Review Article
Male reproductive health and infertility

pISSN: 2287-4208 / eISSN: 2287-4690
World J Mens Health 2025 Oct 43(4): 748-757
https://doi.org/10.5534/wjmh.240290

The World Journal of MEN's HEALTH

Recent Guidelines and Perspectives for Varicocele: A Clinical Consensus and Recommendations from the Korean Society for Sexual Medicine and Andrology

Dae Keun Kim[1,*], Dong Soo Kim[2,*], Sung Chul Kam[3], Hyo Serk Lee[4], Won Ki Lee[5], Seung-Hun Song[6]; Korean Society for Sexual Medicine and Andrology Clinical Practice Guideline Committee

[1]Department of Urology, CHA Fertility Center Seoul Station, CHA University School of Medicine, Seoul, Korea, [2]Department of Urology, Kyung Hee University College of Medicine, Seoul, Korea, [3]Department of Urology, Gyeongsang National University Changwon Hospital, Changwon, Korea, [4]Department of Urology, JTS Urology Center, Seoul, Korea, [5]Department of Urology, Hallym University College of Medicine, Chuncheon, Korea, [6]Department of Urology, CHA Gangnam Medical Center, CHA University School of Medicine, Seoul, Korea

Varicocele is a common urological disease and varicocele has long been recognized as a condition that could affect male fertility. Although varicocele is the most common surgically correctable cause of male infertility, not all varicoceles require treatment. Because the appropriate diagnosis and management of varicoceles remain less clear in many patients, it is important to diagnose clinically significant varicoceles that can benefit from treatment. Even in the era of widespread assisted reproductive techniques, varicocele has substantial implications in infertility treatment. The Korean Society for Sexual Medicine and Andrology (KSSMA) has sought to develop guidelines for varicocele treatment tailored to clinical practices in Korea. This review summarizes the latest evidence for varicocele treatment, including clinical practice guidelines from various international professional societies, and represents the consensus opinion of experts within the KSSMA.

Keywords: Azoospermia; DNA fragmentation; Infertility, male; Reproductive techniques, assisted; Varicocele

INTRODUCTION

Varicocele is a common urological disease that can affect male fertility. The association between varicocele and male infertility dates back to the first century AD, recognized by Celsius, who described dilation of scrotal veins and reported an association between a varicocele and testicular atrophy. Since a case on spontaneous pregnancy after varicocele repair was first reported by Tulloch [1] in 1955, numerous studies on varicocele have been published worldwide [2-4]. Although varicocele remains the most common surgically correctable cause of male infertility, not all varicoceles require treatment. Because the appropriate diagnosis and management

Received: Dec 15, 2024 **Revised:** Jan 1, 2025 **Accepted:** Jan 8, 2025 **Published online** Feb 25, 2025
Correspondence to: Seung-Hun Song https://orcid.org/0000-0003-4649-9129
Department of Urology, CHA Fertility Center Gangnam, CHA Gangnam Medical Center, 566 Nonhyeon-ro, Gangnam-gu, Seoul 06135, Korea.
Tel: +82-2-3468-3413, **Fax:** +82-2-3468-3449, **E-mail:** shsong02@cha.ac.kr
*These authors contributed equally to this work as co-first authors.

of varicoceles remain less clear in many patients, and because the likelihood of spontaneous regression after initial development is low, appropriate clinical guidelines on the proper diagnosis and treatment of varicocele are necessary. The Korean Society for Sexual Medicine and Andrology (KSSMA) has reviewed international clinical guidelines on the diagnosis and treatment of varicocele, as well as the most recent perspectives on its management. This review aimed to provide clinical recommendations on varicocele based on the consensus opinion of an expert panel of the KSSMA, including the definition of this condition and diagnosis and treatment protocols.

METHODS

A project team belonging to the Committee of Clinical Practice Guideline of the KSSMA searched the PubMed and MEDLINE databases for studies related to varicocele. The team also referred to the most recent clinical guidelines for varicocele formulated by the European Association of Urology (EAU), the American Urological Association (AUA), and the American Society for Reproductive Medicine (ASRM). The Korean guidelines were subsequently revised based on the advice and agreed opinions of domestic experts. These guidelines have been approved by the KSSMA and the Association of Korean Urologists.

