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INVITED REVIEW

Male Fertility

The varicocele: diagnostic dilemmas, therapeutic challenges and future perspectives

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A varicocele is defined as the abnormal dilation of the internal testicular vein and pampiniform venus plexus within the spermatic cord. If a semen analysis is not obtained from the adolescent male, in the absence of other symptoms, the main clinical indication used by many urologists to recommend repair is testicular atrophy. The varicocele may result in testicular damage in some males causing testicular atrophy with impaired sperm production and decreased Leydig cell function, while in other males the varicocele may seemingly cause no ill effects. In adult men, varicoceles are frequently present and surgically correctable, yet the measurable benefits of surgical repair are slight according to a Cochrane review. While occurring more commonly in infertile men than fertile men, only 20% of men with a documented varicocele will suffer from fertility problems. Most varicoceles found in adolescents are detected during a routine medical examination, and it is difficult to predict which adolescent presenting with a varicocele will ultimately show diminished testicular function in adolescence or adulthood. As in adults, the mainstay of treatment for varicocele in adolescents is surgical correction. However, unlike an adult varicocelectomy (the microsurgical approach is the most common), treatment for an adolescent varicocele is more often laparoscopic. Nevertheless, the goals of treatment are the same in the adolescent and adult patients. Controversy remains as to which patients to treat, when to initiate the treatment, and what type of treatment is the best. This review will present the current understanding of the etiology, diagnosis and treatment of the adolescent varicocele.
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INTRODUCTION

Varicocele is essentially a varicose vein in the scrotum resulting from an abnormal dilation of the internal spermatic vein and pampiniform venus plexus within the spermatic cord. The causes of varicocele largely remain unknown, as does the pathophysiology of varicoceles. Elevated testicular temperature,[1] increased venous pressure,[2] hypoxia,[3] oxidative stress,[4] hormonal imbalances[5] and reflux of toxic metabolites from adrenal or renal origin[6] may result from a varicocele, each of which is theorized to contribute to varicocele-associated testicular failure.

Varicocele is the most common correctable cause of male infertility, affecting approximately 40% of men with primary infertility and 80% of men with secondary infertility.[7,8] Varicocele is found in 25% of men with abnormal semen parameters, compared with 12% of men with normal semen parameters, suggesting that it is associated with impaired testicular function and male infertility.[9] Nevertheless, only 20% of men suffer from fertility problems among adults with documented varicocele,[10,11] which means that no treatment may be required for the remaining 80% men with varicocele. The purpose of treating varicocele in adults is to improve current fertility status. In contrast, in most cases the goal of treatment for adolescent varicocele is to prevent testicular injury and maintain testicular function for future fertility. Thus, the decision whether to treat adolescents with varicocele is controversial. Considering that a number of adult men with varicocele do not suffer from testicular failure, treatment for varicocele may be unnecessary for the majority of adolescents. However, among a small proportion of adolescents, varicocele has a detrimental effect on testicular growth and can lead to irreversible testicular damage. Thus, the most important issue in the management of adolescent varicocele is to appropriately select patients who actually need treatment. Of note, there is no consensus in the literature as to when to initiate treatment and what modality to use. In this review, we sought to summarize the current controversies in diagnosis and management of adolescent varicocele, as well as those of adult varicocele.

ADOLESCENT VARICOCELE

Epidemiology

Varicoceles are common in adolescent males. Although rarely seen in prepubertal boys, varicoceles are the most commonly seen urological condition in boys after puberty.[12] In large population studies, the prevalence of varicocele in adolescence varies widely from 5% to 30%.[13–15] Zampieri *et al.* screened 2107 adolescents and reported 609 (28.9%) adolescent males had varicoceles.[16] In contrast, Kumanov *et al.* reported a 7.9% prevalence of varicocele among Bulgarian boys aged 10 to 19 years (n = 3100).[17] The reason for the marked differences between studies remains unclear,[18] although the differences can be attributed to diagnostician's lack of experience or perhaps inconsistency in diagnosis in the case of smaller varicoceles. Because not all varicoceles cause infertility, it is important to define the true prevalence of adolescent varicocele, in order to better understand the natural history of the disease.

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Diagnosis

Typically, men with varicocele are asymptomatic, although some present with complaints of chronic fullness or swelling in the scrotum. While many adult varicoceles are identified by a physical examination for infertility evaluation, most adolescent varicoceles are detected during routine medical examination for school or sports.

