

Varicocele Repair Prior to Assisted Reproductive Technology: Patient Selection and Special Considerations

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Abstract: Clinical varicoceles are one of the most commonly identified physical exam abnormalities in men presenting with infertility. Clinical varicoceles can cause impaired spermatogenesis and surgical correction can improve semen parameters in select men. Increasingly, andrologists are performing varicocele repairs prior to intrauterine insemination (IUI), in vitro fertilization (IVF), and intracytoplasmic sperm injection (ICSI) to boost male fertility potential. In this review, we evaluated the available literature 1) to determine if varicocelectomy prior to IUI or assisted reproductive technologies proved to improve sperm production or pregnancy outcomes; and 2) to identify who may be the ideal candidate for pre-IUI/ART varicocelectomy. Overall, few studies have explored this topic and little can be concluded about the impact of varicocelectomy prior to IUI. The evidence, however, does support that correcting a clinical varicocele can increase pregnancy outcomes in couples who plan to pursue IVF or ICSI. When selecting patients for varicocelectomy prior to IUI or ART, clinicians should evaluate female age as improvement in semen parameters can take 6 months after varicocelectomy and this duration of time may be deleterious in cases of advanced maternal age when each cycle becomes increasingly important. Overall, the currently limited literature regarding clinical varicoceles correction demonstrates that pregnancy rates can be increased when comparing patients who have undergone varicocelectomy prior to ART with those who had clinical varicocele but did not undergo surgery.

Keywords: varicocele, varicocelectomy, sperm, intrauterine insemination, in vitro fertilization, intracytoplasmic sperm injection

Introduction

Infertility is defined as the inability of a sexually active couple to conceive after 12 months of unprotected intercourse when the female partner is under the age of 35 years.¹ One in six couples will experience infertility, with a malefactor being present 50% of the time.^{2,3} Multiple controversial meta-analyses have suggested that semen parameters have been globally declining by 50% over the past decades.^{4,5} Whether this decline is real or secondary to changing laboratory techniques, there has been an increased effort to identify surgical and medical therapies to improve fertility potential for men. The varicocele is perhaps the most commonly described diagnosis in men presenting with infertility. A varicocele is an enlargement of the pampiniform venous plexus, which is one of three sets of veins that drain blood from the testicle.⁶ Varicoceles are not always associated with infertility – 15–20% of post-pubertal males will be found to have a varicocele on clinical

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examination; however, varicoceles are more common in infertile men with 35% of men with primary infertility and as many as 81% of men with secondary infertility being diagnosed with a clinical varicocele.^{7,8} In oligozoospermic men, a meta-analysis by Baazeem et al found that, post-varicocelectomy, sperm concentrations improved by 12.3 million sperms per mL (95% CI: 9.5–14.2) and total motility improved by 10.9% (95% CI: 7.1–14.7%).⁹

Varicoceles often develop during puberty and more often occur on the left side as the gonadal vein inserts into the left renal vein at a perpendicular angle on the left while on the right the gonadal vein less abruptly drains into the inferior vena cava.^{10–12} Clinical varicoceles are graded on the basis of physical examination.¹³ A grade III varicocele is large and easily visible without palpation. A grade II varicocele is moderate in size and palpable when standing without Valsalva. A grade I varicocele is smaller and is only palpable with Valsalva. A subclinical varicocele is not detected on physical exam but is only identified on ultrasound examination. The American Urological Association's guidelines on Varicocele and Infertility recommend treatment for a varicocele only if 1) the clinical varicocele is palpable; 2) the couple has known infertility; 3) the female partner is normal or has a potentially treatable cause of infertility; and 4) the male partner has abnormal semen parameter(s).¹⁴ These guidelines do not recommend treatment of subclinical varicoceles. A recent meta-analysis demonstrated that varicocelectomy for subclinical varicocele do not result in improvement of semen parameters nor pregnancy outcomes.¹⁵

