



Varicocele and male infertility conundrum: Making sense of a never-ending story for the busy clinician

Parviz Kavoussi^{a,b}, Ponco Birowo^{b,c}, Ramadan Saleh^{b,d,e}, Rupin Shah^{b,f} and Ashok Agarwal^{b,g}

^aDepartment of Reproductive Urology, Austin Fertility & Reproductive Medicine/Westlake IVF, Austin, TX, USA; ^bGlobal Andrology Forum, OH, USA; ^cDepartment of Urology, Faculty of Medicine, Universitas Indonesia, Dr. Cipto Mangunkusumo Hospital, Jakarta, Indonesia; ^dDepartment of Dermatology, Venereology and Andrology, Faculty of Medicine, Sohag University, Sohag, Egypt; ^eAjyal IVF Center, Ajyal Hospital, Sohag, Egypt; ^fDivision of Andrology, Department of Urology, Lilavati Hospital and Research Centre, Mumbai, India; ^gCleveland Clinic Foundation, Cleveland, OH, USA

ABSTRACT

Background: Varicocele is a common occurrence, particularly among men with primary and secondary infertility. There has been extensive research into the management of varicocele in the context of male infertility.

Methods: This article aims to explore the variations in clinical practice in diagnosing and managing varicoceles in infertile men. A summary of the current recommendations on varicocele management from professional societies is included.

Results: Substantial gaps in knowledge persist regarding varicoceles and male infertility, with significant variation in clinical approaches, despite the wealth of existing data in the medical literature.

Conclusion: The existing literature leaves many questions surrounding varicocele management in infertile men unanswered. This lack of clarity contributes to the ongoing controversy among clinicians in the field. New research is essential to address these contentious points and areas of debate.

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Introduction

Varicocele is established to be the most common correctable cause of male infertility [1]. Varicoceles are present in approximately 15% of men in the general population and are diagnosed in 19% to 41% of men presenting with primary infertility and up to 80% of men presenting with secondary infertility [2]. The number of studies on varicoceles has demonstrated an upward trend from 1988 to 2018, and between 1998 and 2020 there has been a 4-fold increase in publications on surgical treatment for varicoceles, over non-surgical options [3,4]. Despite this level of focus in the medical literature and the apparent level of importance of varicoceles in male fertility, several aspects of the management of infertile men with varicoceles remain controversial. The aim of this minireview is to highlight the current state of varicocele research and conundrums related to the management varicoceles in infertile men.

Current status of varicocele research

Studies related to varicoceles have shown an increasing trend over the last few decades based on a scientometric analysis by Agarwal et al. [4]. Around

2000 original articles have been published to explore the relationship of varicoceles with male fertility. While the diagnosis, treatment, and prognostic aspects are mainly studied, a limited number of articles address epidemiology and pathophysiology of varicoceles. Hyperthermia, reactive oxidative stress, hypoxia and apoptosis, accumulation of toxins, and metabolite reflux are commonly suggested mechanisms underlying varicocele-induced male infertility [1,5]. However, the exact mechanism of varicocele-mediated male infertility is still unclear. There is also a lack of uniform criteria defining a varicocele, which may result in variable prevalence reported. The available published studies primarily focus on surgical treatments to assess the efficacy of varicocele treatment [4]. While some aspects of varicoceles are well established, various varicocele facets remain unanswered.

Current conundrum in the management of varicoceles in infertile men

Currently, a considerable amount of controversy surrounds the management of varicoceles in infertile men worldwide. Specifically, there is a lack of clear criteria for clinical and radiological diagnosis of varicoceles. Additionally, there is a lack of consensus on the

CONTACT Ashok Agarwal agarwaa32099@outlook.com Global Andrology Forum, Moreland Hills, Ohio 44022, USA

