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INVITED REVIEW

Male Fertility

Prognostic factors for a favorable outcome after varicocele repair in adolescents and adults

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The effect of varicocele repair on male fertility remains controversial. It would be helpful to determined which men would benefit most from varicocele repair, and target repair efforts at those individuals. A detailed review of the literature on prognostic factors for varicocele repair was performed using the PubMed NLM database. We found that the best predictor of postvaricocelectomy semen parameters is the preoperative semen parameters. The greatest improvements in semen parameters were found in men with larger varicoceles. While there is controversy, higher testosterone, younger age and larger testis size, in some studies predict for improvements in semen parameters postvaricocelectomy. A nomogram has been developed to predict the postvaricocelectomy semen parameters based on the preoperative semen parameters, varicocele grade and the age of the man (www.fertilitytreatmentresults.com). Limited data consistently demonstrates the greatest improvements in DNA fragmentation rates in men with higher baseline DNA fragmentation rates. With respect to reproductive outcomes, higher baseline sperm density consistently predicts for natural pregnancy or assisted reproductive technology (ART) pregnancy rates. In addition, varicocele repair does seem to reduce the need for more invasive modalities of ART. In conclusion, we can now start to use specific parameters such as baseline semen quality, varicocele grade and patient age to predict post-repair semen quality and fertility potential following varicocelectomy.

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INTRODUCTION

The effect of varicocele repair on male fertility remains debatable.[1] Though the majority of studies report that varicocele repair results in improved semen parameters, not all reports support this finding.[2,3] The impact on natural pregnancy rates is even more controversial.[1] Based on current evidence, both the American Urological Association (AUA) and the American Society for Reproductive Medicine (ASRM) have recommended varicocele repair for infertile men with a clinical varicocele and one or more abnormal semen parameters.[4]

Although most men with abnormal semen parameters will have an improvement in semen parameters after varicocelectomy, until recently we had no way to predict which men would respond positively to varicocelectomy.[5] An abundance of literature focuses on specific aspects of varicoceles and varicocele repairs, male reproductive parameters and reproductive outcomes. However, even with all of this data, the debate continues on which men should be offered varicocelectomy and the benefit expected. It would be useful to determine which men would benefit most from varicocele repair and target repair efforts at those individuals.

At present, there have been several published studies evaluating predictive factors for improvements in male fertility after varicocele repair. The first was by Marks *et al.*[6] in 1986, looking at 130 men with oligozoospermia and clinical varicoceles. In this study, the control group was a group of 83 oligozoospermic men who had received empirical medical therapy with clomiphene citrate. The treatment group underwent varicocelectomy. The primary outcome evaluated was pregnancy rate. The authors found that in men undergoing varicocele repair, the pregnancy rate was 38.5%, and the preoperative variables predictive of pregnancy were a lack of testicular atrophy (testicular length <4.5 cm), sperm concentration >50 × 10^6 per ejaculate, sperm motility 60% or more and serum follicle-stimulating hormone (FSH) <300 ng ml^{-1}. Interestingly, varicocele grade was not predictive of pregnancy in this study.[6]

In a more recent study by Huang *et al.*, prognostic factors for successful varicocelectomy were determined by grouping men into "responders" and "nonresponders", as determined by semen analyses at 3, 6, and 12 months postoperatively. In this study, the mean age was 34 years (range 23–42) and mean sperm density was 18.2 × 10^6 ml^{-1}; On linear multivariate logistic regression, age (OR: 0.56, $P < 0.001$) and preoperative sperm density (OR: 1.22, $P = 0.001$) were significantly associated with the likelihood of successful varicocelectomy.[7]

Finally, the first online predictive nomogram was recently developed to predict semen parameters after varicocele repair: www.fertilitytreatmentresults.com.[5] This was published in 2014, using prospectively collected data, with a primary outcome of developing a tool for clinicians and patients to estimate changes in semen parameters after varicocele repair. The authors found that

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after varicocelectomy, improvements in semen parameters were related to patient age, varicocele grade and preoperative semen parameters (ejaculate volume, sperm concentration, motility, morphology and total motile sperm count [TMC]). The preoperative predictive factors varied based on the specific outcome. Post-varicocelectomy TMC varied depending on the left varicocele grade, ejaculate volume, sperm concentration and motility. Final sperm concentration depended on the left varicocele grade, sperm concentration and motility. Of note, baseline testicular volume and hormones were not evaluated.