There have been numerous proposed theories regarding the mechanism by which varicocelectomy improves impaired fertility in men. Goldstein et al demonstrated that intra-testicular temperatures were elevated in men with a varicocele compared to men without varicocele.¹⁶ Men exposed to heat stress and even elevated fevers have demonstrated significant impairment of semen parameters,¹⁷ thus perhaps persistent elevated temperatures, secondary to varicocele, could impair spermatogenesis. More recently, several studies have suggested that the congestion of venous blood results in much higher concentration in the testicles of reactive oxygen species (ROS) – a byproduct of many metabolic pathways including mitochondrial respiration.^{18,19} These elevations in ROS can result in DNA fragmentation and thus impair replication necessary for spermatogenesis.^{20,21} Elevated ROS has also been shown to impair testosterone production from Leydig cells.²² This theory is further supported by studies demonstrating that DNA fragmentation appears to improve following varicocelectomy.²³ Lastly, some evidence supports a theory

that venous stasis impairs arterial flow to the testicle, resulting in hypoperfusion, stasis of blood, impaired intratesticular hemodynamics, and toxin accumulation.^{24,25} Researchers have found that both hypoxia-inducible factor-1alpha (a marker of hypoxia) and Bcl-2 (an anti-apoptotic protein) were expressed in higher concentrations in testicular venous samples from patients with clinical varicoceles compared to controls.²⁶ Further evidence of hypoxia and testicular injury was shown in a recent study that demonstrated elevated levels of apoptotic-associated microRNA in seminal fluid of men with varicoceles compared to men without varicocele.²⁷ Overall it is likely that the pathology seen as a result of varicoceles is a combination of these various insults.

Following varicocelectomy, semen parameters generally take about 6 months to improve. While varicocelectomies generally do not completely restore a man to normozoospermia, often the procedure can improve semen parameters to a degree that men can undergo a trial of intrauterine insemination (IUI) when previously sperm counts would only qualify men for in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI).^{28–31} This opportunity to achieve sperm counts sufficient to trial IUI (often a total motile sperm count >5 million motile sperm) implies that varicocelectomy surgery is often cost-effective; however, several meta-analyses have also suggested that varicocelectomies in azoospermic and severely oligospermic men can improve the success rate when IUI, IVF, and ICSI are performed.^{32,33}

In this review, we will discuss the available literature to determine the effect of surgical correction of a clinical varicocele on pregnancy rates in couples undergoing assisted reproductive technology and IUI treatments.

Methods

A literature review was performed in MEDLINE and EMBASE using terms related to varicocele (varicocele, varicocelectomy, varicocele repair, varicocele treatment, varicocele correction) and assisted reproductive technology (assisted reproductive technology, intrauterine insemination, IUI, in vitro fertilization, IVF, intracytoplasmic sperm injection, ICSI). All article types were included. Searches were performed by limiting the language only to English.

Impact of Varicocelectomy on Intrauterine Insemination Outcomes

Three studies have examined the effect of IUI after varicocelectomies. The first of these studies was published in 1992 by Marmar et al. In this retrospective cohort study of

71 infertile men, 52 men underwent surgical correction of ultrasound-confirmed varicocele and 19 men did not undergo surgical correction.³⁴ Couples included in the study had experienced on average 42 months of infertility. Those undergoing surgical correction went on to perform 145 IUI cycles with only 4 resultant pregnancies (2.8% pregnancy per cycle rate). Rates of IUI success were similar in those who did not undergo surgical correction – 19 men underwent 50 IUI cycles with only 2 resultant pregnancies (4%), $p=0.64$. Of the 6 pregnancies across both groups, 5 live births and one spontaneous abortion resulted (though authors did not specify which group experienced this spontaneous abortion). One significant limitation of this study is the very low pregnancy rates, as IUI cycles were performed without female ovarian stimulation. This study suggests that varicocelectomy does not significantly impact pregnancy rates of those undergoing IUI.

