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INVITED REVIEW

Male Fertility

Cost-effectiveness of varicocele surgery in the era of assisted reproductive technology

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The advent of innovative techniques for addressing infertility has made for exciting times in the arena of andrology. The success of microTESE for retrieving sperm has enabled azoospermic men to have the opportunity to father biological children when it was previously impossible. The ability to offer a variety of assisted reproductive techniques that includes intracytoplasmic sperm injection has opened the door for couples with male factor infertility who were otherwise untreatable. With the multitude of options available to infertile couples, however, comes an unsurprising degree of controversy regarding what treatments should be offered and when. Complicating the picture is the question of if and when varicocele repair should be undertaken, and the financial implications of the treatment decisions that are made. The infertile couple with varicocele warrants careful consideration. The overall efficacy of varicocele repair as well as cost-effectiveness of repair compared to immediate microTESE in azoospermic men and assisted reproductive technology in men with suboptimal semen parameters will be reviewed.

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INTRODUCTION

Varicoceles are dilated spermatic cord veins of the pampiniform plexus that are diagnosed by palpation on physical examination; subclinical varicoceles are those which can only be appreciated on imaging such as ultrasound. The prevailing theory regarding the etiology of varicoceles is that they develop during puberty because of the growth of the testis and spermatic cord structures, and are secondary to incompetent venous valves as well as the insertion of the left gonadal vein at a 90° angle into the left renal vein.[1] Regardless of their origin, varicoceles have been demonstrated to affect Leydig, Sertoli, and germ cells, and have the potential for affecting spermatogenesis as well as hormone production and function.[2]

There are multiple theories regarding how varicoceles may impact testicular function, but no mechanisms have definitively been elucidated.[3] It is most commonly thought that the temperature of the scrotal contents can be increased when poor venous circulation disrupts the testicular countercurrent cooling system. Another theory posits that metabolic by-products that would typically have been quickly removed from the testicular microenvironment negatively affect function; reflux from renal and adrenal metabolites have also been implicated.[4] The increased hydrostatic pressure found over the tortuous course of the spermatic veins may also augment the negative affect on testicular function, and any of these proposed mechanisms could result in dysfunctional and decreased spermatogenesis as well as increased oxidative stress and DNA damage.

Because varicoceles can be found in 30% of men with primary infertility and up to 80% of men with secondary infertility, the question regarding whom to repair is important.[5] Although it is broadly apparent that varicocele repair is beneficial to men, identifying the specific patient and couple who would benefit most from surgical intervention remains embedded in controversy.[6] The American Society for Reproductive Medicine updated their guidelines for varicoceles management in infertile couples in 2014, and best practice guidelines from the American Urologic Association mirror these recommendations.[7] The practice committee concluded that varicocele repair for infertility is indicated under the following conditions: (i) couple is infertile (ii) male partner has a palpable (clinical) varicocele (iii) female partner has normal fertility or a treatable cause of infertility and (iv) the male partner has at least one abnormal semen parameter (not including isolated teratozoospermia).

EFFICACY OF VARICOCELE REPAIR

The definition of success after varicocele repair has been a moving target that warrants consideration. Even though surgical repair may be successful in eliminating dilated veins of the spermatic cord, clearly the outcome of interest is related to enhancing fertility potential. Improvement in semen parameters is an easily assessed outcome; however, ultimately this may not be an outcome that is relevant to infertile couples if the improvements do not translate to improved live birth rates or improved assisted reproductive technology (ART) outcomes that preclude the need for additional ART cycles. In addition, studies that are utilized to elucidate the efficacy of varicocele repair in the infertile couple should be limited to men who meet society standards for a recommendation for varicocele repair. Therefore, studies that include men who had subclinical varicoceles and normal semen parameters do not inform our understanding of the outcome of varicocele repair on infertility.

Multiple studies of varying quality have been published which attempt to address the success of varicocele repair in the management of infertile couples. Richardson *et al.* critically reviewed treatment outcomes in publications from 1994 to 2008 and indicated that in addition to improvements in semen parameters, 2291 couples involved

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in 24 studies had an average natural pregnancy rate of 39.4% after varicocele repair.[8] Abdel-Meguid *et al*. randomized 145 men with clinical varicoceles and at least 1 year of infertility to either observation ($n = 72$) or varicocele repair ($n = 73$).[9] The natural pregnancy rate was 13.9% in the observed arm and 32.9% after varicocele repair, with an odds ratio 3.04 (95% confidence interval [CI]: 1.33–6.95). Furthermore, these authors demonstrate a number needed to treat of 5.27 (95% CI: 1.55–8.99) to achieve natural pregnancy after varicocele repair.

