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Is a Varicocelectomy Beneficial in the Era of Assisted Reproductive Technologies?

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by

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Table of Contents

List of Figures

List of Tables

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Abstract

Clinical varicoceles are the most frequent physical finding associated with infertile men and impaired semen parameters. There is evidence that suggests varicocele repair improves semen parameter and increases the chances of natural pregnancy. Today, varicocele repair is often combined with assisted reproductive techniques (ART) such as intrauterine insemination (IUI), in Vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI). In this literature review, data examining whether varicocelectomy before ART leads to improved pregnancy outcomes is reviewed. Current data suggest that there is a significant clinical benefit when correcting a varicocele in oligospermic men before IVF/ICSI. Similarly, men with non-obstructive azoospermia also benefit from varicocelectomy before IVF/ICSI, but not significantly. Furthermore, in couples seeking to use ART to conceive, varicocelectomy may offer improvement in semen parameters and therefore, decrease the level of ART needed to achieve pregnancy.

Keywords: Varicocele, varicocelectomy, in Vitro fertilization, intracytoplasmic sperm injection, efficacy, cost effectiveness

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Introduction

A varicocele is an enlargement (or dilation) of the veins within the scrotum that provide testicular venous drainage. This allows for blood to pool in the scrotum, an unfavorable condition. It is the most common and treatable cause of low sperm production and decreased sperm quality leading to male infertility worldwide (Concuzza et al., 2009). Clinically, it is graded by a size scale: grade I (palpable only during Valsalva maneuver), grade II (palpable in the standing position) and grade III (visible without palpation) (Clavijo, Carrasquillo & Ramasamy, 2017). Although only present in 15% of the male population, varicoceles are prevalent in 30 – 50% of men with primary infertility and up to 85% of men with secondary infertility (Clavijo, Carrasquillo & Ramasamy, 2017; Concuzza et al., 2009; Johnson & Sandlow, 2017).

Several mechanisms for the formation of varicoceles have been proposed. First, venography and cadaver studies have shown that the left spermatic vein drains into the left renal vein at a perpendicular angle, which leads to increased venous pressure compared to the right spermatic vein which drains into the inferior vena cava (Sedaghatpour & Berookhim, 2017). This may explain why the prevalence of left-sided varicoceles is greater than right-sided varicoceles (Clavijo, Carrasquillo & Ramasamy, 2017). Second, defective venous valves permit retrograde blood flow and pooling of blood close to the testicle. As such, identifying this defect is imperative when treating patients, as omission may be a reason for recurrence of varicocele post repair (Clavijo, Carrasquillo & Ramasamy, 2017). The third mechanism of varicocele formation results from compression of the left renal vein by the aorta and superior mesenteric arteries (classically termed the nutcracker effect or syndrome) which culminates in impeded outflow

from the left renal vein into the inferior vena cava (Clavijo, Carrasquillo & Ramasamy, 2017; Concuzza et al., 2009; Johnson & Sandlow, 2017).

Although the precise mechanism in which varicoceles contribute to the impairment of semen production remains unclear, several studies have reported a link between varicoceles and increased reactive oxygen species (associated with abnormal sperm morphology, and reduced motility) testicular hypoxia and stasis, elevated testicular temperature, DNA fragmentation and increased testicular venous hypertension (Clavijo, Carrasquillo & Ramasamy, 2017; Concuzza et al., 2009; Johnson & Sandlow, 2017; Sedaghatpour & Berookhim, 2017). A combination of these factors likely contributes to decreased fertility in the male population and are shown in *Figure 1*.

