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INVITED REVIEW

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Pathophysiology and treatment options of varicocele: An overview

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Abstract

Varicocele is the most common correctable cause for male infertility, but not all men with varicocele are affected equally by this condition. The pathophysiology of varicocele-induced fertility remains ill-defined. While evidence suggests that oxidative stress remains a central factor, other mechanisms likely include scrotal hyperthermia, reflux of metabolites, hypoxia and cadmium accumulation. Microsurgical varicocelectomy remains the gold standard treatment option for infertile men with a clinically palpable varicocele and abnormal semen parameters. Newer evidence suggests a potential role for antioxidant supplementation and a meaningful role of varicocelectomy for patients destined for ART to improve pregnancy outcomes.

KEYWORDS

infertility, oxidative stress, spermatozoa, varicocele, varicocelectomy

1 | INTRODUCTION

A varicocele is an abnormally enlarged collection of tortuous veins of the pampiniform plexus. This network of veins provides drainage of the testicles and coalesces into a single gonadal vein (internal spermatic vein). Varicoceles occur in 15% of the general population and usually first appears in adolescence (Agarwal, Hamada, & Esteves, 2012). They are generally left-sided, as the left gonadal vein drains perpendicularly into the left renal vein, resulting in higher hydrostatic pressure in the left testicular venous tributaries than the right.

Varicoceles are classically described as a feeling like a 'bag of worms', that increases with Valsalva manoeuvre and decompresses in recumbent position. Varicoceles are commonly graded according to physical examination findings and size. Additional measures, such as scrotal ultrasound, can be performed if the physical examination is inconclusive but it should not be used to diagnose varicoceles in patients without a palpable abnormality. Varicoceles may be asymptomatic or can be accompanied by dull, aching or throbbing pain in the scrotum. Atrophy of the testicle can also be observed, possibly secondary to the loss of germ cell mass from increased scrotal temperature (Lipshultz & Corriere, 1977). Tall height has been associated with the development of varicoceles, whereas increased BMI may have a protective role (Nielsen, Zderic, Freedland, & Jarow, 2006). Tall height or accelerated growth during puberty is hypothesised to decrease the angle of the superior mesenteric artery with the aorta and thus increase compression on the left renal vein, whereas increased adipose tissue could lessen this effect (Bae et al., 2014; Tsao et al., 2009).

Varicoceles are often identified in infertile men, and it is present in up to 44% of men with primary infertility. It is also commonly found in 45%–81% of men with secondary infertility, as varicoceles are speculated to have a detrimental effect on testicular function over time (Jarow, Coburn, & Sigman, 1996). However, many men with varicocele still have preserved fertility, with at least 45% of those affected having normal semen quality (Damsgaard et al., 2016). While the exact relationship between varicocele and infertility is still not fully elucidated, varicoceles can nevertheless negatively affect sperm concentration, motility and morphology, as well as sperm DNA integrity.

In this review, we discuss the pathophysiologic mechanisms behind varicocele-induced male infertility, especially oxidative stress and involved molecular pathways. We also compare various treatment options for varicoceles, their benefits and limitations, and their current and future role in achieving a successful pregnancy.

2 | PATHOPHYSIOLOGIC MECHANISMS ASSOCIATED WITH VARICOCELE-INDUCED MALE INFERTILITY

2.1 | Central role of oxidative stress

The pathophysiology behind varicocele-induced male infertility is complex; however, oxidative stress (OS) appears to play a crucial role. OS reflects a disturbance in the balance between reactive oxygen species (ROS) and the buffering capacity of antioxidants. Multiple studies have demonstrated that OS can induce peroxidative damage to the sperm membrane and DNA, impair spermatogenesis and decrease sperm motility (Erfani Majd, Sadeghi, Tavalaee, Tabandeh, & Nasr-Esfahani, 2019; Ko, Sabanegh, & Agarwal, 2014). Pathophysiologic mechanisms that can promote OS include scrotal hyperthermia, reflux of metabolites, testicular hypoxia and cadmium accumulation (Figure 1).