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benefits of varicocele repair (VR) for isolated sperm abnormalities such as asthenozoospermia, teratozoospermia, or high sperm DNA fragmentation (SDF) levels. The management becomes challenging when clinical varicoceles are found in the context of azoospermia or in conjunction with a contralateral subclinical varicocele. A recent survey of 574 clinicians selected for their expertise in male infertility practice, from 59 countries demonstrated divergent practice patterns in their response to an online questionnaire directed at the management of infertile men with varicoceles [6]. For example, nearly 10% (57/574) of the respondents indicated that they use imaging alone to diagnose varicoceles, where 18.6% (404/574) made the diagnosis of varicocele based on physical examination alone without ultrasonography, and the majority (70.4%, 404/574) used combination of a physical exam and ultrasonography. The American Urological Association (AUA)/American Society for Reproductive Medicine (ASRM) guidelines recommended that the diagnosis of varicocele be made on physical examination, reserving ultrasonography for cases in which physical examination is equivocal or difficult [7]. The European Association of Urology (EAU) agrees that the diagnosis of varicocele should primarily be based on physical examination but recommends the use of ultrasonography when varicocele palpation is unreliable or when semen parameters do not improve following VR and clinical varicocele persistence, or recurrence is suspected [8]. The survey by Shah et al. also demonstrated inconsistency in the criteria used to diagnose a varicocele by ultrasound [6]. In the latter survey, 56% of the respondents used a venous diameter of 3 mm to diagnose varicocele, while 29% used 2.5 mm, and 11.3% used 2 mm, as the diagnostic criteria. The AUA/ASRM guidelines use the criteria of multiple veins with a diameter >3 mm with reversal of blood flow during Valsalva for the diagnosis of a varicocele and do not specify a certain position for the patient during evaluation [7]. The EAU recommends a diameter of 3 mm or greater than the largest vein measured in the upright position during Valsalva with a venous reflux duration greater than 2 seconds to diagnose a varicocele [8].

The survey by Shah et al. also demonstrated diversity in practice patterns regarding indications for VR [6]. Of the survey respondents, 68.3% stated that they would repair a varicocele as the first-line treatment in a couple with moderate oligoasthenoteratozoospermia (OAT) and primary infertility. In couples with secondary infertility, 58.5% of respondents would directly proceed with VR. In men with severe OAT (sperm concentration < 1 mill/mL), 73.3% of the respondents indicated that they recommend VR as first-line treatment [6]. The AUA/ASRM guidelines recommend VR in infertile men with abnormal semen parameters, with the

exception of azoospermia [9]. The EAU guidelines expand on the indications for VR further to include some cases with non-obstructive azoospermia (NOA) and unexplained infertility [8]. In the study by Shah et al., 63% of survey respondents recommended VR for isolated asthenozoospermia, 41.1% for isolated teratozoospermia, 42.5% for severe necrozoospermia, and 34.7% for isolated increase of SDF [6].

When clinicians were asked about the technique they use for VR, 43.2% of the respondents indicated that they routinely use an operative microscope, while 26% use magnifying loupes and 2.6% of recommended varicocele embolization over surgical repair [6]. The AUA/ASRM guidelines recommend surgical VR with a preference for sub-inguinal microsurgical repair [9]. Similarly, the EAU guidelines consider microsurgical VR to be the most effective treatment with the lowest recurrence and complication rates [8]. However, high-level evidence from well-designed studies that compare different techniques for VR is lacking, and current recommendations are mainly based on observational studies or indirect comparison of clinical trials. Hence, the EAU guidelines stated that the other techniques are 'viable options' as well [8].

Discrepancy among practitioners was also evident in the in follow-up protocols after VR, with 14.8% of clinicians recommending post-operative ultrasounds, while 21.7% never used it during follow-up, and the remaining proportion indicated that they used scrotal ultrasound conditionally [6].

Insights for future research to overcome varicocele conundrum

New research is warranted to address several clinical questions related to varicoceles including exact criteria of sonographic diagnosis of varicocele and the role of VR in selected cases with isolated sperm abnormalities such as asthenozoospermia, teratozoospermia, or elevated SDF [6]. Additionally, future research is needed to assist clinical decisions in subsets of infertile men that present with clinical varicoceles and azoospermia. Further, well-designed clinical trials are needed to compare different techniques of VR [10]. Moreover, new research may expand to investigate the efficacy of doppler-assisted microsurgical VR compared to those without doppler. The update on the studies should be translated into professional guideline recommendations. Finally, creating a registry and a large database on varicoceles can be beneficial for further comprehensive analysis. Addressing these issues will help better management of varicocele in infertile men and improve reproductive outcomes [4]. Prospects for research into this very controversial condition.