Although these three studies yield in partly conflicting results, they all support the concept that initially better sperm parameters predict for favorable fertility outcomes following varicocelectomy, with higher pregnancy rates and better semen parameters. For the purposes of this article, we will review all of the following factors: patient age, testicular volume, varicocele grade, sperm concentration and reproductive hormones (FSH, luteinizing hormone [LH], testosterone), and their predictive value with respect to reproductive outcomes following varicocele repair. The vast majority of the varicocele literature uses semen parameters as the primary outcome. However, pregnancy or live birth is what most couples are ultimately interested in.

A systematic search of the National Library of Medicine PubMed database was performed, up to and including June 2015. Search terms included "varicocele", "varicocele repair", "varicocelectomy", "prediction", "fertility", "sperm" and "hormones". The search was limited to English language publications involving human subjects. Studies relating to outcomes other than sperm or semen parameters, hormones or reproductive outcomes were excluded.

The first section of this review will be dedicated to a breakdown of factors that predict the expected semen parameters following varicocele repair. The second section will review prevaricocelectomy factors that predict natural, intrauterine insemination (IUI) and *in vitro* fertilization (IVF) pregnancy rates and live birth rates.

PREVARICOCELECTOMY FACTORS PREDICTING POSTREPAIR SEMEN PARAMETERS

Unilateral or bilateral repair

The majority of varicoceles are left-sided, but right-sided may also be seen, either independently or together. There have been studies looking at a variety of combinations of these, with the majority reporting a positive outcome following the repair of the larger varicocele, plus any clinically palpable contralateral varicoceles. The first of these studies was in 1999 by Scherr and Goldstein.[8] The authors prospectively evaluated 91 men with a large (Grade III) or moderate (Grade II) left varicocele and small but palpable (Grade I) right varicocele. Of these men, 65 underwent bilateral and 26 underwent unilateral left repair. The authors found that in men undergoing bilateral repair there was a 95.8% increase in motile sperm concentration, compared with 42.6% change in the unilateral group.[8] In a similar study with the same baseline patient population by Fujisawa *et al.,* similar improvements in the seminogram of patients following bilateral and unilateral varicocelectomy were found.[9] Finally, a third similar study evaluating semen parameters and reproductive outcomes found that while semen parameters improved in both groups after surgery, the improvement was more pronounced in the bilateral group, and also the natural pregnancy rate was higher in the bilateral group (49% [54/110] *vs* 36% [53/146], $P < 0.05$).[10]

Some groups have looked at the bilateral repair of left clinical and right subclinical varicoceles. One of the largest studies was in 2009 by Zheng *et al.* who found no significant difference in the postoperative sperm concentration, sperm motility, normal morphology, bilateral testicular volume, serum testosterone level and natural pregnancy rates in 103 men treated for subclinical varicoceles ($P > 0.05$).[11] Sperm counts increased from 7.6 to 24.4 $\times 10^6$ ml^{-1} and motility increased from 29.5% to 50.9% following a left varicocelectomy alone, while sperm counts and sperm motility increased 7.1 to 23.7 $\times 10^6$ ml^{-1} and 30.3% to 48.7% following a bilateral varicocelectomy (no significant difference in the changes between the unilateral *vs* the bilateral varicocelectomies). In a similar study, Grasso *et al.*[12] reported on the randomization of 65 men with bilateral varicoceles (the right-side being Grade I) to undergo either unilateral or bilateral varicocele ligation. The authors found that there were no significant differences in the changes in semen parameters between the two groups, with sperm counts increasing an average of 36.52 $\times 10^6$ ml^{-1} versus 23.19 $\times 10^6$ ml^{-1} in the bilateral versus the unilateral group (nonsignificant).[12] However, a different study of 145 men found that men undergoing bilateral repair (even for a subclinical varicocele) had greater improvements in sperm concentration (15 $\times 10^6$ ml^{-1} pre- to 23 $\times 10^6$ ml^{-1} postoperatively, compared to 15.1 $\times 10^6$ ml^{-1} pre- to 21 $\times 10^6$ ml^{-1} postoperatively [$P = 0.008$]), motility (36.7% preoperatively and 50.5% postoperatively, compared to 37.8% preoperatively and 40.5% postoperatively [$P = 0.001$]) and a higher natural pregnancy rate (61.6% [45/73] *vs* 31.9% [40/72], $P = 0.001$), compared with men undergoing left varicoclectomy only.[13] While these data comparing the effect of unilateral or bilateral varicocele repairs on semen parameters (concentration, motility, morphology) are somewhat conflicting, based on current evidence, both the AUA and the ASRM have recommended varicocele correction only for men with clinical varicocele.[4]