EPIDEMIOLOGY

1. Definition and epidemiology

Varicocele is defined as excessive dilatation of the pampiniform venous plexus of the spermatic cord. Varicocele is known to affect approximately 10% to 20% of the general male population, including about 35% to 40% of men with primary infertility and 45% to 80% of men with secondary infertility [5,6]. Varicocele occurs mostly on the left side as the gonadal vein inserts into the left renal vein at a nearly perpendicular angle with increased hydrostatic pressure while on the right the gonadal vein less abruptly drains into the inferior vena cava. Varicocele generally develops during puberty, accompanying the rapid body growth during that period. The prevalence of varicocele in prepubertal boys aged <10 years is less than 1%, increasing to about 10% to 14% in adolescent boys aged 15 to 19 years [7,8].

2. Pathophysiology

The exact mechanisms by which varicocele can ultimately lead to male infertility are not fully understood; however, the main pathophysiologic mechanisms include increased scrotal temperature, hypoxia, and reflux of toxic metabolites caused by varicocele. Excessive production of reactive oxygen species (ROS) may also be an important pathogenic factor throughout the course of varicocele. The temperature of the human testes is approximately 2 to 3 ℃ lower than the core body temperature to facilitate the ongoing hypermetabolic processes in the testes. Varicoceles have been reported to increase scrotal temperature, which could disrupt the intratesticular microenvironment and impair normal spermatogenesis. Markers of hypoxia are increased in dilated veins of patients with varicocele, with increased pressure in the internal spermatic vein thought to induce testicular tissue ischemia. The reflux of renal and adrenal metabolites into the spermatic vein may also contribute to varicocele pathophysiology. Varicocele may have a negative effect on Sertoli cell and Leydig cell functions, resulting in a perturbation in the hypothalamic-pituitary-gonadal axis with decreased testosterone levels ultimately affecting spermatogenesis. Studies using animal model have shown that experimental varicocele led to subsequent reductions in blood and intratesticular testosterone levels [9-12].

3. Summary and recommendation

Varicocele is defined as excessive dilatation of the pampiniform venous plexus of the spermatic cord. Varicocele affects approximately 10% to 20% of the general male population, including about 35% to 40% of men with primary infertility and 45% to 80% of men with secondary infertility. The main pathophysiologic mechanisms include increased scrotal temperature, hypoxia, reflux of toxic metabolites and excessive ROS production.

DIAGNOSIS

1. Physical examination

Meticulous physical examination is crucial in the diagnosis of a varicocele. Abnormalities in the testicles and spermatic cord can also be detected by palpation. Large varicoceles are easily identified by simple inspection alone and may feel or look like a 'bag of worms.' Although most varicoceles are asymptomatic,

some patients may present with a dull pain localized to the scrotum. When a varicocele is suspected but not obviously palpable, a Valsalva maneuver in the standing position is recommended. Clinical varicoceles are generally classified according to the system of Dubin and Amelar: A grade III varicocele is large and visible without palpation. A grade II varicocele is moderate in size and palpable when standing without a Valsalva maneuver. A grade I varicocele is smaller and is only palpable with a Valsalva maneuver. A subclinical varicocele cannot be detected by physical examination, but is only identified on ultrasound examination. However, substantial inter-observer and intra-observer discrepancies are noted in the diagnosis and the grading of varicoceles by physical examination. Accurate physical examination of scrotum sometimes may be difficult in an obese patient or when the dartos muscle remains contracted, even in a warm room. In these patients, color Doppler ultrasound is useful for evaluation of the spermatic cord veins.

2. Imaging test

Although assessment of varicocele by Doppler ultrasound is more objective than detection by physical examination, Doppler ultrasound is not recommended as a routine practice. Rather, Doppler ultrasound is generally recommended for patients with an uncertain diagnosis of varicocele by physical examination and those with persistent or recurrent varicoceles after corrective surgical treatment. On ultrasonography, a varicocele appears as a hollow, tubular structure that becomes larger during a Valsalva maneuver. Testicular volume can be calculated using Lambert's formula (V=L×W×H×0.71). Although there are no standard and clearly defined consensus criteria for diagnosing varicocele by ultrasound, venous dilation >3 mm and venous reflux flow >2 seconds on ultrasound after a Valsalva maneuver have been considered diagnostic of varicocele by most clinicians [13-16]. Of several ultrasound-based varicocele grading systems, the most widely accepted is the Sarteschi grading system. This system categorizes varicoceles into five grades according to the venous reflux during the Valsalva maneuver in supine and erect positions at three anatomical sites: the inguinal, supratesticular and peritesticular areas (Table 1) [17]. An isolated right-sided varicocele is a rare condition, the underlying causes of which can be identified by abdominal imaging, with several case reports finding that the underlying causes were retroperitoneal abnormalities including malignancy. The quality of this evidence, however, is insufficient to support a recommendation for additional abdominal imaging due to isolated right-sided varicoceles [18].