2.1.1 | Scrotal hyperthermia

In men with varicoceles, retrograde blood flow into the pampiniform plexus can cause an elevation in scrotal and intratesticular temperature, aberrantly stimulating spermatozoa and leucocytes to produce more ROS (Ko et al., 2014). Heat stress can also cause a decrease in levels of antioxidants and the down-regulation of antioxidant enzyme expression (Tawadrous, Aziz, & Mostafa, 2013). Similar increase in ROS has been observed in cryptorchidism, in which chronic elevation of testicular temperature is a main factor for the impairment of testicular function (Smith et al., 2007). Furthermore, various animal models have also demonstrated that scrotal hyperthermia can impair androgen production, increase germ cell apoptosis and

AUTHOR'S PERSPECTIVE

Key points

- The effects of oxidative stress extend beyond the local scrotal environment, involving other hormonal axes.
- Microscopic subinguinal varicocelectomy confers high pregnancy rate, compared to other procedures.
- Empirical use of antioxidants supplementation can be beneficial in men with suboptimal outcomes following varicocele repair.
- Varicocelectomy may reduce the need of ART or improve the efficacy of ART in achieving a pregnancy.

Potential areas of research

- Long-term end points, such as pregnancy, and safety profiles of various antioxidants are required before these therapies can become a standard treatment option.
- Only a portion of men who undergo varicocelectomy will achieve spontaneous pregnancy. Future studies can seek to better stratify those who are most likely to benefit.
- Prospective longitudinal data comparing surgical intervention and observation are needed to guide diagnosis and management of pediatric and adolescent varicocele.

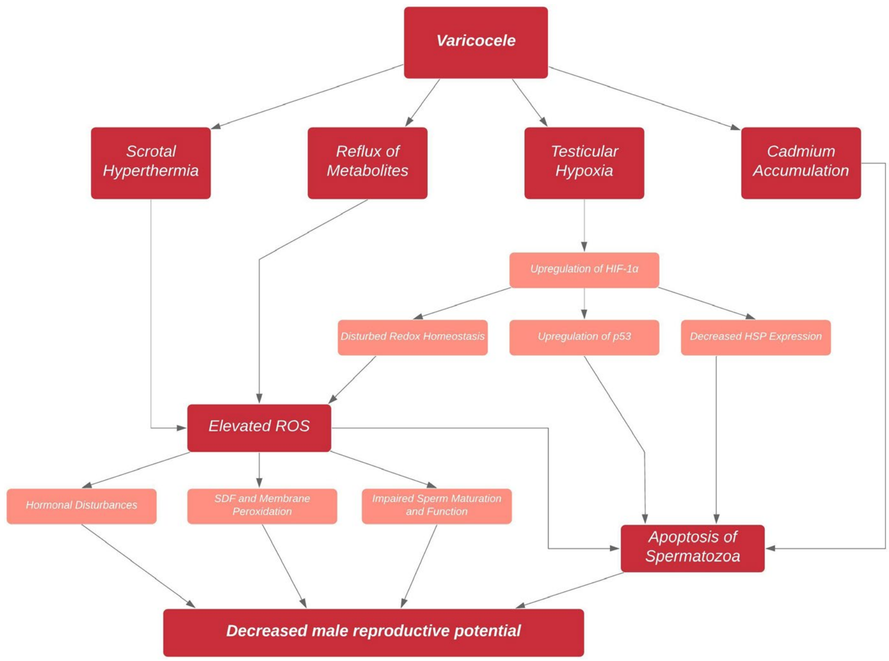

FIGURE 1 A representation of the pathophysiology of varicocele. Increase in oxidative stress remains a key event in decreasing male reproductive potential

reduce the expression of heat shock proteins (Shiraishi, Takihara, & Matsuyama, 2010).