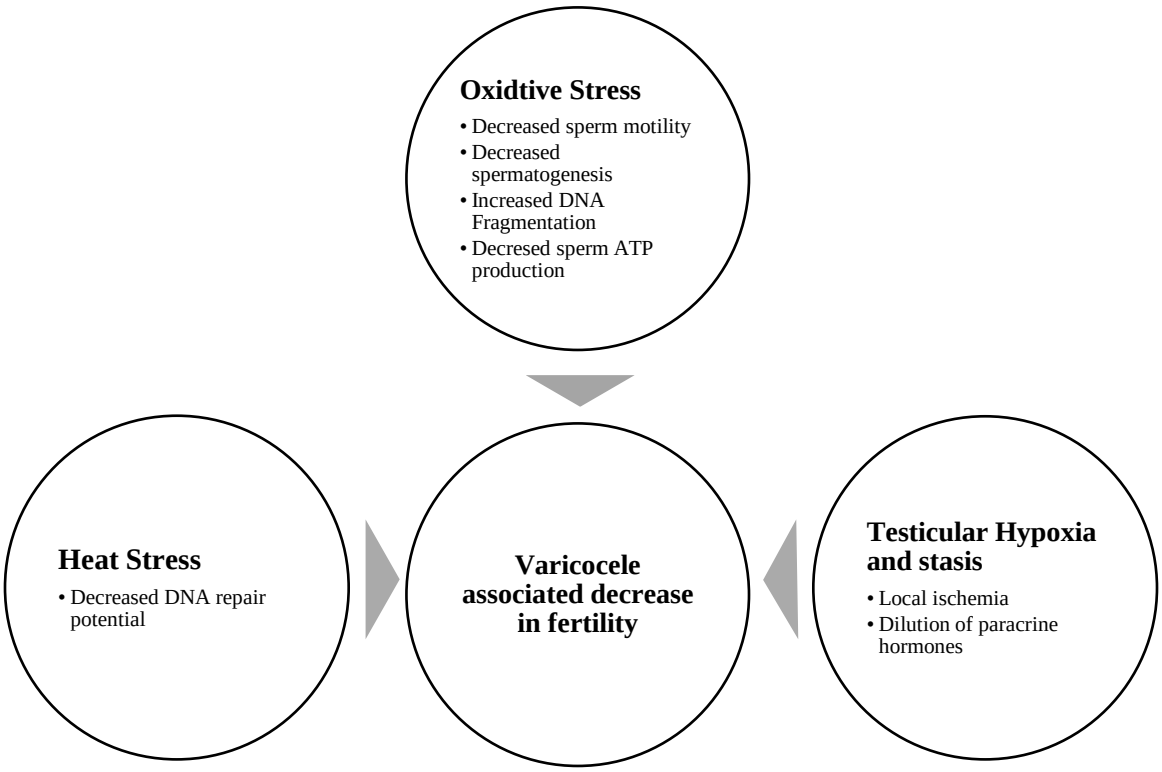

Figure 1. Summary of the proposed molecular mechanisms for the pathologic impact of varicoceles on fertility potential.
Adapted from Varicoceles: Prevalence and pathogenesis in adult men by Clavijo, R. I., Carrasquillo, R., and Ramasamy, R, 2017, *Fertility and Sterility*, 108(3), 364–369. Copyright 2017 by American Society for Reproductive Medicine.

With the rise of assisted reproductive technologies (ARTs) such as in vitro fertilization (IVF) and intracytoplasmic sperm injections, questions have been raised about the need for a varicocelectomy. This paper aims to explore and summarize current varicocele treatment options and their efficacy, varicocele repair in combination with ART and finally, cost effectiveness for treatment of infertility using varicocelectomy versus ART or a combination of both.

Statement of the Problem

The role of clinical varicocele in male infertility and reduced semen parameters has been well established, dating back to studies conducted as early as 1965. Subsequently, studies have shown that varicocele repair can improve live birth rates for men with clinical varicocele. However, in the advent of ARTs and their proven effectiveness in achieving live birth for couples with infertility issues, the question remains whether varicocele repair should be considered before ART in order to increase success with ARTs.

Research Questions

In men with clinically diagnosed varicocele, does the method of varicocelectomy chosen (ligation vs embolectomy) improve fertility outcomes?

In men with oligospermia vs azoospermia with a varicocele, does varicocelectomy before ART improve fertility outcomes?

In men with clinically diagnosed varicocele, is it cost effective to undergo a varicocelectomy before ART?

Methodology

The databases searched for this research topic include CINAHL, PubMed and ClinicalKey, with selected articles dating from September 2017 through December 2018. Keywords were used to narrow the research topic and included: varicocele, therapy, ICSI, IVF, ART, varicocele repair, surgery, cost effectiveness, oligospermia, azoospermia, male infertility,

pregnancy, pathology, and complications. These keywords found articles that were added into a search builder. The builder allowed for a more extensive search throughout each database. To further narrow the search, advanced settings and limits of exclusion were used to select articles only relating to comparative study, meta-analysis, and systemic reviews. Further exclusion was performed on articles that were not published in the English language and not written in the last 10 years. Based on the pooled results, a refined search to just subject headings were used to further narrow the search. The subject headings used include: “Varicocele” [Mesh], “Varicocele repair” [Mesh], “Varicocele Therapy” [Mesh], “ART” [Mesh], “IVF” [Mesh], “ICSI” [Mesh], “Cost effectiveness” [Mesh], “Oligospermia” [Mesh], “Azoospermia” [Mesh], and “male infertility” [Mesh]. The subject headings allowed for the research topics to be combined or for topics to be searched alone by using “AND” and “OR” between each subject heading. Articles were selected and evaluated for use within this literature review based on the subject headings, refined searches, and exclusion criteria.

Anticipated Results

Varicocele, although the most treatable cause of male infertility, is simply just “one” variable that negatively impacts male infertility. I anticipate that varicocelectomy will show improvements in live birth rates, however this improvement will not be statistically significant. In men with oligospermia vs azoospermia, I anticipate that the beneficial results of varicocelectomy will favor men with oligospermia. Moreover, that these improvements (however slight), will reduce the cost of using ART.