Physical examination is the mainstay of varicocele diagnosis. The examination should be performed in a warm room, with the patient examined in both supine and standing positions. The scrotum should be visually inspected and then examined by palpation, and the patient should be asked to perform a Valsalva maneuver. Both adult and adolescent varicoceles are graded as follows: grade I, palpable impulse in the spermatic cord veins during Valsalva maneuver without enlargement of the veins at rest; grade II, palpable engorged veins with the patients standing without Valsalva maneuver, but not visible; grade III, veins easily visible through the scrotal skin while the patient is standing.[19]

The size of each testis should be determined using an orchidometer and/or ultrasonography. Ultrasonography reportedly offers greater accuracy than an orchidometer[20] for testicular volume measurement. Nevertheless, in clinical practice an orchidometer is still a reliable tool to measure testicular volume, since there is a close relationship between ultrasonography-derived and orchidometer-derived testicular volume.[21] In either case, it is critical to determine whether there is a discrepancy in volume between left and right testicle, as such a discrepancy could guide intervention.

Most varicoceles occur on the left side. It is reported that a palpable left-sided varicocele occurs in 85% to 90% of cases, while a palpable right varicocele is normally found in cases of bilateral varicoceles.[22] The presence of an isolated right-sided varicocele is extremely rare. Hence, the physician should look for an underlying retroperitoneal mass in such cases, especially if the varicocele does not shrink when the patient is in the supine position.[23]

Evaluation

The challenge with adolescent varicocele is to determine which varicocele is clinically significant (i.e., will affect testicular functions). Currently, the most important factor in deciding to treat a varicocele in adolescence is testicular volume. Varicoceles may be associated with testicular atrophy and histologic abnormalities of the testis.[24] Ipsilateral testicular atrophy or growth arrest is perceived as a harbinger of testicular dysfunction and possible progression to infertility.[25] The American Society for Reproductive Medicine (ASRM) Practice Committee guideline indicates that adolescent males who have a varicocele may be considered as candidates for varicocele repair if they have objective evidence of reduced testicular size.[26] If objective evidence (typically ultrasound) of reduced testicular size is not present, then adolescents with varicoceles should be followed annually.[26]

For the definition of "reduced testicular size," the normal contralateral testis size can be provided as a relative control for the ipsilateral testis size. One must consider that when the patient has bilateral varicoceles or has a large unilateral varicocele, the use of size discrepancy between the testes is not always appropriate because both testes can be affected.[27] In such cases, the standardized table showing the average testicular volumes for adolescents at different Tanner stages can be used as a reference (**Table 1**).[28] A meta-analysis encompassing 14 studies and 1475 patients showed a clear advantage of surgical intervention in reducing testicular atrophy when the discrepancy between the testes was ≥10%.[29] However, this study focused on the efficacy of adolescent varicocelectomy on testicular catch-up growth, without taking semen parameters into account.

Table 1: Testicular volumes in 348 adolescents

Tanner stage	*Left testes (ml)*	*Right testes (ml)*
1	4.76±2.76	5.20±3.86
2	6.40±3.16	7.08±3.89
3	14.58±6.54	14.77±6.1
4	19.80±6.17	20.45±6.79
5	28.31±8.52	30.25±9.64

Adapted with permission from reference[28]

Semen analysis, which would be a more decisive variable to guide treatment strategy, can be recommended for adolescents with a varicocele.[10] However, it is difficult to interpret semen analyses in adolescents because there are currently no standard norms to interpret semen parameters in this younger population.[25] Diamond *et al.* performed semen analysis in 57 Tanner stage 5 adolescent males with varicoceles and showed that inter-testicular size discrepancy ≥10% correlated with a decreased sperm concentration and total motile sperm count, and the difference was much greater when the size discrepancy was ≥20%.[30] Kurtz *et al.* recently reviewed 100 adolescents with varicocele and reported that total testicular volume and the testicular volume differential determined by ultrasonography are associated with semen analysis outcome.[31] A testicular volume differential of >20% and a total testicular volume of <30cc were significant risk factors of decreased total motile sperm count in adolescents with varicocele.[31] At the same time, it is important to consider that testicular growth in young men is variable between sides. Several articles reported spontaneous testicular catch up growth in adolescent with varicoceles.[32–34] Although commonly, the use of testicular volume as a surrogate for global testicular function may not be accurate.