2.1.2 | Reflux of metabolites

Venography in men with varicocele has also demonstrated an increase in retrograde flow, which may lead to an increase in the reflux of adrenal or renal metabolites (Comhaire & Kunnen, 1976). Elevated levels of catecholamines have been speculated to impair spermatogenesis and hormonal levels through the effects of vasoconstriction (Comhaire & Vermeulen, 1974). Other mediators, such as prostaglandin, serotonin and nitric oxide, have also been found to be elevated in the spermatic veins of patients with varicocele; however, their direct role in altering testicular function and fertility is unclear and have not been consistently observed (Tian et al., 2018).

2.1.3 | Testicular hypoxia

The impaired venous blood flow in varicoceles may also create local testicular hypoxia, supported by an increase in hypoxia-inducible factor-1α (HIF-1α) expression in testicular tissues of rats with varicocele (Hu, Zhou, Zhang, Xu, & Wang, 2015). While HIF-1α modulates multiple gene transcription and translation to promote cellular survival under hypoxia (Greijer & van der Wall, 2004), recent studies suggest that HIF-1α could also contradictorily decrease stem cell proliferation in the setting of decompensated or prolonged hypoxia (Wang et al., 2010). Some investigators propose that enhanced HIF-1α expression induces an increase in p53 expression, thus leading to/causing apoptosis acceleration in testicular tissue (Liang, Wen, Dong, Zhao, & Shi, 2015). A recent proteomic analysis has revealed that HIF-1α down-regulates the expression of heat shock proteins in men with unilateral varicocele. This study also demonstrated a decreased expression of oxidative phosphorylation proteins and an overproduction of reduced nicotinamide adenine dinucleotide (NADH), suggesting that spermatozoa from affected men have impaired mitochondrial efficiency and redox capabilities (Swain et al., 2019). More studies are needed to elucidate the effect exerted by these factors and their utility in predicting the degree of hypoxia.

2.1.4 | Cadmium accumulation

Cadmium accumulation is also known to contribute to male infertility, impairing spermatogenesis and sperm function (Benoff et al., 2009). Cadmium may cross the blood-testis barrier through direct activation of endothelial junctions and accumulate in the interstitium, with subsequent entry into the cells of the seminiferous epithelium. This metal ion can directly trigger apoptosis through the induction of Fas ligand and generation of ROS (Liu et al., 2008; Yuan et al., 2018). Other suggested mechanisms include disruption of actin filaments and calcium concentration (Benoff et al., 2005).

2.2 | Impact of varicocele-associated oxidative stress on sperm DNA integrity

Sperm DNA fragmentation (SDF) is one of the major findings in varicocele-induced infertility. SDF, which includes both single- and double-strand DNA breaks, has been widely observed to be positively associated with ROS production (Abdelbaki, Sabry, Al-Adl, & Sabry, 2017). In multiple systematic reviews, SDF rates were significantly higher in men with varicocele than that in healthy controls (Wang, Zhang, Lin, Zhang, & Zhang, 2012; Zini & Dohle, 2011). Furthermore, a recent review of over 20 studies accounting for more than 1,200 patients reported that surgical correction of varicocele significantly reduced SDF rates within 3–12 months post-operatively (Roque & Esteves, 2018). Other data also demonstrated that varicocelectomy is associated with improvements in OS markers and other advanced sperm function, emphasising the relationship among varicocele, OS and SDF (Mostafa, Nabil, Rashed, Abo-Sief, & Eissa, 2020). Despite these emerging evidence, the American Urological Association (AUA) and the American Society of Reproductive Medicine (ASRM) do not yet recommend the routine use of DNA integrity testing in the evaluation and management of male factor infertility (American Urological Association, 2011).