Literature Review

Current treatment approaches to varicocele repair include surgical ligation (retroperitoneal/open, suprainguinal ligation, ligation, inguinal ligation, microsurgical

subinguinal ligation and laparoscopic) or percutaneous embolization. With surgical ligation, an incision is made on the aponeurosis of the external oblique muscle around the inguinal ligament to display the spermatic cord. The spermatic cord is carefully inspected to reveal the veins, which are then ligated (Gray's Anatomy, 2015). The less invasive percutaneous embolization technique uses a small catheter inserted through the right femoral vein. The catheter is then advanced along the external iliac, and common vein then into the inferior vena cava and finally into the left renal vein. At the left renal vein, a venogram is performed to identify the left testicular vein which the catheter is advanced through and into the veins of the inguinal canal and pampiniform plexus. Metal coils are then injected to occlude the vessels and the catheter is withdrawn (Gray's Anatomy, 2015). A review of the literature shows that safety issues may warrant the use of one method of varicocele repair over another, but outcomes are typically the same in terms of fertility restoration. The literature also shows that there is variability in success rates amongst oligospermia vs azoospermia although results are not statistically strong. In addition, varicocele repair before ART may show improved outcomes and cost effectiveness for couples trying to have biological children.

Efficacy or Outcome of Varicocele Treatment

According to current guidelines by the American Urological Association and American Society of Reproductive Medicine, varicocelectomy should be considered for men with a palpable varicocele, abnormal semen parameters, documented infertility, and a female partner with normal fertility or potentially correctable female infertility (Johnson & Sandlow, 2017; Sedaghatpour & Berookhim, 2017). Additionally, treatment is indicated when aimed at preventing or reversing testicular atrophy in adolescent males, correcting pain associated with varicoceles, improving testicular function in hypogonadal men with varicoceles and addressing

elevated sperm or DNA fragmentation (Johnson & Sandlow, 2017). The following four studies assess the efficacy of the more commonly used surgical approach. Studies discussed focus on comparisons amongst these approaches, as well as their adverse effects and varicocele recurrence rates.

In a meta-analysis by Schauer, Madersbacher, Jost, Hübner, and Imhof (2012), the authors compared three surgical techniques for varicocelectomy (suprainguinal ligation, inguinal and subinguinal approach) to determine their impact on sperm parameters (motility and count) and pregnancy rates. The study included 14 articles from a literary search between January 1975 and February 2011 that met the inclusion criteria: Suprainguinal ligation was discussed in 6 articles and included 649 patients, inguinal varicocelectomy in 6 articles with 534 patients, and subinguinal varicocelectomy in 6 articles with 293 patients. All three techniques led to significantly improved semen parameters. After suprainguinal varicocelectomy, sperm count increased by a mean of 10.85 million per ml (95 confidence interval [CI] 3.16-18.54; P = 0.006) and motility by a mean of 6.80% (95% CI 3.95-9.66; P < 0.00001). Inguinal varicocelectomy led to a mean increase of 7.17 million per ml in sperm count (95% CI 3.73-10.61; P < 0.001) and by a mean of 9.44% (95% CI 3.72-15.16; P = 0.001) in sperm motility. Subinguinal varicocelectomy led to a mean improvement of 9.75 million per ml in sperm count (95% CI 3.48-16.02; P 0.002), and a mean increase of 12.25% in motility (95% CI 4.76-19.75; P = 0.001). The numerical difference between procedures were not significant for sperm count or motility (P = 0.973 or P = 0.372, respectively). In regard to pregnancy rates, inguinal varicocelectomy had the highest outcome (41.48%), then suprainguinal ligation (26.90%) and subinguinal varicocelectomy (26.56%) with an overall statistically significant difference of P = 0.035 (the

difference between suprainguinal and subinguinal varicocelectomy was not significant, P = 0.248) (Schauer, Madersbacher, Jost, Hübner, & Imhof, 2012).

In evaluating pregnancy rates, Schauer et al., (2012) state only "spontaneous" pregnancies were included in this meta-analysis. However, in the articles that report these values for the suprainguinal and inguinal group, none comment on how the couples achieved pregnancy. Only the articles on subinguinal varicocelectomy make this distinction. As such, the value reported for suprainguinal and inguinal varicocele repair techniques may not be a true representation of actual pregnancy rates after varicocele alone. Other limitations discussed by the authors include the inclusion of only 2 randomized controlled trials (RCT) and the use of 3 retrospective studies. In hindsight, they realize that although RCTs are desirable, convincing patients with the unfulfilled wish for parenthood of the benefits of such trials is difficult, since some will have to fall into the untreated group.

In another study, Enatsu, Yamaguchi, Chiba, Miyake, and Fujisawa (2014) assessed the clinical outcome of subinguinal varicocelectomy in severely oligospermic men with infertility and subsequently evaluated predictive parameters associated with the efficacy of varicocelectomy in a cohort of patients. Retrospectively, they evaluated 102 patients with severe oligospermia (sperm count <5 million per ml) who underwent subinguinal varicocelectomy. The mean follow-up time post operation was 7.4 ± 3.9 months and according to the level of improvement at that time, the patients were divided into two groups: Responders (defined as patients with increased sperm motility rate postoperatively and with an increase in sperm concentration from < 1 million per ml to ≥ 5 million per ml or from 1-5 million per ml to ≥ 10 million per ml) and non-responders. After surgical repair, 42 (41.1%) qualified as responders with a significant change in mean sperm count from 3.0 ± 1.4 million to 23.4 ± 16.3 million (P <