Table 1. Sarteschi's classification of varicocele

Grade	Feature
1	Reflux in vessels in the inguinal channel is detected only during the Valsalva maneuver, while scrotal varicosity is not evident in the standard US study
2	Small posterior varicosities that extend to the superior pole of the testis. Their diameters increase and venous reflux is seen in the supratesticular region only during the Valsalva maneuver
3	Vessels appear enlarged at the inferior pole of the testis when the patient is evaluated in a standing position; no enlargement is detected if the patient is examined in a supine position. Reflux observed only under during the Valsalva maneuver
4	Vessels appear enlarged even when the patient is studied in a supine position; the dilatation is more marked in the upright position and during the Valsalva maneuver. Testicular hypotrophy is common at this stage
5	Venous ectasia is evident even in the prone decubitus and supine positions. Reflux is observed at rest and does not increase during the Valsalva maneuver

3. Semen analysis

Semen analysis is recommended for accurate evaluation of treatment indications in men with clinical varicocele. Semen analysis provides primary information about a man's fertility status, with this information serving as a reference for classifying infertile male patients and planning for secondary tests and further treatment. The World Health Organization (WHO) manual has set worldwide standards for semen analysis, with the latest guidelines published in 2021 (Table 2) [19]. The WHO guidelines set the lower fifth percen-

Table 2. The World Health Organization (WHO) reference manual for semen analysis

Semen parameter	WHO 5th (2010)	WHO 6th (2021)
Semen volume (mL)	≥1.5	≥1.4
Sperm concentration ($\times 10^6$/mL)	≥15	≥16
Total sperm count ($\times 10^6$)	≥39	≥39
Total motility (%)	≥40	≥42
Progressive motility (%)	≥32	≥30
Vitality (%)	≥58	≥54
Normal morphology (%)	≥4	≥4

tile of distribution of values from men with proven fertility as a threshold limit for normal semen parameters. A comprehensive interpretation is necessary by taking into consideration of other factors, because one or two abnormal semen parameters cannot definitively distinguish between fertility and infertility. Endocrine evaluation, including measurement of serum reproductive hormone levels such as testosterone, follicle stimulating hormone (FSH) and luteinizing hormone (LH), is recommended for men with varicocele who show clinical signs or symptoms of endocrinopathy.

4. Summary and recommendation

Meticulous physical examination is crucial in the diagnosis of a varicocele. Doppler ultrasound is generally recommended when physical examination alone results in an uncertain diagnosis of varicocele. Semen analysis is recommended for accurate evaluation of treatment indications in men with clinical varicocele. Men with varicoceles who show clinical signs or symptoms of endocrinopathy should undergo endocrine evaluation, including measurement of serum reproductive hormone levels such as testosterone, FSH and LH.

TREATMENT

Indications for varicocele treatment include persistent scrotal pain despite conservative measures, infertility combined with abnormal semen parameters, and testicular atrophy in adolescent males (>20% reduction in testicular volume). Pain has been frequently associated with varicoceles, often described as being of a dull nature that may worsen with long standing or physical exertion. Because scrotal pain from varicoceles is seldom successfully managed with conservative therapy alone, patients with consistent pain with clinical varicocele should be offered varicocele repair. The overall response rate to varicocele repair for scrotal pain is approximately 80%. Varicocele has shown a detrimental impact on male reproductive capacity, with proper treatment of clinically significant varicoceles resulting in significant improvements in semen parameters and a chance of successful conception [20-22]. Most patients with varicoceles during adolescence, however, do not have fertility problems during adulthood, and surgical correction of varicoceles has shown no benefits in patients with subclinical varicocele or normal semen parameters. Therefore, it is important to diagnose clinically significant varicocele that could benefit from treatment. AUA/ASRM and EAU guidelines on the association between varicocele and male infertility have been recently updated [23-25].