2.3 | Impact of varicocele-associated oxidative stress on epididymal sperm maturation and functions

The epididymis is involved in sperm development and transportation. In the epididymis, ROS can be generated by metabolically active principal cells. Regular production of antioxidants is essential in maintaining the microenvironment for sperm maturation (Agarwal et al., 2012). Changes in epididymal function have been investigated in several experimental varicocele models, with one study showing an increased in apoptosis within the epididymal tubules and concurrent decreased in epididymal weight and tubular diameters (Ozturk et al., 2008). Another study demonstrated similar findings as well as a decrease in epididymis-specific biochemical markers, such as neutral α-glucosidase (NAG), after varicoceles were induced in adolescent rats (Zhang, Qiu, Ma, Yu, & Wu, 2003). Semen analysis on men with a varicocele also revealed lower levels of NAG activity and diminished sperm integrity and maturation, reflected by tests evaluating water transport across sperm membrane and binding to hyaluronic acid (Vivas-Acevedo, Lozano-Hernández, & Camejo, 2014). It is hypothesised that hypoxia and heat stress are two main factors that lead to principal cells to overproduce ROS, impairing the maturation of spermatocytes and normal function of epididymal cells.

2.4 | Hormonal disturbance

Elaboration of OS can also disrupt Leydig cell steroidogenesis, leading to dysregulation of spermatogenesis in producing mature spermatozoa. A recent retrospective review demonstrated an association between varicocele repair and a mean increase of 109.1 ± 12.8 ng/dl in serum testosterone levels in 78 patients (Hsiao, Rosoff, Pale, Powell, & Goldstein, 2013). A prospective study also observed that post-varicocelectomy testosterone changes correlated significantly and inversely with baseline testosterone level (Abdel-Meguid et al., 2014). Other studies have also shown that varicocelectomy leads to an improvement in hormonal markers reflecting improved Sertoli and Leydig cell function and spermatogenesis (Hurtado de Catalfo, Ranieri-Casilla, Marra, Alaniz, & Marra, 2007). Furthermore, recent studies have established that adrenomedullin, a polypeptide hormone that is associated with increased OS, also reduces antioxidative capacity and steroidogenesis (Hu et al., 2015). ROS in the male reproductive system can also disrupt other hormonal axes. Activation of the HPA (hypothalamus–pituitary–adrenal) axis may lead to an increase in cortisol and reduce pituitary hormone secretion (Darbandi et al., 2018). Similarly, in the HPT (hypothalamus–pituitary–thyroid) axis, ROS can reduce thyroid hormone secretion, which decreases the expression of StAR (steroidogenic acute regulatory) protein in Leydig cells, thereby decreasing testosterone biosynthesis (Manna, Tena-Sempere, & Huhtaniemi, 1999). While it has long been implicated that OS causes infertility through disruption of local hormonal levels, the effect of OS may be more systemic and further studies are necessary to elucidate the impact of such complex metabolic functions on spermatogenesis and other semen parameters, especially in men with varicocele.

3 | TREATMENT OPTIONS

3.1 | Varicocelectomy

Numerous studies have observed that treatment of varicocele leads to an improvement in sperm DNA integrity, OS levels, semen parameters and sperm function (Baazeem et al., 2011), but more importantly, improvement of pregnancy outcomes, albeit this is somewhat controversial. In the first decade of the 21st century, a Cochrane Review proposed that there is no significant improvement in pregnancy rates following varicocelectomy (Jensen et al., 2017). However, these results were faulted for including men with subclinical varicoceles, which generally do not negatively affect fertility. Subsequently, one randomised trial involving 145 infertile men with abnormal semen parameters and clinically evident varicocele reported a spontaneous pregnancy rate of 32.9% in the treatment arm versus 13.9% in the control arm (OR: 3.04; 95% CI: 1.33–6.95) (Abdel-Meguid, Al-Sayyad, Tayib, & Farsi, 2011). The result of this trial was similar to that of an earlier meta-analysis that also demonstrated an improved odds of spontaneous pregnancy with surgical varicocelectomy (Marmar et al., 2007). These findings led to a subgroup analysis of the Cochrane Review that suggested a beneficial outcome with treatment of clinical varicoceles (OR: 2.39; 95% CI: 1.56–3.66) (Kroese, de Lange, Collins, & Evers, 2012). Treatment of varicocele is therefore recommended to all infertile men with a palpable varicocele and with one or more abnormal semen parameters or sperm function test results (American Society for Reproductive Medicine & Society for Male Reproduction and Urology 2014).