0.001) and sperm motility change from 31.1 ± 20.4% to 50.7 ± 18.9% (P < 0.001). Of the 42 patients, 16 (38.1%) would go on to achieve spontaneous pregnancy during the follow-up period of this study (6 months post surgery). Although only 42% of the pooled patients qualified as responder, the overall mean sperm concentration and sperm motility rate increased significantly for all patients post surgery from 2.4 to 11.6 million/mL (P < 0.001) and from 32.8% to 42.2% (P = 0.0024), respectively. However, these improvements did not translate to hormonal (FSH, LH, and testosterone) levels where no significant differences were noticed between pre – and posttreatment measurements. Using univariate and multivariate analysis, the authors were able to classify parameters that might affect the efficacy of varicocele repair. Univariate analysis showed that response to treatment in men with severe oligospermia was significantly associated with sperm concentration and laterality (unilateral or bilateral varicocele) (P = 0.034). However, on multivariate analysis, only sperm concentration was noted to be an independent predictor of varicocelectomy efficacy, with patients at concentrations > 2 million per ml showing better improvement in semen parameters and spontaneous pregnancy (56.3% and 25% respectively) than patients with < 2 million per ml sperm concentration (Enatsu, Yamaguchi, Chiba, Miyake & Fujisawa, 2014).

The authors identify the nonrandomized, retrospective and small sample size as limitations in this study. In addition, they did not include ultrasound examinations in diagnosing clinical varicocele and allude that this may explain the low incidence of patients with bilateral varicoceles. The latter is assumed because it has been established that ultrasound is more reliable at diagnosing varicoceles, especially those with grade 1 (Enatsu et al., 2014). Furthermore, due to lack of data, this study only relied on sperm concentration (considered less reliable) compared to the more reliable total motile sperm count (TMSC).

In one of the few prospective studies on treatment outcomes post-surgical treatment of varicoceles, Bryniarski et al. (2017) conducted a non-masked, RCT with one to one distribution, in which they assessed whether microsurgical approach was superior to laparoscopic varicocelectomy in terms of pregnancy rates, improved semen parameters and hormonal levels (FSH, LH, and testosterone). Between December 2012 and June 2015, 84 patients were randomly divided into two groups: Group 1 consisted of 42 patients who underwent laparoscopic varicocelectomy, and group 2 included 42 patients who underwent microsurgical varicocelectomy (specifically utilizing the subinguinal approach). From each, five patients were lost during follow up. Per the results, although pregnancy rates were higher amongst the microsurgical group (40.5%) than in the laparoscopic group (29.7%) this difference was not statistically significant. In addition, sperm parameters were significantly improved in both groups ($P < 0.001$) post surgery. However, progressive motility, total motility and normal morphology were significantly higher with the microsurgical approach than with laparoscopy ($P = 0.03$, 0.04, and 0.03, respectively). Other sperm parameters (total sperm number, concentration and vitality) were similar. There were also no statistical difference in hormonal concentration between the microsurgical and laparoscopic groups. Bryniarski et al. also noted a few side effects associated with each treatment approach: Five patients in the laparoscopic group developed hydrocele (13.5%), whereas epididymitis was noted in one (2.7%) of the patients in the microsurgical group one week after operation. Furthermore, recurrent varicocele was observed in three patients (8.1%) from the laparoscopic group while none was seen in the microsurgical group (Bryniarski et al., 2017).

A major limitation of this paper was the small population size. Additionally, information about the10 patients that were lost during follow-up was not made clear. However, the authors'

strict inclusion and exclusion criteria assisted in making a more homogenous cohort for this study making comparison more assessable. Furthermore, this study is one of a few that discusses various aspects of varicocele – pregnancy, sperm concentration, hormonal changes, erectile function and testis volume – in a prospective randomized study.

In a meta-analysis by Yuan, Zhuo, Cao, and Wei (2017), they reviewed the efficacy and safety of three surgical approaches for varicocele repair: Microsurgical, laparoscopic, and open varicocelectomy. Seven RCTs encompassing 1,781 patients were analyzed. All seven studies were without significant differences in baseline for age, laterality of varicocele and varicocele severity. When comparing pregnancy rates, the meta-analysis showed that the microsurgical approach had a greater outcome than open varicocelectomy (Risk Ratio [RR] = 1.37, 95% CI 1.12-1.69; P=0.002), however, between microsurgical and laparoscopic varicocelectomies (RR = 1.14, 95% CI 0.91-1.42; P = 0.25) or between laparoscopic and open varicocelectomies (RR = 1.09, 95% CI 0.76-1.56; P = 0.66) there were no significant differences. Data assessing sperm parameters post operatively showed that both microsurgical and laparoscopic groups had significant improvements in sperm concentration over open varicocelectomy (mean difference, [MD] = 5.59, 95% CI 1.46-9.72; P = 0.008 and MD = 5.10, 95% CI 1.29-5.13; P = 0.001, respectively) while there was no significant difference between the microsurgical and laparoscopic groups (MD = 3.21, 95% CI -0.78 to 10.98; P = 0.09). Moreover, microsurgical varicocelectomy also showed greater improvement in postoperative sperm motility than the open group (MD = 5.56, 95% CI 0.77-10.36; P = 0.02), whereas no significant difference was found between the microsurgical and laparoscopic group (MD = 2.09, 95% CI -3.78 to 7.97; P = 0.49) or between the laparoscopic and open group (MD = 1.89, 95% CI -2.02 to 5.81; P = 0.34). Furthermore, the incidence of complications and varicocele recurrence post repair was