In a recent survey study examining diagnostic and management approaches to pediatric and adolescent varicoceles, 28% of pediatric urologists said they would consider varicocelectomy depending on varicocele grade, even in patients with asymptomatic varicocele and symmetric testes.[35] Obviously, there are conflicting opinions on whether there is a correlation between varicocele grade and testicular damage in adolescents with varicocele.[14,36,37] Although the higher grade varicoceles appear to be more concerning, varicocele grade alone is not thought to be an indication for treatment.[38,39]

Although the diagnosis of a varicocele is usually made primarily by physical examination, scrotal ultrasonography is a useful tool as an adjunct to the physical diagnosis of varicocele. As described above, it offers an accurate measurement of testicular volume. In addition, it can demonstrate the dilated internal spermatic vein, in which a diameter >2–3 mm is usually used for a diagnosis of a varicocele.[40] Using Doppler mode, reflux of venous flow can be evaluated. Several parameters acquired from Doppler ultrasonography are associated with spermatogenic dysfunction induced by varicocele.[41–43] Of these parameters, venous reflux grade, peak retrograde flow, and hemodynamic pattern are correlated with testicular dysfunction in adolescent varicocele. Zampieri and Cervellione conducted a study screening 2107 adolescents of whom 609 had a varicocele.[44] They used the Hirsch classification[45] for grading varicoceles, and suggested that grades II and III vein reflux (spontaneous venous reflux) closely correlate with the onset of testicular hypotrophy and abnormal semen analysis, regardless of clinical grade of varicocele.[44] Kozakowski *et al.* evaluated 77 adolescents with varicocele who had at least 2 duplex Doppler ultrasonographies without surgery, and revealed that peak retrograde flow was a significant parameter to predict persistent or worsening testicular asymmetry.[46]

No definitive single finding can consistently predict impairment of testicular function in adulthood. Clinical decisions on whether or not to operate should be made individually considering factors such as testicular size, semen parameters and ultrasound findings (**Figure 1**).

Treatment

The cornerstone of varicocele treatment is to block the reflux in the internal spermatic vein while preserving the internal spermatic artery, lymphatics and *vas deferens*. Treatment options are limited to either percutaneous venous embolization or surgical correction, the latter of which has several approaches. Currently, the best procedure for the treatment of adolescent varicocele has not been established.

Surgical varicocelectomy

There are three options for a surgical varicocele repair: retroperitoneal (Palomo), inguinal (Ivanissevich) and subinguinal approaches. Of these, a retroperitoneal procedure can also be performed laparoscopically, and inguinal and subinguinal approaches are usually performed using an operative microscope or surgical loupes. In adult infertile men with varicocele, microsurgical inguinal or subinguinal varicocelectomy is reported to have the highest success rate with lowest morbidity, although duration of surgery may be longer than that with conventional approaches.[47,48] In adolescents, a recent survey of pediatric urologists found that the most common surgical approach to adolescent varicocelectomy was laparoscopic (38%).[35] Currently, laparoscopic varicocelectomy gained traction, as pediatric urologists have become increasingly facile with laparoscopic techniques.[49] One of the reasons for this discrepancy may be the difference in the level of practitioner comfort with the microsurgical technique. Urologists trained in infertility who treat adults are comfortable with this microsurgical technique.[50]

Table 2 summarizes outcomes of surgical techniques, and side effects such as hydrocele formation, varicocele recurrence and testicular atrophy.[10] Despite the wide variability among eight studies evaluated, it appears that an inguinal or subinguinal approach results in a low hydrocele rate and low recurrence rate. An open Palomo procedure is associated with relatively high hydrocele rate, whereas the rate is decreased when modified to spare lymphatics. As for a laparoscopic approach, it seems that lymph sparing may not increase the recurrence rate, although it would decrease the postoperative hydrocele rate.[51] Artery sparing during laparoscopic varicocelectomy is controversial. A study comparing 122 adolescent patients who underwent laparoscopic varicocelectomy with or without artery sparing showed that postoperative sperm density was significantly improved when the artery was preserved, compared to those without.[16] Considering that the testicular artery basically is preserved with an inguinal or subinguinal approach, artery-sparing should be encouraged during laparoscopic varicocelectomy. In addition, even though it is rare, a laparoscopic procedure could introduce inherent complications such as hypercapnia, injury to intra-abdominal organs, port site hernia and delayed bowel obstruction due to adhesions.[49]