Numerous techniques have been adopted in the treatment of varicocele, each with its own benefits and risks. The spontaneous pregnancy rate and failure or recurrence rate reported in Table 1 are largely from a recent systematic review of 56 studies (Lundy & Sabanegh, 2018). The review reported a significantly higher pregnancy rate with microsurgical varicocelectomy (41%) versus other surgical approaches (37%, 26% and 26% for retroperitoneal, inguinal and laparoscopic, respectively) and angiographic embolisation (36%). Microsurgical subinguinal varicocelectomy also has the lowest failure/recurrence rate (1.2%) versus other surgical approaches (12.6%, 9.6% and 8.4% for retroperitoneal, inguinal and laparoscopic, respectively) and angiographic embolisation (7.4%). The meta-analysis also suggests that the microsurgical subinguinal approach is more effective for men who underwent varicocelectomy for pain, with 90% reporting partial/complete improvement (Table 1).

3.1.1 | Conventional varicocelectomy

An open retroperitoneal ligation approach (i.e. the Palomo technique) utilises an incision just medial to the anterior superior iliac spine (ASIS), allowing for visualisation of the internal spermatic vein more proximally, avoiding the extensive venous branching seen more distally (Palomo, 1949). This approach to varicocele ablation has the following disadvantages: high recurrence rate and hydrocele formation. In an inguinal (i.e. Ivanissevich) approach, an incision is made over the external inguinal ring and dissection is carried down to the inguinal canal to expose the spermatic cord (Ivanissevich, 1960). The dissection of the external spermatic fascia, however, may

TABLE 1 Effects of the various treatment options for varicocele repair (Lundy & Sabanegh, 2018)

Technique	Spontaneous pregnancy rate (%)	Failure or recurrence rate (%)	Sperm concentration improvement (10^6/ml)	Hydrocele rate (%)	Partial or complete improvement in pain (%)
Retroperitoneal ligation	37	12.6	12.5	7.5	76
Inguinal	26	9.6	11.5	5.3	75
Microsurgical subinguinal	41	1.2	12.1	0.6	90
Laparoscopic	26	8.4	19.8	6.7	85
Embolisation	36	7.4	10.3	0.0	–

lead to increased post-operative pain, risk of hernia and injury to the ilioinguinal nerve.

3.1.2 | Microsurgical varicocelectomy

A subinguinal (i.e. Marmar) approach is performed similarly but an incision is made more caudally below the external ring near the pubic tubercle (Marmar & Kim, 1994). A microscopic approach also allows identification of lymphatics and the testicular artery, minimising the risk of hydrocele formation and arterial ligation, respectively (Goldstein, Gilbert, Dicker, Dwosh, & Gnecco, 1992). Other well-established advantages include significant improvement in sperm count and motility and high pregnancy rate following the procedure (Jungwirth et al., 2001).

3.1.3 | Laparoscopic varicocelectomy

The laparoscopic approach, which is generally performed transperitoneally, offers the advantages of an easy identification of the internal spermatic artery proximally, and fewer number of veins that need to be ligated. Other benefits include an efficiency in treating bilateral varicoceles. The major downside to this approach is the greater rate of hydrocele formation, arterial ligation and all the potential complications associated with transperitoneal laparoscopic surgery (bowel injury, hernia, etc.) (Chan, 2011).

3.2 | Angiographic embolisation

Other nonsurgical treatment options include percutaneous embolisation, during which a coil or a sclerosing agent is released to generate controlled scarring, diverting blood flow away from the affected veins. In addition to their minimally invasive nature, several studies have established that angiographic embolisation leads to an improvement in sperm quality and pregnancy rate, similar to surgery (Abdulmaaboud et al., 1998; Bou Nasr et al., 2017). Percutaneous embolisation is also an attractive option for men who are not ideal surgical candidates, such as those with recurrent varicoceles or high anaesthesia risk. However, recurrence rate with this treatment has been reported to vary between 0% and 24% and overall technical failure to be 13.05% (Halpern, Mittal, Pereira, Bhatia, & Ramasamy, 2016). Due to the clear benefits of microsurgical varicocelectomy and the lack of large prospective, randomised trials comparing the two procedures, microsurgical subinguinal varicocelectomy is preferred if available.