significantly lower for the microsurgical group than for the laparoscopic group (Odds Ratio [OR] = 0.22, 95% CI 0.11-0.46; P <0.0001 and OR = 0.17, 95% CI: 0.07-0.37; P < 0.00001 respectively) and the open group (OR = 0.21, 95% CI 0.12-0.37; P <0.00001 and OR = 0.11, 95% CI 0.06-0.21; P < 0.00001, respectively). There was no significant difference when comparing complications and recurrence rates between laparoscopic and open groups (OR = 1.17, 95% CI 0.68-2.03; P = 0.57 and (OR = 1.39, 95% CI 0.82-2.37; P = 0.22, respectively) (Yuan, Zhuo, Cao, & Wei, 2017).

A limitation noted by the author in this meta-analysis study was high heterogeneity. The authors allude that factors affecting this include: time span of included studies (2000-2015), surgical skill of surgeon performing the surgery in the individualized groups and use or nonuse of surgical techniques i.e. microscopes. To amend some of these issues, a random effect model was utilized.

Efficacy of Varicocelectomy in Men with Oligospermia Before Assisted Reproduction

In men with severe oligospermia, IVF/ICSI may be required to achieve pregnancy. As discussed earlier, it has been shown that patients with improved semen parameters after a varicocelectomy are more likely to achieve pregnancy naturally (Schauer et al., 2012). As such, the studies described below, explore the efficacy of varicocelectomy in men with oligospermia before IVF/ICSI.

In 2010, Esteves, Oliveira and Bertolla sought to be one of the first to explore the relationship between IVF/ICSI and varicocelectomy by comparing IVF/ICSI clinical outcomes in infertile men with treated and untreated clinical varicoceles. Between January 2002 and July 2008, medical records of 476 infertile men with clinical varicocele who underwent ICSI were reviewed. 242 met the inclusion criteria and were grouped by their varicocele repair history to

include: 80 oligospermic men with clinical varicocele who underwent a varicocelectomy (treated group) and 162 oligospermic men with clinical varicocele who did not (untreated group). They found that men in the treated group achieved pregnancy with ICSI in 60% of the cases with a live birth rate of 46.2%, whereas men in the untreated group achieved pregnancy in 45% of the cases with a live birth rate of 31.4%. Overall, there was a significant increase in achieving pregnancy and live birth by IVF/ICSI with prior varicocelectomy compared to non-varicocelectomy with an odd ratio (OR) 1.82 (95% confidence interval [CI] 1.6-3.15; P = 0.03), and OR 1.87 (95% CI 1.08-3.25; P = 0.03), respectively (Esteves, Oliveira, & Bertolla, 2010).

This study suggests that varicocele repair improves clinical pregnancy and live birth rates by ICSI in couples in which the primary cause of male infertility is varicocele. The authors assert that due to the design of the selection process in this retrospective study, some inherent bias exists. Particularly, patients were not randomized to treatment or no treatment and the decision regarding varicocele treatment was made solely by the couples. Furthermore, the indication for ICSI may have not been influenced solely by varicocele induced infertility since about a third of the couples also had significant female infertility problems. However, the demographic characteristics (mean male and female ages, varicocele grade distribution [I-III], and female factor infertility) and pretreatment semen analysis results were similar in both groups.

The noted association between varicocelectomy and IVF/ICSI by Esteves et al. was challenged by Pasqualotto et al. (2012). Their study argued that there were no differences in pregnancy rates in men with treated vs untreated grade III varicoceles who utilized ICSI. In a large retrospective study, Pasqualotto et al., analyzed data from 2000 to 2008 of 242 men with oligospermia of which 167 underwent a varicocelectomy (treated group) and 79 with clinical varicoceles who did not (untreated group). They found no significant difference in pregnancy

rates with IVF/ICSI among the treated and untreated groups (30.9% vs 31.1%; P = 0.9806, respectively). They also assessed miscarriage rates, which also showed no significant differences between the treated and untreated groups (23.9% vs 21.7%; P = 0.8401, respectively) (Pasqualotto et al., 2012).

Although the authors did not discuss any limitations to this study, it is important to note that there was a significant difference in time to pregnancy between couples in the treated group (6.0 ± 0.5 years) and those in the untreated group (2.7 ± 0.4 years) (P<0.001). This significant difference calls to question the validity of the findings because the couples with a longer time to conceive (treated group) may have had other factors contributing to this greater difficulty in getting pregnant. Had these factors been accounted for, the outcome might have been skewed differently to favor men with a varicocelectomy.