Percutaneous venous embolization

Percutaneous embolization of the internal spermatic vein is a nonoperative approach, which promises minimal pain and quick recovery from the intervention. A study evaluating 71 children treated with a percutaneous retrograde endovascular occlusion procedure who presented with

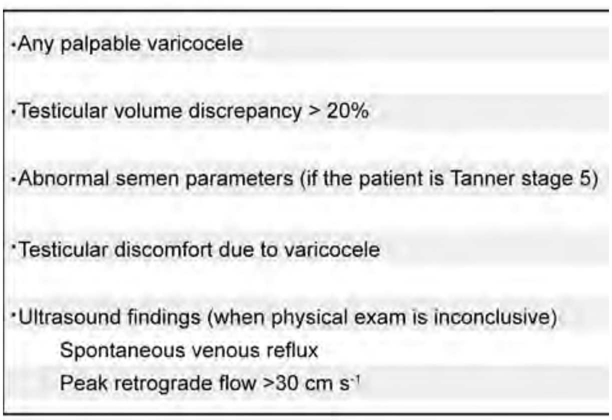

Figure 1: Possible indications for adolescent varicocele treatment.

Table 2: Outcomes in adolescent varicocele surgery

Study, year	*Technique*	*Patients (n)*	*Artery spared?*	*Lymphatics spared?*	*Hydrocele (%)*	*Recurrence (%)*	*Testicular atrophy (%)*
Kass and Marcol 1992[79]	Inguinal	53	Yes	Yes	NA	16.00	0
	Palomo (modified)	17	Yes	No	NA	11.00	0
	Palomo	32	No	No	NA	0.00	0
Misseri *et al.* 2001[80]	Inguinal	21	Yes	Yes	14.00	14.00	NA
	Palomo	56	No	No	28.00	3.00	NA
Riccabona *et al.* 2003[81]	Laparoscopic	19	Yes	No	5.00	11.00	0
	Inguinal	21	Yes	Yes	0.00	14.00	0
	Palomo (modified)	32	No	Yes	13.00	0.00	0
Schiff *et al.* 2005[82]	Subinguinal	97	Yes	Yes	1.00	1.00	0
Kocvara *et al.* 2005[83]	Laparoscopic	104	Yes	Yes	1.90	6.70	0
	Laparoscopic	67	Yes	No	2.90	8.90	0
Hassan *et al.* 2006[84]	Laparoscopic	89	No	No	22.80	1.30	0
Yaman *et al.* 2006[85]	Subinguinal	92	Yes	Yes	0.00	1.60	0
VanderBrink *et al.* 2007[86]	Subinguinal	31	Yes	Yes	0.00	3.20	NA
	Laparoscopic	28	No	Yes	3.60	0.00	NA
Feber and Kass 2008[87]	Palomo	312	No	No	29.00	3.90	0
Glassberg *et al.* 2008[50]	Laparoscopic	132	Yes	Yes	3.40	2.90	0
	Laparoscopic	59	Yes	No	11.40	4.50	0

Adapted with permission from reference.[10] NA: not available left-sided, grade III varicocele reported a varicocele-free rate of 93% without major complications. The procedure was performed safely under local anesthesia in most patients at a mean age of 13.2 years. However, catheterization of the internal spermatic vein was not successful in three patients, who subsequently underwent surgical ligation.[52] Another study showed that in 27 patients with a mean age of 16 years who underwent retrograde embolization, the varicocele resolved in 91% of subjects without any hydrocele formation. Again, the internal spermatic vein could not be safely selected in two patients, who subsequently underwent surgical ligation.[53] Although complications such as hydrocele or testicular atrophy did not occur when this procedure was performed, selective catheterization of the internal spermatic vein was technically difficult in certain cases. In addition, although rare, embolization carries the unique risks of contrast reactions, extravasation, and migration of embolization material.