Clinical case scenarios

Case 1

A 33-year-old man presented with a history of secondary infertility of 3 years duration. His wife is 29 years old and has no fertility issues. Bilateral grade 2 varicocele were found during physical examination without any other genital abnormalities. The patient underwent an ultrasound, which revealed prominent veins measuring 3.5 mm in diameter and 2 seconds of reflux during the Valsalva maneuver. Both testes appeared normal on ultrasound. Hormonal assessment was normal. Semen analysis was normal, including the SDF rate.

Management

Diagnosis of varicocele should be based on physical examination unless there is an uncertainty. Based on the recommendations of EAU and AUA/ASRM, VR can be offered to infertile men with clinically palpable varicocele and abnormal semen analysis [7,8]. Currently, there is no evidence to perform VR in normozoospermic men with clinical varicocele. In the current case, the wife may be counselled to seek further gynecological evaluation.

Case 2

A 38-year-old man presented with a history of primary infertility of 4 years duration. His 31-year-old wife has no remarkable fertility issues based on a gynecologist's assessment. During physical examination, bilateral testicular atrophy with bilateral grade 3 varicocele were noted. The scrotal ultrasound showed multiple refluxing veins bilaterally with diameters of 4 mm, and testicular volume of 4 cc on both sides. The hormonal assessment in serum showed follicle-stimulating hormone level of 18.7 mIU/mL (reference value (RV) = 1.5–12.4 mIU/mL), luteinizing hormone level of 5.7 mIU/mL (RV = 1.7–8.6 mIU/mL) and testosterone level of 4.91 mIU/mL (RV 4.94–32.0 ng/mL). Repeat semen analysis revealed azoospermia. No chromosome abnormalities or Y chromosome microdeletions were identified.

Management

The AUA/ASRM guidelines do not recommend VR in infertile men with NOA [9]. However, the EAU guidelines suggest VR for some cases of NOA and recommend the discussion of risk and benefit with the patient [8]. Therefore, this couple should be informed about the existing controversy and lack of strong evidence supporting VR in presence of NOA. Generally, three options can be offered to patients presenting with NOA and clinical varicocele. First: conduct VR before sperm retrieval with the potential to have sperm recovery in the ejaculate. Studies have shown that VR for NOA can result in sperm appearing in ejaculate or at least reducing the need for ART and

opting for less invasive procedures [11,12]. However, this benefit may not be evident in men with Sertoli-cell only compared to those with hypospermatogenesis and maturation arrest [12]. Second: concomitant VR with surgical sperm retrieval. Third: proceeding directly to sperm retrieval and ART. In the present case, offering VR before sperm retrieval is acceptable as the female partner is still 31 years old and presumably still has a good ovarian reserve and, therefore, has the time to wait for a minimum of 6 months to get sperm in the husband's ejaculate. If the wife is older than 35 years, direct approach to ART should be considered to avoid further delay [13].

Case 3

A 34-year-old man presented with a history of primary infertility of 2 years duration. His wife is 29 years old and has a tubal factor infertility that needed her to undergo an assisted reproductive technique to achieve pregnancy. Upon physical examination, grade 2 bilateral varicoceles were identified. On the semen analysis, the sperm concentration was less than 10 million/ml with normal morphology and motility. He also had an SDF rate of 38% based on the TUNEL test.

Management

Although the present EAU and AUA/ASRM guidelines do not clearly state the contraindication of varicocele repair based on female factor [8,9], the previous guideline of AUA/ASRM in 2012 recommends against varicocele repair if in vitro fertilization (IVF) is indicated due to a female factor [14]. In the present case, the patient had an abnormal sperm concentration, high SDF rate, and clinical varicocele. Varicocele repair has proven to improve semen quality, including sperm concentration, and lower the SDF rate [15,16]. A previous meta-analysis demonstrated that a high SDF rate had a detrimental effect on implantation and pregnancy rates in IVF and intracytoplasmic sperm injection [17]. However, as there is no clear recommendation from the professional guidelines, therefore; varicocele before ART should be performed after counseling the patient, including its pros and cons.

Case 4

A 36-year-old man presented with a history of secondary infertility of 4 years duration. His wife is 31 years old and has no remarkable fertility issues based on a gynecologist assessment. The patient had a varicocele repair performed a year prior which was not performed microsurgically. Compared to the semen analysis before varicocele repair, the result of semen analysis after varicocele repair showed only slight improvement, and he remained in the

Table 1. Summary of EAU and AUA/ASRM guidelines for diagnosis and treatment of varicocele in infertile men.