1. AUA/ASRM guidelines

a. Surgical varicocelectomy should be considered in men attempting to conceive, who have palpable varicocele(s), infertility, and abnormal semen parameters, except for azoospermic men. (Moderate Recommendation; Evidence Level: Grade B)
b. Clinicians should not recommend varicocelectomy for men with non-palpable varicoceles detected solely by imaging. (Strong Recommendation; Evidence Level: Grade C)
c. For men with clinical varicocele and non-obstructive azoospermia (NOA), couples should be informed of the absence of definitive evidence supporting varicocele repair prior to assisted reproductive technology (ART). (Expert Opinion)

2. EAU guidelines

a. Treat infertile men with a clinical varicocele, abnormal semen parameters, or otherwise unexplained infertility in a couple in which the female partner has a good ovarian reserve to improve the fertility rate. (Strong)
b. Varicocelectomy may be considered in men with raised sperm DNA fragmentation (SDF) with otherwise unexplained infertility or who have suffered from failed ART, including recurrent pregnancy loss or failure of embryogenesis and implantation. (Weak)

The majority of published studies regarding the varicocele repair have shown that treatment of clinical varicoceles improves sperm parameters and enhance both pregnancy and live birth rates. A recent meta-analysis found that pregnancy rates were significantly higher in the partners of men who did than did not undergo surgical repair of clinical varicocele [26]. Compared with a pregnancy rate without treatment of 17%, pregnancy rates for men who underwent subinguinal microsurgical varicocelectomy and inguinal microsurgical varicocelectomy were 42% (95% CI, 26%–61%) and 35% (95% CI, 21%–54%), respectively, whereas those for men who underwent laparoscopic surgery were 37% (95% CI, 19%–61%). A recent Cochrane review also reported that treatment of varicocele in men with un-

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explained subfertility significantly improved spontaneous pregnancy rates (OR 1.47, 95% CI, 1.05–2.05; p=0.03, I^2=67%) [27]. These studies, however, did not measure birth rates and had a low level of evidence. A systematic review and meta-analysis regarding subclinical varicocele showed that varicocele repair had no demonstrable benefits on pregnancy rates or on seminal parameters [28]. These findings highlight the importance of the appropriate diagnosis and treatment of clinically significant varicoceles [29].

3. Treatment methods

Various methods have been used for treatment of varicocele over the past decades. They can be categorized as open surgery, laparoscopic surgery, and radiographic venous embolization, with each having advantages and disadvantages. Varicocele repair has been reported to improve semen parameters by 60%–80%, and spontaneous pregnancy rates by 26%–37%. Surgical repair for scrotal pain was found to have a success rate of approximately 80% [30,31]. The main principles of surgical management are ligating all relevant spermatic veins while preserving the testicular arteries and lymphatics. Micro-Doppler ultrasonography could be applied for better identification of the testicular arteries during surgery. Surgical techniques can be subclassified into retroperitoneal, inguinal, and subinguinal approaches according to the incision site. Subinguinal microscopic varicocelectomy allows surgical repair without opening the aponeurosis of the external oblique muscle, facilitating faster recovery and less postoperative pain. This lower-level approach, however, requires the ligation of greater numbers of spermatic veins and small spermatic veins surrounding the testicular arteries. Advantages of inguinal microsurgical varicocelectomy include the need to ligate fewer internal spermatic veins, due to the proximal merge of vessels, and fewer distal arterial tributaries, enabling the surgeon to deal with fewer vascular branches and simplifying the operation [32-36]. The principles of laparoscopic surgery are similar to those of the posterior retroperitoneal approach. Laparoscopy allows clear visualization of the testicular arteries and lymphatic vessels, enabling the simultaneous treatment of bilateral varicoceles using a single laparoscopic port. Laparoscopy has drawbacks, however, including relatively higher recurrence and hydrocele rates [37,38]. Radiologic varicocele embolization is a minimally invasive option for treatment of varicocele, with advantage of lesser postoperative pain and lower risk of hydrocele formation than surgical repair. Proper access and navigation of the catheter into the spermatic vein under fluoroscopic guidance is required for successful embolization. Failure to access this vein has been observed in 8% to 30% of patients undergoing radiologic percutaneous varicocele embolization [39,40]. Moreover, although very rare, embolic materials might migrate, leading to renal vein obstruction or pulmonary embolism. In consideration of the risks of higher recurrence, radiation exposure and failure to access the spermatic vein, radiologic varicocele embolization is not generally recommended as a first-line treatment method for varicoceles.

The AUA/ASRM guidelines recommend microscopic varicocelectomy using a surgical microscope as the standard treatment. Similarly, EAU guidelines regard microsurgical varicocelectomy as the most effective treatment with the lowest recurrence rate. Radiologic percutaneous embolization is often recommended as a minimally invasive procedure for patients with recurrent varicocele following an initial treatment due to its relatively high recurrence rate and the risk of complications [24].

