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INVITED REVIEW

Male Fertility

Varicocele management in the era of *in vitro* fertilization/intracytoplasmic sperm injection

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Varicocele is the most common surgically treatable cause of male infertility, and often results in alterations in semen parameters, sperm DNA damage, and changes to the seminal milieu. Varicocele repair can result in improvement in these parameters in the majority of men with clinical varicocele; data supporting repair in men with subclinical varicocele are less definitive. In couples seeking fertility using assisted reproductive technologies (ARTs), varicocele repair may offer improvement in semen parameters and sperm health that can increase the likelihood of successful fertilization using techniques such as *in vitro* fertilization (IVF) or intracytoplasmic sperm injection (ICSI), or may decrease the level of ART needed to achieve successful pregnancy. Male infertility is an indicator of general male health, and evaluation of the infertile male with an eye toward future health can facilitate optimal screening and treatment of these men. Furthermore, varicocele may represent a progressive lesion, offering an argument for its repair, although this is currently unclear.

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INTRODUCTION

Testicular varicocele is an abnormal dilation of the pampiniform plexus of veins draining the testicle and can result in testicular discomfort, atrophy, infertility, and possibly hypogonadism. Varicocele represents the most common surgically treatable cause of male infertility worldwide and is found in approximately 15% of all adult males and 40% of males presenting for infertility evaluation.[1] While the etiology of varicocele has not clearly been established, poor testicular venous drainage may be the primary underlying cause of varicocele-associated testicular dysfunction.[1,2] Three etiologies of venous flow compromise have been identified: (1) absence or dysfunction of venous valves, facilitating retrograde blood flow, (2) differences in the angle of insertion of the left and right testicular veins into the left renal vein and vena cava, respectively, and (3) renal vein compression between the superior mesenteric artery and aorta (the "nutcracker effect"), which can limit venous outflow.[2–4]

More proximal causes of testicular dysfunction associated with varicocele include higher intratesticular temperature, testicular hypoxia, incomplete removal of testicular gonadotoxins, accumulation of oxidants in semen, reflux of renal and adrenal metabolites, and antisperm antibodies.[5–8] In many cases, these causes may reflect downstream effects of compromised venous flow. Varicocele can decrease testicular DNA polymerase activity, increase testicular cell apoptosis and reactive oxygen species (ROS) levels, alter Sertoli cell function, and decrease production of testosterone by Leydig cells.[7,9–11] Ultimately, multiple varicocele etiologies may contribute to the development of any individual patient's varicocele.

Although the link between clinical varicocele and infertility was established by Tulloch as early as 1955,[12] strong evidence supporting varicocele repair in men with unexplained infertility was lacking as recently as 2001.[13] Over the past decade, however, well-designed randomized controlled trials (RCTs) and other studies have firmly established varicocele repair as an effective treatment in infertile men with abnormal semen parameters.[14–16]

Since the advent of *in vitro* fertilization (IVF) in the late 1970s, even men with potentially treatable infertility have relied on assisted reproductive technologies (ARTs), especially IVF, and later intracytoplasmic sperm injection (ICSI), in lieu of specific therapies to treat their infertility. Although ART provides infertile couples with an avenue to biological parenthood, disadvantages including multiple gestation pregnancies, ovarian hyperstimulation, increased risk of birth defects, and high costs should not be overlooked. Special consideration must be given to ICSI, the use of which has more than doubled since 1996, rising from 36% to 76% of all fresh IVF cycles in 2012.[17] Unlike conventional IVF, ICSI bypasses natural barriers to fertilization, facilitating transmission of genetic defects; ICSI pregnancies have been associated with 1.5–4-fold increases in chromosomal abnormalities,[18,19] imprinting disorders,[20] autism,[21] intellectual disabilities,[21] and birth defects[22,23] when compared with pregnancies resulting from conventional IVF.

Recent studies have also linked male infertility to more general parameters of men's health, demonstrating an increased risk of cancer and several other health problems in infertile men.[24–28] Often, the health of these men is overlooked in efforts to initiate a pregnancy. In this setting of increased ART utilization and emerging health risks

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associated with infertility, varicocele repair offers a 2-fold advantage: improvement in the quality and quantity of sperm available for ART and, in some cases, a decreased need for ART by virtue of an increased rate of spontaneous pregnancy.

In this review, we discuss the effects of varicocele on sperm and the advantages of varicocele repair in patients considering ART, toward the goal of improved understanding and consideration of varicocele in the global approach to the infertile couple.