Future perspectives

Given that only a small proportion of adolescents diagnosed with varicocele will ultimately experience infertility in adulthood, a deeper understanding of molecular and genetic factors is imperative to identify the patients who should be treated. It is suspected that preexisting genetic lesions or defects in molecular mechanisms can play a role in varicocele-mediated testicular injury.[54] In fact, several factors that could be involved in varicocele-mediated testicular injury have been investigated. Of these, heat-shock protein, which is a molecular chaperone that has a protective action on cellular auto-regulation in response to heat stress, is one of the factors investigated. Lima *et al*. evaluated ejaculated spermatozoa from adolescents with and without varicocele, and demonstrated that *heat-shock protein A2* (*HSPA2*) gene expression was down-regulated in sperm from adolescents with varicocele and oligozoospermia, compared with adolescents with varicocele and normal sperm concentration.[55] Interestingly, *HSPA2* gene expression was higher, albeit not significant, in adolescents with varicocele and normal sperm concentration, compared with normal controls, suggesting its role in cellular protection.[55] Similarly, Ferlin *et al*. investigated the gene expression of several proteins involved in heat-shock stress using ejaculated sperm obtained from men with or without varicocele.[56] They found that the gene expression of HSFY, one of the heat-shock factor family proteins, was highest in men with varicocele and normal semen parameters, suggesting its protective role on spermatogenesis.[56] Collectively, these studies suggest that evaluation of heat-shock proteins in ejaculated sperm could be used as a measure of varicocele-associated spermatogenic damage, which could help define those patients requiring treatment in adolescence.

Oxidative stress is another important factor of varicocele pathophysiology. Romeo *et al*. evaluated the nitrotyrosine concentration, which is identified as a marker of nitric oxide damage, in the spermatic veins of varicoceles in adolescents.[57] These investigators showed that nitrotyrosine concentrations were significantly greater in the spermatic vein than the peripheral vein among adolescents with varicocele. However, peripheral blood analysis showed no difference in nitrotyrosine concentration between varicocele patients and controls.[57] Another study evaluating adolescents with left-sided varicocele and ipsilateral testicular hypoplasia measured basal thiobarbituric acid reactive substances (TBARS) and plasma peroxidation susceptibility, which are useful to assess lipid peroxidation.[58] In this study, these parameters were measured using peripheral venous blood. The basal TBARS were reduced and the plasma peroxidation susceptibility lag time was increased after surgery, which suggested that varicocelectomy reduced oxidative stress in these patients.[58] Evaluation of oxidative stress at the level of the peripheral blood may provide a clue in making the decision to treat adolescent varicocele patients. Ideally, identifying mutations in specific genes that are involved in varicocele and infertility may help select adolescents who need intervention.

In addition to concern for future infertility among adolescents with varicocele, recent data shows that varicocele may also have a detrimental effect on testosterone production.[59] Although currently there are no data assessing the testicular steroidogenesis associated with adolescent varicocele, future study is needed to reveal the effect of varicocele on testosterone production in this younger population.

ADULT VARICOCELE

In contrast to adolescent varicoceles, adult varicoceles are identified on a physical examination for infertility evaluation. As described above, a number of men with varicocele are fertile without any reproductive problems. However, varicocele is still the most common correctable cause of male infertility. Although a systematic review including patients with subclinical varicoceles or normal semen parameters reported that there was no sufficient evidence to support the efficacy of varicocele treatment to improve the likelihood of conception,[60] several articles reported the efficacy of varicocele treatment when men with subclinical varicoceles or normal semen parameters were excluded.[61,62]

The ASRM Practice Committee guideline indicates that treatment of the varicocele should be considered when most or all of following conditions are met: (1) the couple is attempting to conceive; (2) the varicocele is palpable on physical examination; (3) the couple has known infertility; (4) the female partner has normal fertility or a potentially treatable cause of infertility, and time to conception is not a concern; and (5) the male partner has abnormal semen parameters.[26] Although the definition of "normal semen parameters" is a major factor of indication for the treatment of the varicocele, the usefulness of 2010 World Health Organization (WHO) reference values may not be ideally in some cases to determine the indications for varicocelectomy. Lee *et al*. reported that more than one half of men whose semen results were normal on the 2010 WHO reference but abnormal on the previous reference showed improvement in seminal results after varicocelectomy.[63] This indicates that some infertile men with varicocele may miss the opportunity of valuable treatment (i.e., varicocelectomy) when current WHO reference was applied.