4. Recurrence of varicocele

Factors associated with varicocele recurrence after treatment include the surgical techniques employed, the surgeon's experience, and, most importantly, incomplete ligation of smaller internal spermatic veins. Incomplete ligation of the cremasteric and gubernacular veins may also be responsible for varicocele recurrence. To minimize recurrence, careful dissection and complete ligation of all spermatic veins need to be performed and ligation should be done for the cremasteric veins, simultaneously. Several researchers suggested that ligation of the gubernacular veins may not be always necessary [41]. The higher recurrence rates observed with the open retroperitoneal and laparoscopic varicocele repair has been suggested to stem from the inability to ligate the external spermatic veins in these procedures. Scrotal Doppler ultrasonography is recommended to detect varicocele recurrence when there is no improvement after treatment. Treatment of recurrence is dependent on the initial method. For example, if the initial method had been a high ligation, such as Palomo technique (retroperitoneal approach), a subinguinal approach would be preferred. If, however, a

subinguinal approach had been used for primary treatment, percutaneous embolization or inguinal varicocelectomy would be preferred [42].

5. Summary and recommendation

Indications for varicocele treatment include persistent scrotal pain despite conservative measures, infertility combined with abnormal semen parameters, and testicular atrophy in adolescent males (>20% reduction in testicular volume). Approaches used to treat varicocele include open surgery, laparoscopic surgery, and radiographic venous embolization. Microscopic subinguinal or inguinal varicocelectomy is recommended as the standard treatment, as this approach has shown the highest success and lowest recurrence rate.

RECENT PERSPECTIVES

1. Adolescent varicocele

Adolescent varicocele is one of the highly debated topics in pediatric urology field. Varicocele usually develops in early puberty during a growth spurt and prepubertal varicocele is rare. Adolescent varicocele is mostly asymptomatic and often incidentally noted by patients themselves or by a primary care provider [43,44]. While the main goal of varicocele treatment in adults is to improve fertility capacity, the objective in adolescents is to prevent further testicular damage and safeguard future fertility [45]. However, standardized criteria for the diagnosis and management of adolescent varicocele are difficult to establish, as adolescent males show rapid physical growth and constant hormonal changes during puberty [46-49]. Most pediatric urologists suggest the correction of varicocele in adolescents with a persistent testicular volume discrepancy >20%, abnormal results on semen analysis, and scrotal pain. Testicular catch-up growth is commonly used to assess the effects of varicocele surgery in adolescents, as semen analysis is difficult to perform in adolescents. Approximately 60% to 90% of patients with affected testes show normal testicular growth after varicocele repair [50,51]. Because most previous studies on adolescent varicocele have been limited by their retrospective nature and the relatively small sample size, large, well-designed prospective studies are warranted [52,53]. Therefore, therapeutic directions for the treatment of adolescent varicocele should be established by comprehensively considering multiple related parameters, such as accompanying pain, the degree of scrotal asymmetry, the results of semen analysis, and hormone levels. Adolescents with varicocele are recommended to be monitored for testicular development for at least 6-12 months to allow for potential spontaneous growth before surgical intervention.

2. Subclinical varicocele

Although the need to treat subclinical varicocele remains unclear, very limited evidence suggests that this treatment may have beneficial effects. A few studies reported that repair of subclinical varicocele has showed improvement in some semen parameters; however, these findings have been limited by differences among studies in diagnosis and treatment methods and included subjects [54,55]. Certain investigators have described subclinical varicocele as a para-physiological condition rather than a definite pathologic condition. Therefore, there is no solid evidence that repair of subclinical varicocele is effective in improving semen parameters and pregnancy rates. The AUA/ASRM and EAU guidelines do not recommend treatment of men with subclinical varicocele, nor do they recommend the use of scrotal ultrasonography to identify non-palpable varicoceles [24-56].

3. Varicocele and sperm DNA fragmentation

In recent years, there has been a growing body of research investigating the role of sperm nuclear DNA integrity in male factor infertility and SDF has become as a useful indicator of sperm function and a potential predictor of reproductive outcomes. Sperm DNA damage is known to be caused by various factors, including high temperature, smoking, chemotherapy, and exposure to radiation. Several tests are available to assess different aspects of sperm DNA integrity such as sperm chromatin dispersion (SCD) test, TUNEL assay, and Comet assay [57]. Many previously published investigations have reported that varicocele repair could achieve a significant improvement in SDF [58,59]. It has been reported to reduce SDF by 6.14% to 7.23%, suggesting that active treatment of varicocele is recommended for men with elevated SDF and ART failure [60-62]. The quality of this evidence, however, was insufficient to show that varicocele repair improved pregnancy and live birth rates [63,64]. Currently, no data exists with regard to specific levels of SDF improvement associated with improved pregnancy rates.