FUTURE FERTILITY – VARICOCELE AS A PROGRESSIVE LESION

An often overlooked consideration in the discussion of varicocele repair is the potential for progressive fertility decline if varicocele goes unrepaired. Observations suggesting a cumulative impact of varicoceles on testicular function date back to 1977, when Lipshultz and Corriere noted a significant decrease in testicular size and semen quality in 61 subfertile men with varicocele compared to 27 subfertile men without varicocele.[29] Since then, relatively few studies have examined the potential for varicocele as a progressive lesion, with conflicting findings.

A retrospective, date-matched study conducted by Witt and Lipshultz identified varicocele as the cause of infertility in 177 of 255 (69%) men with secondary infertility whereas only 128 of 255 men (50%) with primary infertility had infertility attributable to varicocele.[30] In addition, statistically significant elevations in prolactin, FSH, antisperm antibodies, and rates of pyuria and azoospermia ($P < 0.0001$) led us to conclude that a gradual decline in fertility may be associated with varicoceles. Gorelick and Goldstein corroborated these findings in a cross-sectional study of men with male factor infertility, finding palpable varicocele in 35% (352/1001) of men with primary infertility and 81% (79/98) of men with secondary infertility. The latter group also had lower mean sperm concentration (30.2 *vs* 46.1 $\times$ 10^6 ml^{-1}), more abnormally shaped sperm (72% *vs* 40%), and higher mean serum FSH levels (17.6 *vs* 7.9 $mIUml^{-1}$), suggesting that varicocele is a progressive lesion and prior fertility may decline in the presence of untreated varicocele.[31]

Evidence arguing against varicocele as a progressive lesion is limited. Diamond *et al*. conducted a prospective examination of testicular varicocele grade and volume in 41 boys (mean age 13.7 years) during 2–4 sequential visits, with a mean time between visits of 16 months, and found no change in varicocele grade ($P < 0.001$) or testicular volume differential on ultrasound ($P = 0.025$).[32] A more recent prospective study of 32 men with left-sided varicocele and impaired semen quality, and 30 age-matched men with varicocele and normal semen quality followed annually for 5 years (mean follow-up time 63.2 months) showed progressive deterioration of semen quality, defined as a decrease in sperm density, total sperm count, or total motile sperm count of >45% or deterioration of sperm motility or morphology of >20% during follow-up, in 28/32 men in the former group (87.5%) compared to only 6/30 in the latter (20%). These findings suggest that varicocele may not have a cumulative impact on testicular function in all men, and patients with varicocele and abnormal semen parameters may be at greater risk.[33]

All of the above studies have limitations. Data supporting a cumulative effect of varicocele are retrospective or cross-sectional and may introduce selection bias by including as few as 9% of men presenting for infertility evaluation.[34] Evidence suggesting that varicocele is a static lesion likewise suffers from selection bias with the exclusion of patients who desired surgery or refused close follow-up, as well as small cohort size. Thus, the need for well-designed, large prospective studies persists. Nevertheless, present data suggest that varicocele may have cumulative detrimental effects on testicular function, and until convincing evidence to the contrary emerges, the potential impact of varicocele on future fertility in affected males remains an argument in favor of repair.

EFFECTS OF VARICOCELE ON SPERM

MacLeod first observed the effects of varicocele on semen in 1965, noting a decrease in sperm motility and density, as well as the presence of increased numbers of amorphous cells, immature, and tapered forms.[35] This latter, nonspecific "stress pattern" of changes in semen parameters has since been repeatedly observed in men with varicocele but, to date, no morphologic changes specific to varicocele have been identified.[36,37] Despite this, it is clear that sperm from men with varicocele is functionally inferior, showing decreased ability to bind and fuse with both hamster and human oocytes.[38,39] However, even with examination using Kruger strict morphologic criteria, only a decrease in normal forms has been observed in men with varicocele, with significant improvement after repair.[40,41] Such observations suggest that current semen parameters in the evaluation of male infertility are suboptimal, incompletely reflecting sperm quality and function.[1]

Higher levels of reactive oxygen species (ROS) are the predominant known molecular aberrations in men with varicocele. Evidence suggests that ROS and the resulting oxidative stress serve as a common pathway in the pathogenesis of male subfertility, with elevated ROS levels present in 30%–80% of infertile men.[42–44] Increased ROS have also been observed in other conditions related to male fertility, including testicular torsion,[45] cryptorchidism,[46] and genitourinary tract infection.[47]