Grade of clinical varicocele

While there were some early studies that demonstrated that there was no association between varicocele grade and degree of improvement in semen parameters after repair,[6,14] more recent data seems to support an association. There have been several studies dedicated to answering this question. Steckel *et al.* grouped 86 men by varicocele size. Preoperatively, men with Grade III varicoceles had lower sperm counts and TMC compared to men with Grades I and II varicoceles. Postvaricocele repair, a comparison of percent change in TMC among the groups revealed that men with Grade III varicoceles improved to a greater degree (128%) than men with Grade I (27%) or Grade II (21%) varicoceles. Repair of the larger varicoceles resulted in greater improvements in semen parameters than repair of small or medium sized varicoceles.[15] A similar study found that greater improvements in sperm density were seen in the patients with a Grade III varicocele, as compared with Grades I or II.[16] Similarly, Ishikawa and Fujisawa found that improvements in semen parameters were greater after repair of Grade II (7.47 $\times 10^6$ ml^{-1} pre- to 11.04 $\times 10^6$ ml^{-1} post-repair) or III (7.87 $\times 10^6$ ml^{-1} pre- to 12.23 $\times 10^6$ ml^{-1} post-repair), as compared with Grade I (values not given in the manuscript).[17] Recently, Samplaski *et al.* published a nomogram on the expected changes in semen parameters after varicocele repair.[5] The authors found that varicocele grade impacted all of the postvaricocelectomy semen parameters (TMC, sperm concentration, motility and morphology) with the improvements in semen parameters being directly related to the grade of the varicocele.

Pre-repair sperm parameters

Multiple studies have demonstrated an association between pre- and postvaricocelectomy semen parameters.[3] This would seem to be logical,

as a man with a higher baseline sperm density would be expected to have a higher post-repair sperm density. In their nomogram, Samplaski *et al.* found that both post-repair sperm concentration and TMC were correlated with pre-repair sperm concentration.[5] This was similar to the findings of a different retrospective study which found that men with baseline TMC $\geq 5 \times 10^6$ ml^{-1} had greater improvements in semen parameters following varicocelectomy than men with baseline TMC $< 5 \times 10^6$.[18] Finally, Huang *et al.* found that preoperative sperm density had a favorable association with the likelihood of successful (as determined by improvements in semen analysis at 3, 6 and 12 months postoperatively) varicocelectomy, and that a preoperative sperm density of 12×10^6 ml^{-1} or greater was able to predict successful varicocelectomy with a sensitivity of 77.6% and specificity of 77.4%.[7] To our review, there have been no studies demonstrating a negative correlation between pre- and post-repair sperm density.