Category		EAU 2023 (Salonia, 2023)	[7,9,14]
Diagnosis	Clinical assessment	Primarily based on physical examination	Should mainly be based on physical examination
	Ultrasound Usage	Use ultrasound if palpation is unreliable or when recurrence or persistence is suspected	Discourage routine use of ultrasound to investigate varicocele Ultrasound is used in the case of difficult physical examination
	Criteria of ultrasound for varicocele diagnosis	Venous diameter of 3 mm or more of the largest vein measured at any location in the upright position during a Valsalva maneuver and with venous reflux of duration >2 seconds	Multiple veins with a diameter >3 mm and reversal of blood flow during Valsalva
Treatment Indication	Subclinical varicocele	Against	Against
	Normal semen analysis	Against	Against
	Oligoasthenoteratozoospermia	Yes	Yes
	Isolated teratozoospermia	No recommendation	No recommendation
	Isolated asthenozoospermia	No recommendation	No recommendation
	Isolated necrozoospermia	No recommendation	No recommendation
	High sperm DNA fragmentation	Yes in case of previous failed ART after extensive counselling	Optional before In-vitro fertilization and if there is a history of recurrent pregnancy loss
Azoospermia	Acknowledge the benefit of VR although risk and benefit should be fully discussed with the patient	Against	
Treatment modality	Technique of varicocele Repair	Microsurgical varicocelectomy considered to be the most effective although other techniques are viable options	Microsurgical varicocelectomy

EAU: European association of urology. AUA: American urological association. ASRM: American society for reproductive medicine.

oligoasthenoteratozoospermia (OAT) range. The couple still failed to conceive with timed intercourse. Genital evaluation and hormonal assessments are within normal limits otherwise.

Management

In the case of no improvement in semen analysis parameters after varicocele repair, it is advised to do an ultrasonography assessment to assess varicocele recurrence or persistence [8]. Among all the types of varicocele repair procedures, microsurgical varicocele repair had the lowest rate of recurrence and complications [8]. The major reason for varicocele recurrence is the branch of internal spermatic veins that are not ligated and are mainly above the sublingual area [18]. The ideal treatment for varicocele recurrence is arguable; however, clinicians mostly employ different approaches from the initial treatment [19]. Expert opinions from the Global Andrology Forum recommend ligating all the spermatic veins. Repeat surgery at the sub-inguinal or inguinal level if the initial varicocele repair was performed using a high ligation approach. Conversely, if the initial varicocele repair started in the subinguinal approach, repeated surgery can be done at a lower level but is more complicated. In this case, venographic occlusion via embolization or inguinal approach can be considered [6].

Key points

- Varicocele remains a hot topic in andrology being the most common correctable cause of male infertility.
- Current literature fails to answer many questions related to the management of varicocele in infertile men. This may explain, at least in part, the significant controversy in practice of varicocele among clinicians.

- A correct approach to diagnosing and treating varicocele is crucial and weighing the pros and cons of VR in infertile men with varicocele based on the scientific evidence is pivotal.
- With the constantly evolving new research, the discussion on varicocele will continue to be intriguing and provoking by most clinicians involved in male infertility management.

Experts' comment

In the era of evidence-based medicine, clinicians treating infertile men with varicocele should rely on the best available research evidence as well as the updated guidelines of the professional societies. Summary of EAU and AUA/ASRM guidelines for diagnosis and treatment of varicocele is provided in Table 1. The diagnosis of varicoceles should be based primarily on physical examination, with ultrasound being reserved for cases of challenging physical examination. Ultrasound is not recommended in the routine postoperative follow up, but may be indicated if physical examination is suggestive of persistence or recurrence of varicocele or if semen parameters have not improved after surgery. Varicocele repair is indicated in infertile men with OAT. The standard of care technique for VR is the subinguinal microsurgical approach as it offers the best outcomes with the lowest recurrence and complication rates but should be limited to surgeons with microsurgical expertise.

Abbreviation

ART	assisted reproductive technique
ASRM	American Society for Reproductive Medicine
AUA	American Urological Association

EAU	European Association of Urology
NOA	non-obstructive azoospermia
RV	reference value
SDF	sperm DNA fragmentation
VR:	varicocele repair

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ORCID

Ashok Agarwal  <http://orcid.org/0000-0003-0585-1026>

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