Although the mechanisms of ROS action are incompletely understood, studies suggest that they may play a key role in oxidation and reduction reactions regulating sperm hyperactivation, capacitation, zona pellucida binding, and the acrosome reaction.[48,49] ROS are generated at physiologic levels via aerobic metabolism within spermatozoa, as well as leukocytes.[42] Abnormal spermatozoa[50] and leukocytes, particularly when activated in the setting of infection and inflammation,[51] are the major sources of excess ROS production in semen. Normal spermatozoa may also produce higher ROS levels in proximity to ROS-producing abnormal sperm[52] or leukocytes.[51]

At higher than physiologic levels, ROS cause sperm cell membrane and DNA damage, resulting in poor sperm quality,[7,53] with effects compounded by lack of appropriate antioxidant defenses.[54] ROS exert their impact on sperm cell membranes by increasing peroxidation of membrane fatty acids, causing a decrease in sperm head and midpiece cell membrane fluidity, and ultimately resulting in decreased sperm motility and fertilizing ability.[55–57] Sperm motility is further impaired by damage to axonemal proteins, causing accelerated adenosine triphosphate (ATP) consumption.[58]

Excess ROS also overcome seminal defenses against oxidative stress, namely tight packing of sperm DNA and seminal antioxidants, causing spermatozoal nuclear and mitochondrial DNA damage at both the nitrogenous base and phosphate backbone.[59] This may result in a variety of DNA aberrations, including point mutations, polymorphisms, deletions, chromosomal rearrangements, frame shifts, and single-stranded or double-stranded breaks,[60] ultimately leading to activation of caspases and sperm apoptosis.[56] This damage can be especially evident in the long arm of the male Y chromosome whereby microdeletions of the Azoospermia Factor (*AZF*) region result in azoospermia in the offspring of affected individuals.[42,59] Such observations reinforce the clinical importance of oxidative stress and spermatozoal DNA damage, which may increase both the difficulty

of achieving successful pregnancy using ART[59] and the risk of genetic disease transmission to subsequent pregnancies.

While light microscopic examination of sperm from men with varicocele has yielded no specific findings, electron microscopy has demonstrated various ultrastructural alterations. Efforts to understand sperm ultrastructure in men with varicocele began as early as 1978, with the observation of multinuclear spermatids indicating abnormal spermiogenesis.[61] Cameron *et al*. found significant Sertoli cell involvement in varicocele pathology, revealing spermatid-Sertoli cell malorientation and structurally abnormal germ cell junctional complexes with adluminal compartment defects in testicular biopsies of 21 men with varicocele assessed by electron microscopy.[62] Later ultrastructural findings associated with varicocele include increased vacuolization of the endoplasmic reticulum and abnormal retention of cytoplasmic droplets, which correlate with ROS production and DNA damage, defective sperm function, impaired spermatogenesis, and lower IVF success rates relative to fertile males.[63–66] More recently, Blumer *et al*. noted a higher percentage of men with varicocele have inactive mitochondria, resulting in functionally defective sperm tails.[39]

EFFECTS OF VARICOCELE REPAIR ON ROS AND SPERM ULTRASTRUCTURE

Current literature examining the benefit of varicocele repair on semen parameters presents mixed findings, with a majority of studies and meta-analyses reporting improvements in one or more parameters, but some observing no changes.[16,67,68] Overall benefit is reported in meta-analyses evaluating semen parameters following varicocelectomy,[1] but existing semen parameters are not entirely representative of sperm function. As such, molecular and ultrastructural evaluation may present more sensitive alternatives to assess impact of repair.

On a molecular level, ROS are elevated both in the semen and systemically in men with varicocele, and surgical repair results in decreased ROS, higher antioxidant levels, and lower DNA fragmentation.[7,69–71] Various studies have shown that men with varicoceles have significantly higher sperm DNA damage than controls, with a mean difference of 9.84% (95% CI: 9.19–10.49; $P < 0.00001$).[42,70,72,73] A 2012 meta-analysis by Wang *et al*. found that varicocelectomy decreases sperm DNA fragmentation with a mean difference of −3.37% (95% CI: −4.09–−2.65; $P < 0.00001$) relative to control.[73]