Hormones

There are few studies evaluating reproductive hormones as a predictive measure for seminal improvements after varicocele repair. Many of the existing studies have demonstrated conflicting results. Cantoro *et al.* reported on the prognostic value of different serum hormones to predict improvements in semen parameters following varicocelectomy in 118 men.[19] On multiple regression analysis, only the percentage change in FSH (positive correlation) and age >25 years (negative correlation) were predictors for improvement in semen characteristics.[19] Kondo *et al.*[20] also examined a host of preoperative characteristics, including hormones. They found that on logistic regression analysis, low preoperative serum FSH and high testosterone were predictors for sperm concentration improvement.[20] Men with no improvement in semen parameters had an average FSH of 33.8 mIU ml^{-1} and testosterone of 4.5 ng ml^{-1}, compared to men with improved semen parameters who had an average FSH of 10.7 mIU ml^{-1} ($P = 0.008$) and testosterone of 6.24 ng ml^{-1} ($P = 0.04$).[20] Similarly, Chen and Chen found that, among other factors, low serum FSH (<11.3 mIU ml^{-1}) was predictive of improvements in semen parameters after varicocele repair.[21] Likewise, an early study found that FSH <300 ng ml^{-1} was a preoperative predictor of postoperative pregnancy.[6] In addition, lower baseline FSH has been shown to be predictive of greater improvements in semen parameters at redo-varicocelectomy in infertile patients with recurrent varicocele, being 14.4 mIU ml^{-1} in men who had improvements in semen parameters, compared with 18.7 ($P = 0.04$) for men without improvement.[22]

The Kondo study is the first to identify a high baseline testosterone concentration as being predictive of sperm concentration improvement after varicocele repair.[20] Conversely, several other studies have found that testosterone is not a predictive factor for improvements in semen parameters after varicocele repair.[21,23]

There have been no studies identifying any other reproductive hormones, including LH, estradiol or prolactin, as being predictive in the response to varicocele repair. At this point, low baseline serum FSH or percentage change of FSH, and high baseline testosterone remain the only hormones with even small series demonstrating a correlation to improvements in semen parameters after varicocele repair.

Age

There are several conflicting studies on the effect of age on varicocele repair. In one study dedicated to looking at the effect of age on post varicocele repair semen outcomes, age was found to be inversely associated with improvements in semen parameters.[24] Patients aged <25 years demonstrated the greatest increase in sperm counts, motility and morphology following varicocelectomy, and there were significant negative correlations between age and improvements in sperm count, motility and morphology.[24] Huang *et al.* found on multivariate logistic regression that age, with an odds ratio of 0.56 (95% confidence interval: 0.41–0.76), had a significant unfavorable association with the likelihood of improvement in semen analysis parameters after varicocelectomy.[7] Conversely, a study of men with nonobstructive azoospermia found that patient age at the time of repair was not associated with the odds of recovery of sperm in the ejaculate following the varicocelectomy.[21] Likewise, several other studies have not demonstrated a relationship between age and seminal outcomes following varicocele repair.[17,21,25] In a large series of over 350 men, Samplaski *et al.* found that older age was related to less improvement in postvaricocelectomy sperm motility and morphology, but was not related to improvements in sperm concentration or TMC.[5] In this study, patients' age ranged from 23 to 62 years (mean 35.8), and on multivariable linear regression age was related to sperm motility ($P = 0.0289$) and morphology ($P = 0.0386$).[5]

Testicular volume

It is well-known that, with some exceptions, testicular volume is generally correlated with fertility potential. Likewise, a recent meta-analysis of 14 studies comprising 1475 patients found a clear advantage of surgical intervention on reducing testicular hypotrophy when the discrepancy in testicular volume was ≥10% in children and adolescents with varicocele.[26] However, the relationship between testicular volume and seminal or pregnancy outcomes after varicocele repair is not so clear. Several studies have found that there is no association between testicular volume and outcomes after varicocele repair in adults.[27,28] Conversely, other studies have demonstrated that predictive factors of successful (defined as improvements in semen parameters) varicocelectomy in infertile patients include testicular volume >29.6 ml.[21] In addition, in a study of redo varicocele repairs, testicular volume >29.6 ml was one of the factors found to be predictive of greater improvements in semen parameters.[22]

Body mass index

Several studies have demonstrated an inverse correlation between body mass index (BMI) and varicocele incidence.[29,30] There is a paucity of data in the literature on the topic of the correlation of BMI with improvements in postvaricocelectomy semen parameters, with only one published manuscript on the topic. Chen and Chen, in a study of 35 men undergoing subinguinal microsurgical varicocelectomy, found that BMI was not predictive of any changes in semen parameters postvaricocelectomy.[21]