In a larger study assessing the efficacy of varicocelectomy before IVF/ICSI, Gokce et al. (2013) provides corroborating evidence in support of Esteves et al.'s findings. In this retrospective study, they analyzed data of 306 men with clinical varicocele who utilized IVF/ICSI due to infertility between January 2006 and July 2010. 168 of 306 had undergone a varicocelectomy (treated group) and the remaining 138 had untreated varicoceles (untreated group). Both groups were similar in male and female ages, varicocele grade distribution and female factor infertility. Results demonstrated a significant difference in pregnancy rates between the treated and untreated groups (62.5% vs 47.1%; P = 0.001, respectively). Live birth rates were also significantly higher for the treated group compared to the untreated group (47.6% vs 29.0%; P = 0.0002). In all, varicocelectomy was found to significantly increase IVF/ICSI pregnancy rates (OR 2.02, 95% CI 1.25-3.87; P = 0.032) and live birth rates (OR 2.12, 95% CI 1.26-3.97; P = 0.026) (Gokce et al., 2013).

A limitation of this study is in its retrospective nature, which did not allow for randomization. As with the Esteves et al. (2010) study, the decision to undergo a varicocelectomy was solely based on the couples. However, this study does provide support that suggests varicocelectomy improves IVF/ICSI pregnancy rates in oligospermic men with infertility primarily caused by varicocele.

The 2016 systemic review and meta-analysis by Esteves, Rogue and Agarwal assessing the outcome of IVF/ICSI in men with treated and untreated varicocele analyzed studies by Esteves et al., Pasqualotto et al., Shiraishi et al., and Gokce et al. to determine whether varicocelectomy improves the pregnancy and live birth rates when used with IVF/ICSI. A total of 114 articles were identified, and the four aforementioned retrospective studies consisting of 871 ICSI cycles (438 with prior varicocelectomy, and 432 without varicocelectomy) were analyzed. All four studies reported data on pregnancy rates. Overall, there was a significant increase in pregnancy rate (OR 1.59, 95% CI 1.19-2.12; $P < 0.05$; $I^2 = 25\%$) in the treated group vs untreated group. A similar association was seen with all three of studies that reported on live birth rates (OR 2.17, 95% CI 1.55-3.06; $P < 0.05$; $I^2 = 0\%$) (Esteves et al., 2010, Shiraishi et al., 2012 & Gokce et al. (2013). (Esteves, Rogue & Agarwal, 2016).

The authors understand that although these findings indicate that performing varicocelectomy in patients with clinical varicocele prior to ICSI does provide improved pregnancy outcomes, the study is limited by its retrospective nature and lack of randomization; as such this recommendation is low to moderate. They agree that further prospective research is needed to evaluate the efficacy of varicocelectomy in infertile men before assisted conception.

Efficacy of Varicocelectomy in Men with Non-obstructive Azoospermia Before Assisted Reproduction

Unlike with oligospermia where semen parameters, although abnormal aren't severe, nonobstructive azoospermic (NOA) men present with more dire seminal parameters. Data from four studies that aim to provide evidence supporting the efficacy of varicocelectomy in this population are presented. Although varicocele repair doesn't completely reverse semen parameters, it does show promise when combined with testicular sperm extraction (TESE) followed by IVF/ICSI.

In 2009, Inci et al. conducted a retrospective study on men with NOA and clinical varicocele to determine the effect of a varicocelectomy on sperm retrieval success rate using TESE and IVF/ICSI. The study excluded patients with a history of cryptorchidism or testicular trauma, systemic or hormonal dysfunction and genetic anomalies that caused infertility. Of the 96 men studied, 66 had undergone varicocelectomy and 30 had unrepaired varicocele. The mean time between varicocelectomy and TESE was 23.6 months. Results showed that men who underwent a varicocelectomy had a significantly greater sperm retrieval rate (53%) than men without repair (30%) (OR 2.63, 95% CI 1.05-6.60; $P = 0.036$). Subsequently, pregnancy rates were higher in men with treated varicocele (31.4%) than in men with untreated varicocele (22.2%), although not significantly ($P > 0.05$) (Inci et al., 2009).

The authors identified various limitations in the study such as the retrospective and noncontrolled design of the study: Patients were not randomized to treated and untreated groups. A common reason for refusing treatment was the time needed to restore spermatogenesis after treatment. However, varicocele grades in the treated and untreated were well matched as were

other demographic characteristics: mean male and female ages, female factor infertility, duration of infertility, FSH levels and testicular volume.

In 2010, Haydardedeoglu, Turunc, Kilicdag, Gul and Bagis conducted a retrospective study like that of Inci et al. (2009). Their goal was to identify if varicocelectomy in NOA men led to more favorable outcomes with ICSI. This was assessed via effects on sperm retrieval with TESE, clinical pregnancy rates and live birth rates. The study included 96 men with grade III varicoceles of which, 31 had underwent a varicocelectomy and 65 did not. They found that sperm retrieval rates were significantly higher in the treated group vs. the untreated group (60.8% vs. 38.46%; $P = 0.01$), as were pregnancy rates (74.2% vs 52.3%; $P < 0.05$) and live birth rates (64.5% vs 41.5%; $P < 0.05$), respectively. In addition, they noted that within the treated group, those who failed to achieve pregnancy had a significantly lengthier time between varicocelectomy and TESE compared to those who achieved pregnancy (80 months vs 42.2 months; $P < 0.05$) (Haydardedeoglu, Turunc, Kilicdag, Gul & Bagis, 2010).