The next study assessing the impact of varicocelectomy on IUI pregnancy rates was published in 2001 by Daitch et al³⁵. In this retrospective study of 58 men, 34 men underwent correction of a varicocele prior to 101 IUI cycles, while 24 men opted not to have their varicocele corrected and underwent a total of 63 IUI cycles. All men were part of an infertile couple and had clinical varicoceles as well as abnormal semen parameters. Men who had undergone varicocelectomy had significantly higher mean sperm motility ($48.6 \pm 2.3\%$ vs $38.1 \pm 1.8\%$, $p = 0.02$) when compared with men who had uncorrected varicoceles; however, no significant difference was seen in total motile counts. Despite the limited difference in semen parameters, authors found that men who had undergone varicocelectomy had significantly higher rates of pregnancy (11.8% vs 6.3%, $p = 0.04$) and live birth (11.8% vs 1.6%, $p = 0.007$) when compared with men who opted against varicocele correction. Interestingly, all twelve pregnancies resulted in live births in the couples who had undergone varicocelectomy, while only 1 of 4 pregnancies resulted in a live birth for those couples who did not undergo varicocelectomy. This study may suggest that varicocelectomy may not significantly improve traditional semen parameters but may be improving factors that we have yet to identify which can affect the success of conception and carrying a pregnancy to delivery.

Finally, the most recent manuscript to assess the impact of varicocelectomy on IUI success was published in 2008 by Boman et al³⁶. The study retrospectively assessed 118 couples presenting with varicocele and asthenospermia,

defined as less than 50% motile sperm. Of these, 69 men underwent surgical varicocele correction and 49 men opted to not undergo varicocelectomy. The total motile count significantly increased after varicocelectomy from 29.6 million motile sperm to 39.0 million motile sperm, $p < 0.05$. The authors do not report the total number of IUI cycles performed but do note that 74% of men who underwent varicocelectomy were able to conceive a pregnancy with a combination of spontaneous and IUI attempts while only 36% of men who did not undergo varicocelectomy achieved a pregnancy, $p < 0.01$. When assessing pregnancies that resulted after IVF and ICSI cycles, the authors found that pregnancy rates were significantly higher in the group that underwent correction of their varicocele (32% vs 11%, $p < 0.05$). These findings suggest that varicocelectomy can improve pregnancy rates prior to undergoing IUI. While an important study, a very limited number of couples ($n=20$) underwent IUI-only – 10 couples who had undergone surgical correction achieved 5 pregnancies and 10 couples who proceeded with uncorrected varicocele achieved only 1 pregnancy after IUI ($p = 0.14$).

While these three studies suggest that there are increased rates of IUI success following varicocelectomy, these studies are small and do not address several key details (such as female age, number of IUI cycles performed, or duration from varicocelectomy surgery to pregnancy). While several of the studies saw improvement in semen parameters, not all studies demonstrated an increase in traditional semen parameters. No study has yet identified what male factor is improved by varicocelectomy that could account for improvement in pregnancy outcomes, thus the biologic factor resulting from varicocele repair that improves fertility is yet unknown. Given the wide prevalence of varicoceles with variable impact on fertility, future identification of factors that predict improvement in pregnancy rates after varicocelectomy are essential. Until more predictive tests are available, the benefit of varicocele repair likely will remain its ability to improve semen parameters so that men who prior could only attempt IVF, may then be able to trial IUI – a more cost-effective option.^{28,31}

Impact of Varicocelectomy on IVF/ICSI Outcomes in Oligospermic Men

IUI may not be feasible to conceive a pregnancy in oligospermic men and thus IVF with or without ICSI may be

required. In these men, assessment for the presence of a varicocele is crucial prior to proceeding with ART, as four studies have suggested that varicocelectomy before undergoing IVF±ICSI can improve conception rates for men with oligospermia.

Ashkenazi et al retrospectively analyzed a cohort of 22 infertile men with oligospermia and one or more varicoceles over 2 years.³⁷ No couples conceived with IVF before surgical varicocele repair was performed while, after varicocelectomy, 20% of couples conceived using IVF. Though it was a small cohort, this 1989 study was the first to suggest a possible improvement in IVF outcomes after varicocele repair for men with oligospermia.

