen but could not achieve a pregnancy within 6–12-month period after varicocele repair. Surely, in such cases we should consider oxidative stress and sperm DNA fragmentation levels as the indications for supplement therapy [41, 42].

7. New trends in varicocele surgery

Microsurgical subinguinal varicocelectomy is considered the "gold standard" method for varicocele repair due to its low complication rate and higher efficacy compared to other treatment options [6]. But, of course, progress in medicine does not stand still, and some novel surgical methods such as robotic-assisted microsurgical varicocelectomy and microsurgical varicocelectomy using video microsurgery platforms with angiography and lymphography (VITOM® 2D, 3D, visualization system, KARL STORZ SE, Tuttlingen, Germany) develop and begin to implement in daily urological/andrological practice.

TABLE 1. Postoperative management strategies for subfertile men.

Strategy	Description	Indications	Benefits	Limitations	References
Active Surveillance	Continuous monitoring of semen parameters to assess natural conception potential over time (in 6–12 months after varicocele surgery)	Men with significant improvement in semen parameters post-surgery	Non-invasive, cost-effective	Requires regular follow-up, no immediate action	Shomarufov *et al.* [20]
Intrauterine Insemination (IUI)	Introduction of processed sperm directly into the uterine cavity to facilitate fertilization	Men with moderate improvement in semen parameters	Higher pregnancy rates compared to natural conception	Requires medical intervention, may need multiple attempts	Samplaski *et al.* [35], Cayan *et al.* [36]
In Vitro Fertilization (IVF)	Laboratory-based fertilization of oocytes followed by embryo transfer into the uterine cavity	Men with minimal/no improvement in semen parameters or severe subfertility	Highest pregnancy rates among ART methods	High cost, invasive procedure, emotional and physical stress	Samplaski *et al.* [35], Cayan *et al.* [36]

ART: assisted reproductive technologies.

7.1 Robotic assisted microsurgical varicocelectomy

T. Shu *et al.* [43] firstly reported the series of robotic-assisted subinguinal varicocelectomy in 8 patients and demonstrated no difference in surgery time compared with the conventional microsurgical varicocelectomy, but they did not analyze the complications. Then S. Parekattil *et al.* [44] reported their results for robotic-assisted varicocelectomy in 154 patients and complications developed in 5 patients with the overall rate of 3.2% (from this recurrence rate was 1.3%, hydrocele rate was 0.6%). Also, recently, McCullough *et al.* [45] demonstrated results of single-surgeon experience in 140 men who underwent robotic-assisted varicocelectomy for infertility management. Mean surgery time for robotic-assisted versus routine microsurgical approach was 57 ± 16 min versus 49 ± 13 min per side (no information about p significance). Recurrence rate was 9.7%, that was substantially higher than given in the literature for the standard approach. Postoperative improvements were observed in sperm concentration [45]. The limitations of those studies are their retrospective nature, single-institution experience, and lack of comparison groups.

In addition, a systematic review of 31 articles on robotic-assisted microsurgery in andrology by Douroumis *et al.* [46] revealed promising outcomes for varicocelectomy, indicating potential advantages of robotic surgery in this field; however, large multicenter randomized trials are necessary to confirm its routine implementation.

7.2 Video microscopic varicocelectomy (VITOM® 2D/3D)

Most recently some authors reported about cases of microsurgical subinguinal varicocelectomy using VITOM® 2D/3D video exoscopes with or without angiography and lymphography [46–49]. Intra-operative indocyanine green angiography and lymphography assist surgeons to reveal simply arterial and lymph vessels and preserve them.

D. Amartya *et al.* [47] presented case of 43 years old subfertile male with clinical varicocele. Patient was discharged within 24 hours after surgery, and no early postoperative complications were recorded. Unfortunately, post-operative semen analysis was unavailable as the patient was lost to follow-up. Also, C. Cho [48] reported about two patients underwent varicocele repair for grade III varicocele in 2021 using the new platform. Operations were performed under three-dimensional (3D) optical magnification images on the television monitors using the video microsurgery platform with VITOM® 3D system (visualization system, KARL STORZ SE, Tuttlingen, Germany) with indocyanine angiography and lymphography. But they did not report about the outcomes of performed surgeries.

Compared to a surgical microscope, the video microscope is compact and provides the surgeon with a broader visual perspective, not confined to eyepieces. This flexibility enables seamless transitions between microscopic and non-microscopic procedures. Also, it creates a more ergonomic work environment for surgeons, eliminating the need to confine vision to an eyepiece. But, of course, considering the high-definition image is able to offer precise anatomical details, it still needs to be considered slightly inferior to the clarity achieved with a microscope [47–52].

The Table 2 provides a summary of novel techniques in varicocele treatment, detailing the technologies used, their descriptions, benefits, limitations and clinical outcomes.