Esteves *et al*. studied 242 couples who underwent intracytoplasmic sperm injection (ICSI); 80 had prior varicocele repair with no evidence of recurrence and 162 had untreated varicoceles at the time of ICSI.[10] The live birth rate was higher in the couples who had varicocele repair compared to no repair (46.2% *vs* 31.4%, respectively, $P = 0.03$). Notably, Pasqualotto *et al*. did not demonstrate a difference in pregnancy rate after ICSI.[11] When these authors compared ICSI outcomes between 79 couples who had a clinical varicocele and 169 couples who had a varicocele repair, the pregnancy rate was 31.1% *vs*. 30.9%, $P = 0.98$. Importantly, pregnancy rate (defined in this study as visualization of a gestational sac by ultrasound at 7 weeks) is a much less clinically relevant outcome than live birth rate, and the importance of the results should be weighted appropriately as live birth rate is clearly more robust. It is well-established that clinical pregnancy rates cannot be extrapolated to live birth rates, and clinical pregnancy is therefore not an equivalent proxy. In addition, this study only included men with grade III varicoceles, and this selection bias prevents the broad applicability of the results to all men with clinical varicoceles.

The principle that pregnancy rate cannot be directly extrapolated to live birth rate is underscored by the study of Mansour Ghanaie *et al*.[12] These authors randomized 136 men who had clinical varicoceles to surgical repair or observation (68 per group). All female partners had a history of recurrent miscarriage. Pregnancy rate was 44.1% in the group who underwent surgical repair, and 19.1% in the expectant management group ($P = 0.001$). Furthermore, of the pregnancies, there was a significant difference in miscarriage rate that further favored the varicocele repair group (13.3% *vs* 69.2%, $P = 0.001$) beyond the initial outcome of clinical pregnancy that would no doubt lend itself to improved live birth rate in the treated group.

An important consideration regarding the outcomes of studies comparing varicocelectomy to expectant management is the selection of subjects, especially since the bulk of the literature is retrospective and nonrandomized. The bias introduced in nonrandomized studies does not allow definitive conclusions regarding the efficacy of varicocele repair versus expectant management regarding live birth rate. For example, Zini *et al*. compared 363 men who elected to undergo varicocelectomy to 247 men with clinical varicoceles who were offered surgical repair but chose expectant management.[13] In the 64% of patients for whom they had any pregnancy outcome documented, they showed no difference in natural or ART-assisted pregnancy rate between the two groups. These data could be interpreted as supporting the idea that varicocele intervention does not affect pregnancy outcome. However, closer examination of the methodology reveals otherwise. At baseline, the two groups are very different. The varicocele repair group had significantly worse semen parameters, decreased testicular volume, and significantly more men with primary infertility than the expectant management group. It can be argued that because the group that chose surgical repair had notably decreased baseline function, the varicocele repair was able to overcome this baseline deficit and equalize the couple's chance of pregnancy to those who have less severe dysfunction. Without appropriately designed prospective trials, however, this hypothesis remains to be definitively proven.

COST ANALYSIS OF ART

Although the clinical effectiveness of varicocele repair appears substantial, the question of its cost-effectiveness should be addressed because ART is also an effective treatment of infertility. The cost of the various ART procedures is an important consideration for couples and society given that private and public insurance providers cannot be replied on to provide routinely coverage for these interventions, and there is wide variability of cost-effectiveness when comparing across various ART procedures.[14] Omurtag *et al*. found that the average direct cost of one *in vitro* fertilization (IVF) cycle in the US is $9226, and this is associated with an increase in premium absorbed by the couple.[15] Chambers *et al*. found a direct cost of one ART cycle in the US to be $13 000.[16] The out-of-pocket expense to cover these direct costs varies considerably across countries and by insurance provider in the US. Importantly, these estimates of cost do not account for the indirect costs associated with ART that include the loss of productivity and wages which couples encounter, the unexpected cost of managing complications such as ovarian hyperstimulation syndrome, and the increased cost to the family and society for multiple gestation births.[17] The elevated price tag is not unique to the US, and other countries also face substantial cost associated with ART even with government funded support.[18–20] Unequivocally, the direct and indirect costs of ART has been a major driving force behind its lack of utilization nationally and internationally.[21] This cost can be insurmountable to many couples, and interventions that can attenuate the economic price of infertility are worthwhile.

Importantly, the financial benefits of preventing the need for ART extend beyond the initial cost of the procedure, and any steps that increase the spontaneous pregnancy rate are meaningful. IVF/ICSI is associated with an increase in twin pregnancy; the international twin birth rate is 20% after ART compared to 2% after natural conception.[22] Multiple gestations pose greater risk to the mother, and also have an increased rate of premature delivery and perinatal mortality compared to their singleton counterparts, thereby compounding the cost of prenatal care as well as neonatal care.[23] The increased economic cost of twin and higher order births continues lifelong as these children face significantly increased long-term morbidities that are related to preterm delivery.