In 2010, Esteves et al retrospectively compared the outcomes of IVF/ICSI in oligospermic men with clinical varicoceles – 80 of whom underwent elective microsurgical varicocelectomy prior to IVF or IVF/ICSI and 162 of whom did not.³⁸ The rate of clinical pregnancy with IVF ±ICSI was 60% for men after microsurgical varicocelectomy versus 45.0% in men without treatment of varicocele; similarly, the livebirth rate was 46.2% versus 31.4% for those with and without varicocelectomy. Thus, the odds for livebirth comparing varicocelectomy with untreated varicocele was 1.87 (95% confidence interval 1.08–3.25). Importantly, baseline characteristics were similar with regard to female age (32.6 years vs 32.3 years), mean infertility duration, proportion with bilateral varicoceles, and proportion with Grade I, II, or III varicoceles.

The most recent and largest study on this topic was a retrospective cohort study of 306 oligospermic men who were undergoing ART with IVF/ICSI by Gokce et al; 168 had varicocele repair and 138 had untreated varicocele.³⁹ The clinical pregnancy rate was 62.5% in those couples with varicocele repair prior to IVF/ICSI and 47.1% in those couples with untreated varicocele ($p=0.01$). The rate of livebirth was 47.6% versus 29.0% in those with and without varicocelectomy prior to IVF/ICSI, respectively ($p<0.001$).³⁹ The two groups were comparable in female age, male age, proportion of couples with concurrent female infertility diagnoses, and proportion with Grade I, II, or III varicoceles. While all retrospective, these three studies all strongly suggest that varicocelectomy prior to IVF/ICSI improves the rates of both pregnancy and livebirth in couples with an oligospermic male partner.

However, in contrast to the prior three studies, one large retrospective study demonstrated no difference in IVF/ICSI success with and without varicocele repair. In 2012,

Pasqualotto et al compared IVF/ICSI outcomes in 248 oligospermic men with grade III varicocele – 169 underwent varicocele repair prior to IVF or IVF/ICSI and 79 did not.⁴⁰ The rate of clinical pregnancy via IVF/ICSI was 30.9% versus 31.1% ($p=0.97$) in couples with and without varicocele repair, respectively. The two groups were comparable with regard to female age, male age, testicular volume, and semen parameters. However, there was a statistically significant difference the time until conception between the two groups – couples with a male partner who underwent varicocelectomy had a mean of 6.0 ± 0.5 years of infertility prior to pregnancy while men with untreated varicoceles had a mean of 2.7 ± 0.4 years of infertility prior to pregnancy ($p<0.001$). The longer duration of infertility may be due to other factors in addition to varicocele that contributed to greater difficulty in conceiving a pregnancy – in this situation, these factors may have decreased the subsequent success of IVF/ICSI, resulting in the null finding of this study. This is reinforced by the fact that the overall rate of clinical pregnancy in this study was substantially lower in the varicocele repair group compared to the other studies investigating the same question. Unfortunately, a regression analysis to account for time to pregnancy and thus other factors affecting infertility was not performed to assess whether these confounded pregnancy rates between those who did and did not undergo varicocelectomy.

In meta-analysis, Kirby et al examined the effect of varicocele repair on rates of pregnancy and livebirth after IVF/ICSI and included the Ashkenazi, Esteves, Gokce, and Pasqualotto studies.³³ Meta-analysis demonstrated that varicocele repair was not associated with an increase in rate of pregnancy (OR 1.70, 95% CI 0.95–3.02) but was associated with an increase in rate of livebirth (OR 1.70, 95% CI 1.02–2.72). Meta-regression was not performed to address for any confounders that may have influenced the rate of pregnancy or livebirth. Notably, all studies were conducted in couples with a female partner under the age of 35 or with good ovarian reserve. However, this study combining all evidence to date suggests that repair of a varicocele prior to undergoing IVF/ICSI is very important as it can substantially improve the rate of livebirth in couples without advanced maternal age.

