REVIEW ARTICLE

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The Role of Varicocelectomy in Enhancing Fertility Outcomes: A Review Article

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Abstract

Varicocele is the leading cause of male infertility and can often be corrected or improved through a range of surgical and radiological methods. Consequently, it appears logical that varicocele should be treated in infertile men who have this condition. Varicocele, an enlargement of the pampiniform plexus veins affecting 15–20% of men, is more common in those with infertility concerns. Its impact on spermatogenesis is linked to oxidative stress, hypoxia, and immune responses, which may be alleviated by varicocelectomy. Varicocelectomy has been associated with improvements in sexual function, hormonal profiles, and fertility, particularly in men with hypogonadism. This review evaluates its effects on testosterone levels, semen quality, and fertility outcomes, highlighting the advantages of microsurgical varicocelectomy, such as improved sperm quality, higher spontaneous pregnancy rates, and fewer complications. However, patient outcomes depend on surgical indications, pre-existing conditions, and individual expectations. Emerging evidence suggests that repairing varicoceles before assisted reproductive technology (ART) can enhance fertility outcomes. Further studies are needed to refine treatment criteria and expand options for diverse patient groups, including adolescents and men with pain-related varicoceles. The review also emphasizes the need for standardized diagnostic and treatment protocols.

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INTRODUCTION

Varicocele is a common condition among men that is associated with impaired testicular function, reduced testosterone levels, and infertility. The condition involves the dilation of veins within the spermatic cord, affecting testicular blood flow and potentially leading to testicular dysfunction. Infertility affects approximately 15% of couples attempting to conceive globally (1), with the male partner being the sole contributing factor in 17.1% of cases (2). Varicoceles are recognized as the most frequent surgically treatable cause of male infertility (1, 3, 4).

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Varicocelectomy, a procedure to remove or occlude these dilated veins, is a standard treatment option. While evidence suggests that varicocelectomy can improve hormonal and semen parameters, its effects on sexual health, fertility, and testosterone levels are complex. Most varicoceles occur unilaterally on the left side due to venous drainage patterns, with some cases presenting bilaterally (5-8). Varicoceles disrupt the vascular architecture of the pampiniform plexus, impairing sperm quality and testicular function due to increased temperature, compromised oxygen delivery, and retrograde transfer of metabolites from the renal and adrenal systems (5, 9, 10). Given the potential reversibility of infertility through surgical intervention, varicoceles have garnered considerable attention in urology.

Various clinical and sonographic classifications have been proposed for assessing varicocele; however, standardization is lacking, and a clear consensus has yet to be reached, which complicates comparison across studies (3). The World Health Organization's fourth edition classification defines three grades of varicocele based on severity, from 1 to 3, without specifying an absolute vein diameter or providing sonographic criteria for reflux with velocity measurements. In contrast, Sarteschi's classification uses a five-part system, considering factors such as the presence of dilated veins while supine or standing, their anatomical relationship to the testis, reflux characteristics, and testicular size (11). Cavallini et al. emphasize the importance of varicocele grade and reflux level, suggesting that surgical intervention to improve oligoasthenoteratozoospermia (OAT) and increase the chances of successful assisted reproductive technology (ART) should be limited to Dubin and Amelar grade 2 and grade 3 varicoceles with continuous venous reflux identified via duplex Doppler assessment (12).

Researchers have suggested various mechanisms to explain the pathophysiology of varicocele. Scrotal hyperthermia is likely the primary mechanism, as it negatively impacts endocrine function and spermatogenesis, both of which are sensitive to elevated temperatures (13). Another potential mechanism is the reflux of adrenal and renal metabolites, as supported by early anatomic radiographic studies (10, 14). Additionally, increased hydrostatic pressure in the internal spermatic vein caused by renal vein reflux may contribute to varicocele-induced pathology (15).

Varicocele has been associated with spermatogenic damage, leading to altered semen parameters, impaired development and growth of the affected testis, and, in rare cases, symptoms such as discomfort and pain (3, 16, 17). Observational studies indicate that men with varicocele often exhibit a higher proportion of sperm with fragmented DNA, reduced total sperm counts, decreased progressive motility and vitality, and an increased presence of abnormal forms compared to control groups (18). However, the precise pathophysiology and the causal relationship between varicocele and abnormalities in semen analysis remain unclear (17, 19). On the other hand, a recent systematic review and meta-analysis provide robust evidence supporting the positive impact of varicocele repair (VR) on improving conventional semen parameters in infertile men with clinical varicocele (20).