Certainly, to fully adopt and clarify the practical value of the aforementioned novel techniques, further clinical trials are needed to compare their outcomes and costs with those of other validated surgical techniques for varicocele treatment.

8. Discussion

The management of varicocele in subfertile men remains a complex and evolving field, as highlighted by our review. Despite advances in understanding and treating this condition,

TABLE 2. New technologies in varicocele treatment.

Technology	Description	Benefits	Limitations	Clinical Outcomes	References
Robotic-Assisted Varicocelectomy	Uses robotic systems to perform varicocelectomy with enhanced precision.	Higher precision, reduced recovery time, improved ergonomics.	High cost, requires specialized training.	Improved sperm parameters, similar or slightly better than conventional methods.	Shu *et al.* [43], Parekattil *et al.* [44], McCullough *et al.* [45].
VITOM® 3D System	Provides 3D visualization of the surgical field using video exoscopes.	Enhanced visualization, ergonomic advantages for surgeons.	Slightly inferior image clarity compared to traditional microscopes.	Effective in preserving arterial and lymph vessels, comparable outcomes to traditional methods.	Amartya *et al.* [47], Cho & Chu [48, 49], Duarsa *et al.* [50], Pafitanis *et al.* [51], Hashim *et al.* [52].

VITOM: varicocelectomy; 3D: three-dimensional.

several significant challenges and uncertainties persist [53, 54].

Firstly, the lack of clear reference values for semen parameters in the latest WHO manual complicates the diagnosis and treatment of varicocele. The manual provides reference limits but emphasizes their contextual use rather than definitive thresholds for fertility. This ambiguity impacts clinical decisions, as practitioners need concrete guidelines to identify which patients would benefit most from varicocelectomy [22, 55–57].

Our review underscores the ongoing debate about the clinical value of total progressively motile sperm count (TMSC). While TMSC, combined with other semen parameters, appears promising in predicting outcomes post-varicocelectomy, more robust evidence from large-scale studies is needed. Current research suggests TMSC might offer better insights into male fertility status compared to traditional semen parameters [15, 24, 31, 58]. However, there is still a lack of consensus on the exact TMSC threshold that delineates the necessity for surgical intervention.

Additionally, the variability in preoperative clinical and laboratory parameters among patients presents another challenge. Factors such as age, BMI, and hormone levels can significantly influence the outcomes of varicocele repair. Acknowledging these intergroup discrepancies as minor study limitations is crucial for a comprehensive understanding of the treatment's efficacy [21, 34, 59].

The treatment of isolated teratozoospermia remains particularly contentious. Some studies show limited benefits of varicocelectomy in this subgroup, while others report significant improvements in sperm morphology and pregnancy rates. This disparity highlights the need for more targeted research to determine the specific circumstances under which varicocelectomy is beneficial for patients with teratozoospermia [28, 29, 60].

Postoperative management of subfertile men after varicocelectomy also requires further clarification. Identifying patients who would benefit from additional interventions, such as antioxidant therapy or assisted reproductive technologies (ART), is also very essential. The use of prediction tools and nomograms has shown promise in guiding these decisions, but their widespread adoption necessitates validation through large-scale clinical trials [20, 35, 36].

The emergence of new surgical techniques, such as robotic-assisted microsurgical varicocelectomy and video microscopic varicocelectomy using platforms like VITOM® 2D/3D, represents significant advancements. These methods offer enhanced precision and ergonomic benefits but also come with limitations such as high costs and the need for specialized training. Comparative studies are necessary to evaluate their efficacy and cost-effectiveness relative to traditional approaches [46, 50, 52, 61].

9. Conclusions

The topic of varicocele and male infertility is still debated with many unanswered questions. The EAU/AUA recommendations on varicocelectomy following the new WHO Manual (6th edition) are unclear and need immediate clarification. Establishing postoperative follow-up guidelines for subfertile patients who have undergone varicocele surgery is essential. Large-scale international clinical trials are needed to refine the indications for varicocele repair in male infertility treatment and to clarify the clinical value of novel varicocele treatment methods.

ABBREVIATIONS

WHO, World Health Organization; TMSC, total progressively motile sperm count; EAU, European Association of Urology; AUA, American Urological Association; ASRM, American Society of Reproductive Medicine; ART, assisted reproductive technologies; DUS, Doppler ultrasound, DFI, DNA fragmentation index; CSI, clinically significant improvement; IUI, intrauterine insemination; IVF, *in vitro* fertilization; ICSI, intracytoplasmic sperm injection; FSH, follicle stimulating hormone.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

AUTHOR CONTRIBUTIONS

AS—developed the study idea, designed it, collected and analyzed the data, and wrote the manuscript. FA—contributed to the critical review and approval of the final manuscript. SM—revised the draft. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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