Lastly, the question arises as to how long prior to IVF/ICSI a varicocele should be repaired. The mean time between surgical varicocele correction and initiation of IVF/ICSI was 7.2 months and 6.2 months for the Gokce and Esteves studies, respectively,^{38,39} – however, their studies do not adjust for this interval of time in their

final analysis. Neither Pasqualotto or Ashkenazi report the interval of time between surgical varicocele repair and initiation of IVF/ICSI cycles.^{37,40} Additional evidence suggests that, after varicocelectomy, sperm counts peak 3 and 6 months after and have little to no additional improvement beyond 6 months.⁴¹ Thus, while little evidence exists to recommend an “ideal” time to begin ART cycles after varicocelectomy in order to maximize reproductive outcomes, we would recommend that clinicians wait at least three to 6 months.

Finally, while these retrospective studies were conducted to compare the impact of varicocelectomy in groups with similar female age, male age, duration of infertility, and grade of varicocele, future prospective studies should be conducted to determine whether varicocelectomy affects ART outcomes between subgroups that differ in these parameters in order to identify those couples who may experience the maximum benefit from varicocelectomy.

Impact of Varicocelectomy on IVF/ICSI Outcomes in Men with Non-Obstructive Azoospermia

Studies as early as 1998 demonstrated that men with clinical varicoceles and non-obstructive azoospermia experienced improvement in semen parameters after varicocelectomy.^{42,43} The Lipshultz group demonstrated in 28 men with clinical varicoceles and non-obstructive azoospermia that 12 men (43%) subsequently had return of sperm to the ejaculate after varicocelectomy.⁴² Although men had return of sperm to their ejaculate, sperm counts were on average quite low with average sperm concentrations of 1.2 million sperms per mL. While these sperm concentrations are low, these levels would be sufficient for couples to proceed with IVF and couples may not be required to undergo testicular sperm extraction. For this reason, varicocelectomy in men with non-obstructive azoospermia may be cost-effective and fewer invasive procedures may be necessary.²⁸

In cases where sperm does not return to the ejaculate, varicocelectomy has been shown to increase recovery of sperm during testicular sperm extraction (TESE) and microsurgical testicular sperm extraction (mTESE). Zampieri et al found in their prospective study of men with grade III varicocele and non-obstructive azoospermia, that men undergoing varicocelectomy were more likely to find sperm on mTESE than compared with men who opted to not undergo varicocelectomy. The authors demonstrated

that the 19 men who underwent varicocelectomy 3 months prior to mTESE had positive sperm retrieval in 11 men (57.8%); in comparison, of 16 men who did not undergo varicocele correction prior to mTESE, only 6 (37.5%) had positive sperm retrieval ($p < 0.05$).⁴⁴ Thus, varicocelectomy plus mTESE can prove to be a valuable combination.

Two studies have assessed the impact of varicocele repair prior to TESE or mTESE and subsequent IVF/ICSI outcomes. The first study, by Inci et al in 2009, retrospectively reviewed the cases of 96 men with varicoceles who had undergone TESE and IVF/ICSI.⁴⁵ A total of 66 men had previously undergone varicocele correction and 30 men had opted to not undergo correction of their clinical varicocele. Importantly, the two groups had comparable female ages and proportion of couples with a female factor of infertility. In the group that had undergone varicocelectomy prior to TESE, 32 (48%) men had successful sperm retrieval, while the group that did not undergo varicocelectomy 9 (30%) had successful sperm retrieval with TESE ($p = 0.04$). When comparing pregnancy outcomes in couples for whom sperm was found, men who had undergone varicocelectomy had a slightly higher rate of pregnancy (31.4%) compared with those with uncorrected varicocelectomy (22.2%). While the rate was higher in those who had undergone correction, it was not found to be statistically significant ($p > 0.05$). The second study to assess this question was published in 2010 by Haydardedeoglu et al⁴⁶. The authors reviewed the clinical course of 96 men with non-obstructive azoospermia and grade III varicoceles – 31 men underwent varicocelectomy prior to TESE and 65 men did not have their clinical varicocele surgically corrected. Sperm retrieval rates were significantly higher in those undergoing varicocelectomy prior to TESE (60.8%) compared with those who did not (38.5%, $p = 0.01$). Pregnancy and live birth rates were also significantly higher for those undergoing surgical correction (74.2% and 64.5%) versus those who had uncorrected varicoceles prior to TESE (52.3% and 31.5%, $p < 0.01$). Together, these studies suggest that varicocelectomy prior to TESE can improve rates of sperm retrieval, pregnancy, and live birth – providing couples with increased opportunities to achieve their fertility goals.