Although the two groups in this study were similar in male age, testicular volume and FSH levels, a few limitations were noted. The study's sample size of 96 patients was small. Additionally, the authors state the use of retrospective data as another limitation and agree that prospective randomized trials are needed to evaluate the effect varicocele repair in NOA patients. Furthermore, it is important to note that nine patients were excluded from this study for cancellation of embryo transfer due to fertilization failure. This bias may have favored slightly higher pregnancy rates in comparison to other studies discussed.

In providing continued support for performing a varicocelectomy in men with NOA, Alves and Oliveira (2017) conducted a small retrospective study from 2002 to 2015 at a private urologic service in Brazil. They evaluated 25 patients with NOA and clinical varicocele who

underwent bilateral varicocelectomy to recover sperm production. Semen volume greater than 3 mL was also required in the inclusion criteria. Sperm count was conducted every 60 days post-surgery for one year. Of the 25 patients, recovery of sperm production was noted in three (12%) after four months and another two after 12 months: Totaling five patients (20%) in one year. Sperm recovery ranged from 0.5 to 12 million/mL (Normal range > 20 million/mL) (Alves & Oliveira, 2017).

This study was limited by its small sample size (25). In addition, a bilateral varicocelectomy was performed on all 25 patients when only 10 presented with bilateral varicocele – of the remaining 15, left or right varicoceles accounted for 9 and 6 patients, respectively. Furthermore, this varicocele variation was not assessed in the recovery rates. Determination of which varicocele type resulted in greater recovery would have helped in identifying subgroups that may benefit more from varicocelectomy. Despite these limitations, this study was instrumental in a few aspects: Although not reaching the normal sperm concentrations, the recovery of spermatogenesis allows the use of these patients' own sperm for assisted reproduction. Moreover, five of the remaining patients were positive for genetic anomalies affecting male factor infertility and advised of the possibility of using a sperm donor; whereas the remaining 15 patients with idiopathic NOA varicocele were advised to undergo micro-TESE which could be used with assisted reproductive procedures (Alves & Oliveira, 2017).

Esteves, Miyaoka, Roque and Agarwal (2016) conducted a systemic review and meta-analysis to assess whether varicocelectomy in infertile men with nonobstructive azoospermia (NOA) showed any benefit. Benefits were assessed via two outcome measures: (1) Sperm retrieval rates and pregnancy rates following ART with the use of TESE (primary outcome), and

(2) the presence of viable sperm in postoperative ejaculate to eliminate the use of TESE and pregnancy rates using postoperative ejaculated sperm with or without ART. A total of 18 articles were evaluated and accounted for 468 patients diagnosed with NOA and varicocele. Patients in these studies were subjected to either surgical varicocele repair or percutaneous embolization. Three controlled studies assessing sperm retrieval showed a statistically significant increase in sperm retrieval rates in men who underwent a varicocelectomy compared to untreated men (OR 2.65, 95% CI: 1.69-4.14; $P < 0.001$; $I^2 = 0$). Two of these studies also evaluated pregnancy rates in ART cycles using TESE and showed that although increased extraction favored the treated group, the odds of achieving pregnancy (OR 2.19, 95% CI: 0.99-4.83; $P = 0.05$; $I^2 = 0$) and live birth (OR, 2.07, 95% CI: 0.92-4.65; $P = 0.08$; $I^2 = 0$) were not significantly different between treated and untreated men. The remaining 15 studies accounting for 344 patients assessed the presence of sperm in postoperative ejaculate. In 43.9% (151/344) of patients, sperm was found in ejaculates post varicocelectomy. Pregnancy outcomes with postoperative ejaculated sperm with or without ART (IVF/ICSI) was found to be 18.9% and 13.6% respectively (significance was not stated by the authors) (Esteves, Miyaoka, Roque & Agarwal, 2016). This study suggests that varicocelectomy in men with NOA leads to increased sperm retrieval rates, however, this increase doesn't correspond to a significant increase in achieving pregnancy or live birth rates.

Although this study provides valuable support for the recommendation or discussion of varicocele repair in infertile men with NOA, it also demonstrates that limited data on pregnancy outcomes with postoperative ejaculated sperm and extracted testicular sperm impedes any concrete conclusion regarding increased fertility outcomes in treated states. The former is limited by a lack of comparison groups within those studies whereas the latter is limited by the current number of available studies which to date only includes two. Lastly, the retrospective nature of

these studies further supports the notion that more prospective studies are needed to establish a more corroborated conclusion on the efficacy of varicocelectomy in infertile men with NOA and clinical varicocele.