COST-EFFECTIVENESS OF VARICOCELE REPAIR

The question of whether a varicocele repair is cost-effective depends on the degree of abnormality found in the semen analysis. There is clearly an increase in natural pregnancy rate after varicocele repair in men who have suboptimal semen parameters.[24,25] In addition, Ashkenazi *et al*. indicated that varicocelectomy can be a helpful procedure if it is incorporated into the treatment of infertile couples who have previously failed IVF cycles.[26] These authors had six pregnancies occur out of 22 couples who underwent varicocele repair after failing prior IVF, therefore preventing the need for additional cycles in 27% of the couples in this study. While the cost of including the varicocele procedure with IVF is obviously greater than with a single cycle of IVF alone, the increase in ART success will prevent multiple rounds of IVF. Clearly, incorporating varicocele repair with ART is a financially responsible option.

Conversely, the role of varicocele repair in men with nonobstructive azoospermia (NOA) is not nearly as clear. A recent meta-analysis of 233 men with NOA showed a 6% natural pregnancy rate after varicocele repair.[27] These same authors also found that 39% of previously azoospermic men had return of motile sperm to their ejaculate after varicocele repair, thus precluding the need for sperm retrieval procedures such as microTESE. Finding the return of sperm to the ejaculate after varicocelectomy has prompted the ongoing debate regarding whether varicocele repair is appropriate for men with varicoceles and NOA as

initial therapy, or whether an immediate attempt at sperm retrieval via microTESE is indicated. Lee *et al*. performed a cost analysis comparing varicocele to microTESE that soundly demonstrated the greater cost-effectiveness of proceeding directly to microTESE and deferring varicocele repair.[28] These authors utilized both direct and indirect costs and showed that varicoceles repaired in azoospermic men would have to result in a 40% spontaneous pregnancy rate to be favored over proceeding directly to microTESE. In light of the documented 6% spontaneous pregnancy rate for azoospermic men who undergo varicocele repair, immediate microTESE is clearly indicated from a financial perspective.

When comparing cost-effectiveness of varicocele repair in subfertile couples, however, varicocelectomy does have significant advantages. Schlegel modeled the costs of varicocele and IVF/ICSI, and, importantly, used both direct and indirect costs to achieve the most accurate cost per live birth which couples would encounter.[29] This model demonstrated that the cost per delivery per varicocele repair is remarkably less than the cost per delivery with ICSI. Specifically, he found that the average cost per live birth was $89 091 for IVF/ICSI and $26 268 for varicocele repair. Therefore, varicoceles associated with suboptimal semen parameters and infertility should be treated because this intervention has a pointedly better cost-effectiveness ratio per live birth when compared to ICSI.

Penson *et al*. compared the cost-effectiveness of four possible treatment strategies for infertility related to varicocele.[30] The treatment strategies were: (i) observation (ii) varicocele repair followed by up to three IVF cycles if the couple did not conceive in the year after varicocelectomy (iii) three cycles of ovarian stimulation and intrauterine insemination (IUI) followed by three cycles of IVF if the IUI failed and (iv) up to three cycles of immediate IVF. Observation resulted in only 14% live births. Although indirect costs were not accounted for in this analysis, these authors clearly revealed that proceeding directly to IVF is the least cost-effective management of infertility when the outcome measured is cost per live delivery. In addition, immediate IVF was only 61% effective, making this strategy more expensive coupled with a less effective outcome when compared to either immediate varicocele repair or IUI. Importantly, the probability of live delivery for varicocele before IVF was on par with IUI before IVF at 72% and 73%, respectively. The average cost per live delivery of the varicocele group was $32 171 while the average cost per live delivery of the IUI group was slightly higher at $36 322. Varicocele repair is again demonstrably more cost-effective with impressive success rates. Because the authors did not include indirect costs in their analysis, it is likely that the cost benefit of varicocele repair is underestimated because the indirect costs of IUI/IVF are greater than the indirect costs related to varicocele repair.

Meng *et al*. created a decision analysis model for infertile couples with varicoceles.[31] These authors found their direct institutional costs to be $4500 for varicocele repair, $10 000 for one ICSI cycle, and $500 for one IUI cycle. They demonstrate that varicocele repair is more cost-effective than ICSI when men had a preoperative total motile count of <10 million sperm. When men had a total motile count of >10 million sperm, and thus qualified for IUI, varicocele repair was only more cost-effective than IUI when the postoperative pregnancy rate was >45%.

CONCLUSION

Because the prevalence of infertility is increasing, steps to attenuate the economic burden of the treatment of infertility on couples and society are critical. Varicocele repair has been shown to increase natural pregnancy rate, precluding the need for ART and its attendant costs and risks altogether in couples with suboptimal semen parameters. Furthermore, varicocele repair can preclude the need for multiple ART cycles because of the improvement in live birth rate after ART it affords. Couples who are infertile secondary to nonobstructive azoospermia and concurrent varicocele, however, are most likely to benefit from proceeding directly to microTESE and deferring varicocele repair.

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