These two studies were meta-analyzed by Kirby et al. Meta-analysis demonstrated that men with non-obstructive azoospermia and corrected varicocele had significantly higher rates sperm retrieval (OR 2.51; $p < 0.01$), pregnancy rates (OR 2.34; 95% CI 1.02–5.34), and near

significant live birth rates (OR 2.21; 95% CI 0.99–4.90) when compared with men who did not undergo surgical correction of their clinical varicocele.³³ It is important to note that all of these included men had grade III varicocele (the most severe form of varicocele) and these results may not be applicable to grade I and II varicocele repair.

Special Considerations: The Effect of Varicocele on DNA Fragmentation

In the past several years there has been some evidence that increased DNA fragmentation, often defined as a DNA fragmentation index (DFI) >30%, may result in failure of implantation during IUI or ART cycles.^{47–50} Additionally, several studies have shown that sperm DNA fragmentation can be improved in men with varicoceles, as Wang et al in their meta-analysis found that post-varicocelectomy DFI improved by a mean difference of 3.37% (95% CI: 2.65% to 4.09%).⁵¹ Given this improvement in DFI after varicocele correction, there has been some discussion as to whether elevated DNA fragmentation should also be an indication to correct a clinical varicocele. There are however two limitations that may prevent elevated DFI from becoming an indication for varicocele repair: first, the evidence linking miscarriage and recurrent pregnancy loss with elevated DFI remains weak with future prospective studies required. Second, varicocelectomy results in only minor improvement in DFI, in contrast to the significant improvement in DFI that occurs with the use of testicular sperm rather than ejaculated sperm in men with elevated DFI – Esteves et al demonstrated that in men with elevated DFI, sperm retrieved from the testicle had significantly lower DFI (8.3%) compared to the DFI in ejaculated sperm (40.7%).²³ Thus, elevated DFI with a clinical background of recurrent pregnancy loss may be better treated with testicular sperm rather than varicocele correction, but more evidence is needed to identify when to intervene for elevated DFI.

Patient Selection

Microsurgical varicocelectomy is a well-tolerated outpatient surgery with minimal recovery time. Whether unilateral or bilateral, most men return to work within a week.⁵² One major limitation of varicocelectomy is the duration of time required before improvement is seen within semen parameters – often improvement does not occur for 3 to 6 months post-operatively.⁵³ This makes sense from a biological perspective as improvement in testicular conditions after

varicocelectomy would only impact newly produced sperm and sperm production take approximately 70 days. For the majority of couples, this delay for improvement in semen parameters can be tolerated; however, in couple dealing with advanced maternal age, a delay of 3 to 6 months may not be feasible.⁵⁴ For this reason, the reproductive urologist must be aware of female factors contributing to the shared infertility and be aware of the reproductive endocrinologist's plans for future reproductive attempts. In these cases of advanced maternal age, counseling patients about the prolonged time to potential sperm recovery and discussing plans with the reproductive endocrinologist should always occur.

Conclusions

Clinical varicoceles are a potential cause of infertility and one of the most common causes of secondary infertility. The correction of a clinical varicocele has been shown to improve semen parameters, sperm recovery rates, pregnancy rates, and live birth rates. While studies are small, the correction by varicocelectomy can lead to an improvement in pregnancy rates when combined with ART – compared with men the pregnancy rates found in men with uncorrected clinical varicoceles. At present, improvement after varicocelectomy is seen in most, but not all, patients and future efforts are required to identify pre-operative factors that are predictive for successful improvement in spermatogenesis. In order to accomplish this, more work in understanding why varicoceles impair sperm production and how varicocelectomy improves semen parameters.

Disclosure

The authors report no conflicts of interest in this work.

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