Size of veins as measured by imaging

The concept of vein size correlating with post-repair improvements in semen parameters is a logical concept, and follows the idea of the preoperative clinical varicocele grade being correlated with improvements in postvaricocelectomy semen parameters. Shindel *et al.* looked at 42 men who had undergone left-sided microsurgical subinguinal varicocelectomy. Based on preoperative ultrasound, spermatic cord veins were graded as small (<1.0 mm), medium (1.0–3.9 mm) and large (>4.0 mm). Overall, the authors found no clear pattern or correlation between ligated vein size (individual or cumulative) and improvements in semen parameters.[31]

Number of veins

There are no reports specifically correlating the number of veins found on a preoperative ultrasound and the postvaricocelectomy semen improvements, but Pasqualotto *et al.* divided men by the number of veins ligated by a microscopic subinguinal approach: ≤5 veins, 6–10 veins and >10 veins. Men with >10 veins ligated had significant improvements in sperm concentration, but similar improvements were not seen in the ≤5 veins and 6–10 veins groups. Interestingly, FSH levels decreased in all groups of patients, suggesting an improvement in intrinsic testicular function in all of the groups after repair.[32] In addition, the study of Chen and Chen from 2011[21] included number and size of veins in the variables analyzed for varicocele repair outcomes. They found that, among other factors, a larger number of ligated veins did predict for greater improvements in semen parameters, with men showing improvements having a mean 9.3 veins ligated and men not showing improvements having 7.9 veins ligated.[21]

DNA fragmentation index

Multiple papers have correlated varicocele repair with improvements in DNA fragmentation rates.[33,34] However, only one manuscript has looked at factors predicting for an improvement in DNA fragmentation after varicocelectomy. This was a retrospective study using the sperm chromatin structure assay that found that after varicocelectomy there was an improvement in the sperm concentration, TMC, total normal sperm count and DNA fragmentation index (42.6% to 20.5%). A higher preoperative DFI was associated with a larger decrease in postoperative DFI.[35] Although these data are compelling, more studies are needed in this area.

Other factors

One group has looked at preoperative histopathology as a predictive factor for postvaricocelectomy changes in semen parameters. Weedin *et al.* performed a meta-analysis of 233 men with nonobstructive azoospermia. They found that the chance of restoring sperm to the ejaculate or a natural pregnancy was higher in men with maturation arrest (42.1%) or hypospermatogenesis (54.5%), compared to men with the Sertoli-cell-only syndrome (11.3%). Within men with maturation arrest, those with late maturation arrest had a higher probability of success (having sperm in the ejaculate or natural pregnancy) (45.8%) than those with early maturation arrest (0%).[36] Another group looked at baseline seminal nitrous oxide levels and found them to be not predictive of postoperative semen parameters.[34]

Varicocelectomy and pregnancy rates

While semen parameters certainly play a role in fertility, what couples are most interested in are pregnancy and live birth rates. There is a paucity of literature in this area. Zini *et al.*[37] have been the group to look at these relationships most closely. In their first study of 159 infertile couples, they performed a retrospective study looking at assisted and unassisted pregnancy rates in men undergoing varicocelectomy. The mean time interval between varicocele repair and follow-up was 30 months, with a range of 12–44 months. Higher natural pregnancy rates were observed in couples in whom the man's baseline sperm concentration was $\geq 5 \times 10^6$ ml^{-1} compared to $<5 \times 10^6$ ml^{-1} (61% [73/119] *vs* 8% [3/40], respectively, $P < 0.01$), suggesting that in men undergoing varicocelectomy, the initial sperm concentration was predictive of unassisted pregnancy outcome.[38] In a subsequent study of 610 infertile couples, this same group looked at clinical characteristics, pregnancy rates and ART utilization in groups of men who did and did not undergo varicocelectomy for clinical varicoceles. The mean follow-up (for pregnancy) for the entire group was 38 months, with a range of 12–90 months. The authors found no difference in natural (39% for surgery *vs* 32% for observation) and overall (natural and ART) (53% for surgery *vs* 56% for observation) pregnancy rates in men undergoing varicocelectomy versus observation. The variables correlated with natural pregnancy on multivariate analysis were sperm motility and duration of follow-up. The variables correlated with ART utilization were successful prior natural pregnancy, duration of follow-up and female age.[37] Likewise, Marks *et al.* found that a pre-repair sperm concentration of $>50 \times 10^6$ per ejaculate was predictive of a post-repair pregnancy.[6] This was similar to the findings of a different retrospective study which found that men with mild to moderate oligoasthenozoospermia (TMC $\geq 5 \times 10^6$ ml^{-1}) had better seminal improvements following varicocelectomy, and men who achieved a postoperative TMC $\geq 20 \times 10^6$ ml^{-1} were more likely to achieve conception by natural pregnancy or IUI.[18] Finally, in a study of 242 infertile men with clinical varicocele undergoing ICSI, of whom 80 had their varicoceles repaired before ICSI, there was an improvement in the TMC (6.7×10^6 *vs* 15.4×10^6) and a decreased sperm defect score (2.2 *vs* 1.9) in men undergoing varicocele repair. The clinical pregnancy rate (60.0% *vs* 45.0%) and live birth rate (46.2% *vs* 31.4%) after ICSI were higher in the men who had undergone a varicocelectomy than the nonsurgical control group.[39]