Ultrastructural studies have likewise shown improvement in sperm ultrastructure with varicocele repair. Reichart *et al*. quantitatively examined sperm subcellular organelles in men with treated and untreated varicoceles, observing significant increases in normal acrosome structure, chromatin condensation, and sperm head appearance ($P \leq 0.01$), but finding no changes in tail subcellular organelles following treatment. Notably, semen parameters were unchanged between groups, implying that ultramorphology may be a more sensitive means to assess sperm pathology in men with varicocele.[74] A 2011 meta-analysis of prospective studies reported similar findings, with varicocele repair resulting in improvement of sperm head organelle ultrastructural defects in infertile men.[16]

Multiple studies have demonstrated that dietary antioxidant therapy, even without varicocelectomy, leads to semen parameter improvement in men with and without varicocele,[75–77] supporting a contribution of elevated ROS levels to varicocele pathophysiology. A 2014 Cochrane review encompassing 48 randomized controlled trials (RCTs) encompassing 4179 subfertile men found that antioxidant therapy may result in increased live birth rates (OR: 4.21, 95% CI: 2.08–8.51, $P < 0.0001$, 4 RCTs, 277 men) and increased clinical pregnancy rates (OR: 3.43, 95% CI: 1.92–6.11, $P < 0.0001$, 7 RCTs, 522 men), though this pooled cohort was considered low quality given the small sample sizes of the included studies and inclusion criteria not limited to men with varicocele.[78] A variety of antioxidants have been examined for potential benefit in male infertility. A 2010 review of antioxidant therapy in infertile males supports the use of Vitamins C, E, and carnitine as providing the greatest improvement to semen parameters and pregnancy rates.[79] Evidence supporting the use of glutathione, selenium, and coenzyme Q10 use is less robust.[79] These studies, however, are limited by methodologic flaws including small sample size, lack of randomization, and lack of supplement regimen standardization or control of baseline dietary antioxidant consumption.[42,79]

IMPACT OF VARICOCELE REPAIR ON ART CONSIDERATIONS AND OUTCOMES

The benefits of varicocele repair in couples utilizing ART are incompletely elucidated though current literature suggests that varicocele repair before ART may result in higher overall pregnancy and live birth rates. Multiple studies also note that varicocele repair may lessen the degree of ART required or eliminate the need for ART altogether, with one study reporting spontaneous pregnancy rates as high as 37% following repair.[80–82]

A 2001 retrospective study evaluating 58 couples undergoing intrauterine insemination (IUI) found higher pregnancy (11.8% *vs* 6.3%, $P = 0.04$) and live birth rates (11.8% *vs* 1.6%, $P = 0.0007$) in the 34 couples in whom varicocele had been microsurgically repaired despite no difference in postwash sperm counts.[80] The authors suggest that these results support the presence of a functional factor not measured in routine semen analysis that can impact reproductive outcomes. These results were supported by Cayan *et al*. in a prospective evaluation of 540 males with clinical varicocele following varicocelectomy, in which 50% (271/540) of patients had >50% improvement in total motile sperm counts, with an overall spontaneous pregnancy rate of 36.6% with mean time to conception of 7 months. Similarly, Esteves *et al*. found higher pregnancy (OR: 1.82, 95% CI: 1.06–3.15) and live birth rates (OR: 1.87, 95% CI: 1.08–3.25), as well as lower miscarriage rates (OR: 0.43, 95% CI: 0.22–0.84) in 80 men who had undergone varicocelectomy before ICSI, relative to 162 men who had not. In addition, total motile sperm counts increased and sperm defect scores improved in the treatment group.[82]

In contrast, a more recent retrospective study of male partners with clinical varicocele by Pasqualotto *et al*. found no significant difference in spontaneous implantation, pregnancy, or miscarriage rates in 169 men undergoing varicocele repair before ICSI when compared with 79 couples forgoing repair. The authors, however, found significant improvement in fertilization rates between the two groups (73.2% *vs* 64.9%, $P = 0.0377$) and concluded that all patients undergoing ICSI should first undergo varicocele repair.[83]

To date, only one meta-analysis addressing the potential benefits of varicocelectomy on ART outcomes has been conducted, finding significant improvements in both clinical pregnancy rate (OR: 1.59, 95% CI: 1.19–2.12, $I^2 = 25\%$) and live birth rates (OR: 2.17, 95% CI: 1.55–3.06, $I^2 = 0\%$) in patients who had undergone varicocelectomy before ICSI compared to those who had not. The meta-analysis included four studies with a total of 870 ICSI cycles, and notably included the above study conducted by Pasqualotto *et al*.[84]