The purpose of our study is to examine recent reports on varicocele treatment and outline straightforward, practical guidelines for accurately determining treatment indications, with an emphasis on addressing the existing controversies surrounding this topic.

Pathophysiology and Mechanisms of Varicocele-Induced Infertility

Varicoceles are thought to affect testicular function and male fertility through several mechanisms (21). One such mechanism is hyperthermia, as varicoceles can increase scrotal temperature, disrupting the countercurrent heat exchange system, which normally regulates temperature for optimal sperm production (22). Studies have shown conflicting results regarding temperature regulation, with some indicating higher scrotal temperatures in varicocele patients and others showing no difference. Animal models and experiments, such as induced cryptorchidism, suggest that elevated heat impairs sperm production, potentially through increased germ cell apoptosis and disruption of androgen production (22). Another mechanism involves increased venous pressure, which may impair testicular blood flow and heat regulation, leading to metabolic disruptions (23, 24). Some animal studies have shown delayed vascular drainage and increased testicular blood flow, while human studies have produced mixed results (25, 26). Hormonal imbalance also plays a role, with varicoceles potentially affecting Leydig cell function, leading to lower testosterone levels (27). However, results are inconsistent, with some studies showing decreased intratesticular testosterone without changes in serum levels (28, 29). The androgen receptor pathway may also contribute to impaired spermatogenesis (29). Additionally, the accumulation of toxic substances, such as catecholamines and cadmium, may contribute to testicular dysfunction. Cadmium exposure, which is common in smokers and those with varicoceles, has been shown to impair sperm production and function in animal models (30). Lastly, an excess of reactive oxygen species (ROS) can damage sperm membranes, impairing motility and morphology (31). Elevated ROS levels are found in men with varicoceles,

and antioxidant treatment has shown promise in improving semen quality (32).

Treatment and Testosterone Levels, Relationships and Sexual Functioning

The relationship between varicocelectomy and testosterone levels has been explored in multiple studies. Research indicates that testosterone levels may improve after varicocelectomy, especially in hypogonadal men or those with low-normal testosterone levels (33, 34). One study noted a significant increase in testosterone post-surgery in men with follicle-stimulating hormone levels ≤10. Despite this, the degree of improvement varies, and patients need to maintain realistic expectations, as the rise in testosterone may not always be clinically significant. For men interested in fertility preservation, varicocele repair is a preferable alternative to exogenous testosterone therapy, which may induce azoospermia (35).

Numerous studies have explored the dynamics of relationships during men's experiences with infertility and its treatment. Most of these studies (36, 37) have concentrated on how male infertility treatments influence sexual functioning, often using tools that assess sexual health and overall well-being. Consequently, these findings hold significant implications for the sexual dynamics within intimate relationships. Fewer studies (38) have examined the emotional and communicative aspects of relationships, employing a variety of research methods.

Research by Stevenson et al. (39) and Johansson et al. (40) highlighted the mutual support partners provide during their infertility journey. This support often involves improved communication, which has been linked to a stronger bond. Men frequently reported prioritizing their partners' emotional needs over their own, perceiving their partners as experiencing greater distress. Additionally, the outcomes of treatment were found to influence the overall quality of the relationship.

Surgical Treatments

The Palomo technique, introduced in 1949, involves retroperitoneal high ligation above the internal inguinal ring. However, this technique had a high recurrence rate because the ligation did not address collateral vessels and required dissection of the abdominal muscles, leading to prolonged recovery (41). While there have been variations to this approach, treatment has shifted towards microsurgical inguinal or subinguinal varicocelectomy (42). Subinguinal varicocelectomy, with or without microsurgery, offers the advantage of avoiding the external oblique fascia, thereby reducing postoperative pain (43).

Laparoscopic varicocelectomy is another option, technically similar to the open retroperitoneal approach, as it involves high ligation of the spermatic vein without identifying the external spermatic vessels. Consequently, the incidence of postoperative hydrocele and recurrence is higher compared to microsurgical varicocelectomy. However, laparoscopic techniques offer the benefit of easily treating bilateral varicoceles and a quicker recovery time (43).

Adolescent Varicocelectomy and Future Fertility Considerations

The decision to treat adolescent varicocele with surgery requires careful evaluation, as evidence of its long-term fertility benefits remains inconclusive. Some studies suggest varicocelectomy may improve testicular volume without significantly enhancing semen concentration, motility, or morphology. Further randomized controlled trials are necessary to establish optimal intervention criteria for adolescents to prevent unnecessary treatment (44, 45). Evaluating the extent of a varicocele's negative impact on an adolescent's testicular health can be challenging, as teenagers generally are not asked to provide semen samples for analysis. Therefore, alternative indicators, such as differences in testicular size, are used to assess testicular health. Treatment options for adolescent varicocele largely mirror those available for adults (46).