A different group categorized couples with clinical varicoceles based on their total sperm count into those with (1) severe oligozoospermia ($1\text{-}5 \times 10^6$ sperm) who were considered ICSI candidates, (2) moderate oligozoospermia ($5\text{–}20 \times 10^6$ sperm) who were considered IUI candidates and (3) normozoospermic ($>20 \times 10^6$ sperm) where the chance of natural pregnancy was considered reasonable. The authors found that a >50% increase in total sperm count was observed in 50% of patients. An overall natural pregnancy rate of 36.6% was achieved after varicocelectomy with a mean time to conception of 7 months (range 1–19). If the preoperative sperm parameters showed (1) severe oligozoospermia, then 31% of the men had semen improvements to the level where they became IUI or natural pregnancy candidates; (2) moderate oligozoospermia, then 42% improved to the level of normozoospermia. However, in this study, no prognostic variables were assessed.[40]

In addition, one study found that in 547 couples, natural pregnancy rates in men with varicoceles treated by varicocelectomy were negatively correlated with duration of infertility (0–3 years, 3–6 years, 6–9 years and >9 years).[41] After varicocelectomy, couples with a duration of infertility of 0–3 years had a natural pregnancy rate of 43.9%, 3–6 years had a natural pregnancy rate of 38.6%, 6–9 years had a natural pregnancy rate of 38.3% and >9 years had a natural pregnancy rate of 31.7%.[41] However, no subsequent studies have evaluated this. Finally, there is a single study looking at the effect of female age (> or <35 years) on pregnancy outcomes in men undergoing varicocelectomy. Couples with the male undergoing varicocelectomy had similar pregnancy rates (natural pregnancy rate 35% and overall pregnancy rate 41%) compared with couples not undergoing varicocelectomy (natural pregnancy rate 25% and overall pregnancy rate 41%).[42]

CONCLUSIONS

While the data from individual studies can be difficult to interpret given the diverse patient populations, with varied inclusion and exclusion criteria, inadequate study designs, and limited data on preoperative and postoperative parameters, it does appear that certain findings are consistent. The repair of larger varicoceles and men with higher baseline sperm density seem to be predictors for better post-repair semen parameters. The effect of baseline reproductive hormones,

age, testicular volume and BMI is difficult to determine based on the minimal published data. While there is a paucity of literature, the limited data available consistently demonstrates the greatest improvements in DNA fragmentation rates in men with higher baseline DNA fragmentation rates. With respect to reproductive outcomes, higher baseline sperm density consistently predict for natural pregnancy or ART pregnancy rates. In addition, varicocele repair does seem to reduce the need for more invasive modalities of ART. Finally, in a technologically savvy society, a predictive tool is recently available at: www.fertilitytreatmentresults.com. While more studies in some areas are needed, some predictive factors have clearly emerged.

AUTHOR CONTRIBUTIONS

MS performed the literature review and analysis, and wrote the manuscript. KJ provided direction regarding subtopics, as well as clinical expertise, critical review and commentary on the manuscript.

COMPETING INTERESTS

The authors declare that they have no competing interests.

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