Numerous limitations must be considered when interpreting the findings of these studies. First, the above studies were not randomized, resulting in potential selection bias wherein men with good or borderline

semen parameters may have been counseled to defer varicocele treatment in favor of proceeding directly to intrauterine insemination (IUI). In addition, most of the above studies were retrospective analyses and did not include objective measures of the effects of varicocelectomy on semen, which can influence the outcomes of IVF/ICSI.[85] Patients with more severe semen abnormalities were also more likely to pursue surgical treatment prior to IUI as shown by Zini *et al*. in a retrospective analysis of the clinical characteristics of 610 infertile males with varicocele. The study found that 60% (363/610) of patients opted for surgical treatment, reporting higher prevalence of primary infertility (80% *vs* 71%), significantly smaller testicles bilaterally (by ~2 ml), and significantly lower sperm concentration ($19.8 \pm 24.6 \times 10^6$ ml^{-1} *vs* $27.6 \pm 33.9 \times 10^6$ ml^{-1}; $P = 0.001$) and motility (25.5% ±17.1% *vs* 32.8% ± 21.2%; $P < 0.001$) in the surgical group than in men opting for observation.[86] Furthermore, couples who responded well to surgical varicocelectomy may have achieved early spontaneous pregnancy without ART, resulting in exclusion from the final analysis. While it is unlikely that future studies will be randomized given the economics, complexity, and female factor considerations influencing couples' decision-making, the conflicting evidence in the current literature emphasizes the need for further well-designed studies in this area.

VARICOCELE REPAIR IN MEN WITH NONOBSTRUCTIVE AZOOSPERMIA

While use of IVF/ICSI in men with spermatogenic failure may be unavoidable, varicocele repair may restore healthy sperm to the ejaculate in the subset of infertile men with nonobstructive azoospermia (NOA) and clinical varicocele, lessening or eliminating altogether the need for ART in this population.[1] The likelihood of finding sperm in the ejaculate is directly related to testicular histology, with multiple studies finding significant increases in sperm counts only in men with hypospermatogenesis or late maturation arrest whereas men with early maturation arrest or Sertoli cell only (SCO) histology have little to no improvement in semen parameters.[34,87] Despite the possibility of natural conception, initially azoospermic men should therefore be counseled that ART may be necessary to produce pregnancy.[88] Schlegel and Kaufmann found that <10% of NOA men with varicocele had adequate motile sperm for ICSI following repair, and observed no significant difference in sperm retrieval rates at the time of testicular sperm extraction (TESE) in those with prior varicocelectomy.[89] It is worth noting, however, that the study cohort consisted of only 31 men, and more recent studies have shown higher sperm retrieval rates in men with NOA following varicocele repair.[90,91]

Between 5% and 35%[89,92,93] of NOA men have sperm in the ejaculate intermittently even without treatment, compared to only 19% and 22% following varicocelectomy reported by Abdel-Meguid and Schlegel and Kaufmann, respectively.[89,94] Moreover, a gradual decline in spermatogenesis and return to azoospermia in previously NOA men with varicocele has been reported in up to 55.5% of patients 1 year after varicocelectomy, making the long-term benefit of varicocele repair in this population unclear.[92] Given that relatively few men experience return of spermatogenesis following varicocelectomy and a significant proportion of these lose their spermatogenic capability, sperm cryopreservation is recommended following initial improvement after varicocelectomy in these men.[88]

Despite these observations, it is important to consider that man with NOA due to primary testicular failure represents a challenging patient cohort in whom robust return of spermatogenesis is often elusive.[95] However, varicocele repair before ART may offer these men the potential for successful pregnancy and may decrease the costs associated with that pregnancy by potentially decreasing the need for ICSI in cases where sperm return to the ejaculate in sufficient quantities to permit IUI.

COST CONSIDERATIONS

Treatment cost is an important practical consideration in infertility treatment, particularly given the multiple treatment options available with comparable efficacy and safety. Although varicocele repair and ART may be used in conjunction, multiple cost analyses have juxtaposed their overall financial burden.

Schlegel used nationwide charge estimates in the United States in 1994 to estimate cost per delivery for varicocelectomy at $26 268, with ICSI being significantly more expensive at $89 091; spontaneous pregnancy rates were comparable for the two (30% for varicocelectomy *vs* 28% for one IVF cycle with ICSI).[96] A more recent analysis in 2013 showed similar findings in the Korean healthcare system, with varicocelectomy costing $10 534 and ICSI $14 893. Notably, more than half of surgical costs were subsidized in comparison to <10% of ICSI costs, representing an important consideration for the individual patient.[97] While the absolute costs for each treatment approach are significantly different and are representative of costs in only two countries, both analyses showed that varicocelectomy is more cost-effective than ICSI.