Whether to offer varicocelectomy for men with nonobstructive azoospermia (NOA) still remains controversial. Varicocele in association with NOA is estimated to range between 5% and 10%, and studies have shown the beneficial effect of varicocele repair in azoospermic cases.[64,65] Recent literature reported that 21% to 56% of NOA patients had some ejaculate sperm after varicocelectomy. However, the maximum sperm concentration was only 3.8×10^6 ml^{-1}, which still required assisted reproductive technology such as intracytoplasmic sperm injection (ICSI).[66] In addition, Schlegel and Kaufmann reported that even if a patient had ejaculate sperm after varicocelectomy, <10% of 31 patients had viable sperm at the time of ICSI and were able to avoid TESE.[67] When TESE was performed, sperm retrieval rates for men with varicoceles were not affected by a history of prior varicocelectomy.[67] These findings may indicate limited efficacy of varicocelectomy for NOA men with varicoceles. In contrast, other authors have reported the improved sperm retrieval rates after varicocelectomy in NOA patients with varicoceles.[68,69] One of these studies showed the improved rate of clinical pregnancy and live birth.[68] Furthermore, a meta-analysis analyzing 233 NOA patients with varicocele reported a natural pregnancy rate of 6% following varicocele treatment.[70] Taken together, although the efficacy of varicocele treatment for NOA patients may be limited, some benefit may occur in a portion of NOA patients with varicoceles. Clinical factors that can predict good recovery of spermatogenesis after varicocelectomy are expected among these patients.

It is absolutely imperative to predict the patients that would benefit from varicocele treatment. Several basic researches have been carried out to reveal the detail pathophysiology of varicoceles. Previous studies suggest that elevated levels of reactive oxygen species (ROS) and oxidative stress play an important role in reduced spermatogenesis among patients with varicoceles.[71–74] Chen *et al*. investigated the gene polymorphisms of *glutathione S-transferase* (*GST*), which is a molecule to attenuate the toxicity of ROS. Although there was no differences in the frequencies of *GST M1* null homozygous genotype between varicocele and control group, the sperm of varicocele patients with *GST M1* null homozygous genotype were more vulnerable to oxidative damage.[75] As described above, heat-shock proteins are also well-investigated molecules for varicocele-associated spermatogenic failure. A study investigated the expressions of microRNAs (miRNAs) and heat-shock proteins between patients with varicocele and healthy controls. The expression of miR-15a in the ejaculated sperm of varicocele patients was significantly decreased. Furthermore, miR-15a repressed *heat-shock protein A1B* (*HSPA1B*) expression through directly binding to its 3'-UTR.[76] These findings may help select patients who are severely damaged by varicocele-induced oxidative or heat stress. On the other hand, genes indispensable for the precise spermatogenesis are also reported to be associated with varicocele-pathophysiology. A recent article evaluated the polymorphism of methylenetetrahydrofolate reductase (MTHFR), which is important for DNA synthesis and methylation. 1298 AA genotype in MTHFR gene was reported to raise the risk of varicocele approximately 2.3 times more compared with men carrying other genotypes.[77] Another study investigated *Ropporin* gene expression, which is a component of fibrous sheath of mammalian sperm flagella and associated sperm motility. Decreased expression of *Ropporin* gene in the sperm was significantly correlated with impaired sperm motility, and its gene expression was elevated after varicocelectomy.[78] Although further translational research is still required in this field, the more detail understanding of varicocele-pathophysiology may enable us to select the patients eligible for the treatment, or even to provide a novel molecular targeted therapy among infertile patients with varicoceles.

CONCLUSIONS

Given that the majority of men with varicocele do not exhibit any detrimental effect on fertility, it is obvious that intervention is not necessary for most adolescents and adults with varicocele. Nevertheless, it is also true that some adolescents with varicocele will suffer from testicular damage. It is important to identify who should be treated and when the treatment should be initiated. Currently, the most widely accepted indication for treatment is reduced testicular size secondary to the varicocele. There is no established criterion on when to initiate the treatment, even though varicocele can progress and cause irreversible damage on testicular function when left untreated. In adolescents, laparoscopic varicocelectomy is the most frequently used operative approach to treat varicocele. Nevertheless, what remains controversial is identifying who to treat, when to treat, and how to treat. As for adult varicocele, when infertile patients have palpable varicoceles and impaired semen parameters, varicocelectomy appears to be a good treatment option. However, there are also a portion of patients who do not respond to the treatment. Therefore, further investigation is required to identify molecular markers that can help select patients who may benefit from treatment.

AUTHOR CONTRIBUTIONS

KC wrote the manuscript. RR, RJL and LIL revised the manuscript.

CONFLICT OF INTEREST

The authors have no potential conflicts of interest to disclose.

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