Molecular Changes and Seminal Biomarkers in Varicocele

Studies have shown that varicocele impacts seminal protein and metabolite profiles. Patients with varicoceles exhibit altered levels of dipeptidases and metabolites in semen compared to healthy individuals, a condition that improves post-varicocelectomy (47). Notably, levels of Tripeptidyl peptidase-1, an enzyme associated with semen quality, were elevated in men who showed improved fertility post-surgery. This enzyme may serve as a biomarker for positive outcomes following varicocele repair, shedding light on molecular targets for future therapeutic interventions (47).

Classification Systems of Varicocele

Various classification systems have been developed to assess varicocele severity, each with differing approaches and clinical implications. The Dubin and Amelar classification focuses on clinical palpation and observation during the Valsalva maneuver, categorizing varicoceles into three grades based on palpability and visibility. However, this method lacks hemodynamic specificity and does not account for physiopathological changes post-surgery.

The Sarteschi classification, leveraging Doppler ultrasonography, incorporates both clinical and

instrumental findings, assessing reflux characteristics and vein dilation patterns to stratify varicoceles by five grades. Additionally, newer classifications prioritize the Valsalva maneuver to detect retrograde blood flow, providing a more comprehensive hemodynamic understanding essential for treatment planning.

Clinical Outcomes of Varicocelectomy and ART

Varicocelectomy, particularly when conducted before testicular sperm extraction (TESE), has shown promising results in enhancing the success rates of ART. In a study involving 96 men undergoing TESE and IVF/ICSI, those with prior varicocelectomy exhibited a higher sperm retrieval rate (48%) compared to the untreated group (30%). Similarly, couples in which the male partner had undergone varicocelectomy achieved higher pregnancy rates (31.4%) than those without surgical correction (22.2%).

Another comprehensive study involving 306 couples found that varicocelectomy before ART increased pregnancy rates from 47.1% to 62.5%, and live birth rates from 29.0% to 47.6%. These outcomes underscore the potential benefit of varicocele repair in improving ART success, particularly for men with oligospermia and non-obstructive azoospermia (NOA).

The Role of Environmental and Lifestyle Factors in Varicocele-Associated Infertility

Lifestyle and environmental factors, including smoking, exposure to heavy metals, and endocrine-disrupting chemicals, exacerbate the impact of varicocele on fertility. Tobacco use has been linked to increased oxidative stress, DNA fragmentation, and reduced sperm parameters. Heavy metals, found in pollutants and affecting hormonal balance, further compromise sperm motility and count. These factors highlight the need for comprehensive lifestyle modifications alongside medical interventions in varicocele patients.

DISCUSSION

Previous systematic reviews have highlighted a lack of understanding regarding men's experiences with infertility treatment, particularly treatments specific to male infertility (48, 49). This review aimed to address that gap by focusing on the psychological, social, marital, and sexual aspects of this critical phase in a man's infertility journey. Most of the included studies emphasized surgical treatments, shedding light on both the positive and negative psychosocial effects of treatment outcomes, the challenges and coping strategies during the process, and the needs of patients in clinical settings.

Current evidence highlights the variability of varicocelectomy outcomes based on individual patient factors and varicocele characteristics. While microsurgical varicocelectomy is considered the "gold standard" for varicocele repair, few high-quality studies focus on predictors of its effectiveness in actual fertility outcomes, such as pregnancy and live birth rates. Future research should include well-designed randomized controlled trials with extended follow-up periods to identify which patients benefit most from varicocelectomy, particularly in cases involving pain relief or chronic hypogonadism.

CONCLUSION

Varicocele is a significant cause of male infertility, with a complex pathophysiology that includes oxidative stress, immune dysregulation, and genetic factors. Caricoceles likely impair fertility through multiple pathways, including thermal damage, increased venous pressure, hormonal disruption, accumulation of toxic substances, and oxidative stress, with the severity of these effects varying based on genetic and lifestyle factors. Microsurgical varicocelectomy is the preferred treatment, showing improved pregnancy rates, especially when combined with assisted reproductive technologies (ART). While effective for many, varicocelectomy doesn't guarantee success in all cases, with some men showing minimal improvement in sperm parameters. ART remains an alternative for severe infertility. Further research is needed to refine patient selection and develop evidence-based guidelines. Tailoring treatments to individual needs can help optimize outcomes for men with varicocele.

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