Meng *et al*. examined cost from an institution-wide perspective, stratifying patients into two groups depending on whether their postoperative sperm concentrations were greater than or less than 10×10^6 ml^{-1}, with those patients with higher sperm concentrations being more likely to achieve pregnancy via the less expensive IUI, and those with lower sperm concentrations likely requiring sperm extraction/ICSI. Varicocele repair was found to be more cost-effective than ART for a particular institution when postoperative pregnancy rates were consistently >45% for the IUI group and >14% for those requiring ICSI. Of note, the authors report that 2002 Centers for Disease Control (CDC) data cite IVF/ICSI success rates of 28.5% and 30% for the CDC and University of California, San Diego, respectively, well above the 14% model threshold.[98]

In men with NOA, Lee *et al*. found that microsurgical TESE was more cost-effective than varicocelectomy ($65 515 *vs* $76 878 in 1999, $69 731 *vs* $79 576 in 2005) using cost data from the five highest volume IVF facilities in the United States. Costs for both procedures improved relative to inflation over time, and the authors noted that relative cost effectiveness of TESE versus varicocelectomy in the future will only change with increase in spontaneous live delivery rates or change in IVF success rates.[99]

Four treatment strategies, including (1) observation, (2) immediate IVF without treatment, (3) varicocelectomy followed by IVF if varicocelectomy alone is unsuccessful, and (4) gonadotropin-stimulated IUI followed by IVF if IUI is unsuccessful, for varicocele-related infertility were evaluated for cost effectiveness from both patient and insurer perspectives in a 2002 retrospective analysis by Penson *et al*. The study used the United States Consumer Price Index medical care data for cost estimates and found that varicocelectomy followed by IVF and IUI followed by IVF were the most cost-effective treatment approaches. Costs per live delivery were $44 522 and $49 575, and the probabilities of live delivery were 0.72 and 0.73, for varicocelectomy/IVF and IUI/IVF, respectively. However, between these two options, patients and insurers had different preferences. For the insurer, the incremental cost for each additional live birth that IUI/IVF offers over varicocelectomy/IVF is $561 423. From the patient perspective, however, the rational decision maker would always be willing to pay the slightly higher cost of IUI/IVF (incremental cost per live birth *vs* observation of $27 371) for the added benefit in effectiveness if they were initially

willing to invest in varicocelectomy/IVF (incremental cost per live birth *vs* observation of $27 618).[100]

The conclusions outlined above are mitigated by omission of numerous considerations, including the number of children desired by a couple, downstream costs of birth defects and complications associated with ART, and assumption of variable costs between countries or institutions. These limitations, as well as the relative dearth of studies examining cost effectiveness of varicocele treatment across nations and healthcare systems, support the need for further well-designed cost analyses. Nevertheless, the above data largely support the conclusion that varicocele repair is more cost-effective for both institutions and patients, whether used alone or in combination with IVF to initiate a pregnancy, and that varicocele repair in conjunction with IVF offers the greatest economic benefit and success for couples with varicocele-related infertility who require ART to initiate a pregnancy.

CONCLUSIONS

Varicocele often results in alterations in semen parameters, sperm DNA damage and changes to the seminal milieu. Current data also suggest that varicocele may be a progressive lesion though risk factors identifying men susceptible to sequelae of untreated varicocele remain to be determined. Varicocele repair is a cost-effective treatment modality that can result in improvement in semen parameters, pregnancy rates, and live birth rates for most infertile males with clinical varicocele; data supporting repair in men with clinical varicocele and nonobstructive azoospermia are less definitive. In couples seeking fertility using ART, varicocele repair may offer improvement in semen parameters and sperm health that can increase the likelihood of successful fertilization using IVF or ICSI and may decrease the level of ART needed to achieve successful pregnancy.

Future work is needed in evaluating the cost-effectiveness of varicocele treatments globally, and further investigation elucidating the impact of varicocele and its repair on testicular endocrine function and sperm ultrastructure and function will be essential in further driving management recommendations and outcomes of affected men.

AUTHOR CONTRIBUTIONS

PP, AC, TSH, and AWP participated in the conception and design, drafting, and final approval of the manuscript. PP and AWP acquired, analyzed, and interpreted the data, and confirmed the intellectual content of the work.

COMPETING INTERESTS

None declared.

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