Main limitation of SDF testing is that there remains no consensus on the optimal SDF technique or appropriate clinical cut-off levels. AUA/ASRM guidelines do not recommend SDF analysis in the initial evaluation of infertile couples. Currently, evidence for varicocele treatment in patients with elevated SDF levels coupled with normal semen parameters is still limited. Therefore, sufficient discussion with each patient is warranted before performing varicocele repair in these men.

4. Varicocele in the era of assisted reproductive technology

Assisted reproductive technology such as in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) has become globally available for infertile couples, including those with male factor infertility. ART, however, has potential side effects and risks, such as ovarian hyperstimulation, multiple gestation, and premature birth. A number of studies have investigated the potential benefits of varicocele repair in combination with ART [28,65,66]. Varicocele repair before ART has been recommended because varicocele repair is a relatively simple and less expensive procedure than ART. Furthermore, varicocele repair may be able to improve semen quality and facilitate spontaneous pregnancies or enhance the success rate of ART. Varicocele repair before ART for infertility should be performed if 1) the clinical varicocele is palpable; 2) the couple has known infertility; 3) the female partner is normal or has a potentially treatable cause of infertility; and 4) the male partner has abnormal semen parameter(s). Because improvements in semen quality generally require 3 to 6 months after varicocele treatment, varicocele treatment may delay the timing of ART procedures [67-70]. Most women begin to experience a significant decrease in fertility around age of 37 years due to ovarian aging. In couples of advanced female age, varicocele repair and ART procedures may be performed simultaneously. In this way, ART is not delayed and, even if ART is unsuccessful, the couple could benefit from the positive effect of varicocele repair. Therefore, the decision for undergoing varicocele repair before ART has to be made individually based on other contributing factors, such as age of female partner, ovarian reserve, history of prior IVF failure, varicocele grade, and duration of infertility [56].

5. Varicocele repair in patients with non-obstructive azoospermia

NOA, in which impaired spermatogenesis leads to permanent male infertility, is the most severe of all male reproductive disorders. Most medical therapies are ineffective, with the only proven treatment option being the surgical acquisition of mature spermatozoa, followed by IVF/ICSI. Varicocele repair in men with NOA was recently reported to result in reappearance of sperm in the ejaculated semen [71]. The finding of even a small number of sperm is sufficient to avoid invasive microsurgical testicular sperm extraction (micro-TESE) surgery for IVF/ICSI. Even if ejaculated sperm cannot be acquired, varicocelectomy might increase the sperm retrieval rate (SRR) during micro-TESE. A recent meta-analysis reported that the SRR was significantly higher in men with NOA who did than did not undergo varicocele repair (OR 2.65; 95% CI, 1.69–4.14; $p<0.001$) [72]. However, because these studies did not include a control group, there are no solid data to justify varicocele repair in men with NOA. The beneficial effects of varicocele treatment would likely be minimal in patients with advanced NOA status. One study suggested that varicocele repair could be clinically favorable only in azoospermic patients having a testicular histological findings of hypospermatogenesis or late maturation arrest, but not in patients with Sertoli cell-only syndrome, suggesting that testicular biopsy results may guide treatment decisions [73]. Evidence suggesting that varicocele treatment has beneficial effects in men with NOA is insufficient and very limited. The AUA/ASRM guidelines state that "the couple should be informed of the absence of definitive evidence supporting varicocele repair prior to ART."

6. Summary and recommendation

Even in the era of widespread ARTs, varicocele has substantial implications in infertility treatment. Although appropriate diagnosis and treatment of varicocele would help improve natural pregnancy and success rates of ART, the condition of the female partner should be sufficiently considered in decision making. Large, well-designed prospective studies are also necessary.

Conflict of Interest

The authors have nothing to disclose.

Funding

None.

Acknowledgements

We sincerely thank Dr. Byung Kyu Han and Dr. Ki Hyuck Moon of Perfect Urology Clinic for their contribution during this project.

Author Contribution

Conceptualization: SHS, WKL. Data curation: DSK, SCK. Formal analysis: DKK, DSK, SCK, SHS. Investigation: DSK, SCK, HSL. Methodology: DKK, DSK, SHS. Project administration: SHS. Supervision: SHS, WKL. Writing – original draft: DKK, DSK, SCK, HSL. Writing – review & editing: SHS, WKL.

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