3.3 | Varicocele and antioxidant therapy

Because OS has been recognised to play a central role in the pathophysiology of varicocele-induced infertility, there is considerable interest in investigating the utility of antioxidant therapy. One large cohort of infertile men with varicocele demonstrated a higher sperm concentration in 107 men treated with antioxidant combinations (clomiphene citrate, vitamins A and E, selenium, L-carnitine, pentoxifylline and antioxidants) for 3–6 months. Furthermore, spontaneous conception occurred in the partners of 47.1% of males after microsurgical varicocelectomy, 21.5% after drug stimulation and just 3.6% of those untreated (Gamidov, Ovchinnikov, Popova, Tkhagapsoeva, & Izhbaev, 2012). Newer evidence also suggests that antioxidants can be effective in improving other molecular parameters, such as DNA and chromatin integrity and lipid peroxidation (Gual-Frau et al., 2015; Hassani-Bafrani, Tavalaee, Arbabian, Dattilo, & Nasr-Esfahani, 2019).

Antioxidants have also been evaluated as adjuvant therapy. Several randomised trials demonstrated that antioxidant therapy following varicocelectomy or embolisation is associated with an improvement in OS biomarkers and sperm parameters, such as sperm concentration, motility and morphology (Azizollahi et al., 2013; Paradiso Galatioto et al., 2008). However, improvement in clinical outcomes with antioxidant adjuvant therapy is still unclear.

Antioxidant use in the treatment of varicocele-induced fertility has largely remained empirical, and there is lack of well-controlled, randomised prospective studies in evaluating their efficacy and safety. Further research is needed for such therapies to become standard treatment options, especially for men who are not candidates for or those who have failed surgical intervention.

4 | VARICOCELE AND ART

Compared to assisted reproductive technologies (ART), varicocelectomy remains a more cost-effective option and may appeal to those seeking a natural pregnancy (Hamada, Esteves, & Agarwal, 2016). However, varicocelectomy may also improve outcomes of ART or allow for less invasive methods to achieve a pregnancy. For instance, a recent study of 737 men investigated improvements in total motile sperm count (TMSC) following microsurgical varicocelectomy or embolisation, which allowed for 58.8% of men with a baseline TMSC < 5 million to be 'upgraded' from in vitro fertilisation (IVF) candidacy to intrauterine insemination (IUI) or natural pregnancy (NP) (Samplaski, Lo, Grober, Zini, & Jarvi, 2017). In addition, for men with a baseline TMSC 5–9 million, treatment of varicocele allowed 64.9% of men to become candidates for NP. Another meta-analysis reported a higher pregnancy and live birth rate in men who had varicocelectomy before intracytoplasmic sperm injection (ICSI) compared to those who did not have a varicocelectomy before ICSI (Esteves, Roque, & Agarwal, 2016). While there are no large prospective randomised trials evaluating the effect on varicocele repair on ART outcomes, these preliminary studies seem to suggest that varicocelectomy may either reduce the requirement for ART or enhance ART outcomes, and will remain an important step in the treatment of varicocele-induced infertility.

5 | CONCLUSION

Varicocele is the most common and correctable cause of male factor infertility. While the pathophysiology of varicocele-induced infertility may be multi-factorial, extensive evidence supports the central role of oxidative stress in negatively affecting various semen parameters, spermatogenesis and hormonal levels. Varicocelectomy remains the first-line treatment option in infertile men with palpable varicocele and abnormal semen parameters, with the microsurgical subinguinal approach conveying the greatest success rate and fewest complications. The empirical use of antioxidant supplement may confer some benefits in men to reduce oxidative damage. However, more robust data are needed to establish their efficacy as a standard management option. Varicocele repair may obviate the need for ART or augment ART therapy by improving outcomes.

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