Cost effectiveness of varicocelectomy before Assisted Reproduction

Although varicocele repair has shown efficacy in improving IVF/ICSI outcomes, the cost effectiveness of having the surgery prior to ART remains a consideration in health care. The following four studies evaluate whether varicocelectomy is a cost-effective measure prior to IVF/ICSI.

In 2002, Penson, Paltiel, Krumholz and Palter compared the cost-effectiveness of four strategies for varicocele-related infertility: observation only, varicocelectomy followed by up to three cycles of IVF if no natural conception occurred in the year after varicocelectomy, gonadotropin stimulated intrauterine insemination (IUI) followed by up to three cycles of IVF if IUI was unsuccessful, and immediate IVF without varicocele repair. The outcome measure was incremental cost per live delivery of any number of newborns. The probabilities of live delivery (effectivity) and costs were based on a literature search covering the years 1995–2000 with a target population of couples less than 40 years old with clinical varicocele, no other male infertility factors and sperm count of $\geq$ 5 million (thus not excluding azoospermic males). Ranked from least to most expensive, they calculated that varicocelectomy followed by IVF costs $22,114 per live birth (72% effectivity), gonadotropin stimulated IUI followed by IVF costs $22,122 per live birth (73% effectivity) and immediate IVF costs $33,686 per live birth (61% effectivity) (Penson, Paltiel, Krumholz & Palter, 2002). These results reveal that in couples with a clinical varicocele associated with oligospermia, varicocelectomy and IUI provide the least expensive intervention when compared to IVF/ICSI.

Although this current study was strengthened by the treatment strategy approach, the authors note some limitations. They are aware that it is common for some couples in whom varicocelectomy fails to seek IUI before attempting IVF and allude that their reason for not assessing this option were due to: (1) sparse support for the effectiveness of this strategy and (2) the time frame required for IUI post varicocelectomy exceeded that of the timeframe examined in this study. Moreover, they noted that their study is limited by the inability to account for future pregnancies that may occur from successful varicocelectomy. The possibility of the latter would inevitably improve the overall cost-effectiveness for couples, allowing them to conceive naturally. Furthermore, although the observation group acquired no costs, it was the least effective method of achieving pregnancy at only 14%.

In 2009, Lee, Li, Goldstein, Schattman and Schlegel used a simulated decision analytic model with cost data from the United States for the year 2005, to evaluate the economic impact of varicocele repair in NOA men with clinical varicocele versus utilizing TESE with IVF/ICSI. Data used in the decision analytic model were based on outcomes from peer-reviewed literature and the Society for Assisted Reproductive Technology. Whereas cost data were from Medicare Resource-Based Relative value scale and sampling of high-volume US IVF centers. Their data suggests that TESE was more cost-effective ($69,731) than varicocelectomy ($79,576) when direct and indirect costs (cost of complications associated with ART and varicocelectomy) per live birth were calculated. Moreover, using sensitivity analysis, they postulated that varicocelectomy only becomes more cost-effective than TESE when either the rate of natural conception after varicocelectomy substantially improves ≥ 40% in NOA men with clinical varicocele, or when the rate of successful delivery after IVF/ICSI decreases (< 10%) (Lee, Li, Goldstein, Schattman & Schlegel, 2009). These results suggest that men with a clinical

varicocele associated with NOA undergo TESE over varicocelectomy treatment as cost is reduced.

Although such decision models can provide a structured cost-effectiveness analysis of relevant factors in assisted reproduction, they cannot be generalized as costs vary widely between health institutions and countries. As such, factors such as insurance coverage and success rates of both varicocelectomy and TESE with IVF/ICSI should be considered to allow more individualized results. In addition, the author does well to list other limitations that may affect a couple's decision to either undergo varicocelectomy or immediately utilize assisted reproductive technology to include: maternal age, time, and access to ART due to cost.

Samplaski, Lo, Grober, Zini and Jarvi (2017) assessed the capability of varicocelectomy to upgrade semen parameters enough to allow couples needing IVF or IUI to switch to less invasive ART. 373 men who underwent varicocelectomy at a male infertility specialty clinic at the University of Southern California from 2002 to 2012 were included in this study. 68 of the repairs were performed via radiographic embolization, whereas the remaining 305 underwent microsurgical subinguinal varicocelectomy. After repair, semen analyses were performed at three months and for some men again at six months. The principle parameter used was the total motile sperm concentration (TMSC). Men were then divided into three groups per their baseline TMSC: 139 men with TMSC < 5 million were considered candidates for IVF, 66 with TMSC between 5-9 million for IUI, and 168 with TMSC > 9 million for natural pregnancy (NP). Overall, TMSC post varicocele repair increased significantly from 18.22 ± 38.32 million to 46.72 ± 210.92 million (P = 0.007). The most pronounced increase was seen with the IVF group, increasing from a mean TMSC of 2.32 ± 1.50 million to 15.97 ± 32.92 million (P = 0.0000002); in which 53.2% of men were upgraded from IVF candidacy to IUI or NP. For men in the IUI group, the mean

TMSC increased from 6.96 ± 1.16 million to 24.29 ± 37.17 million (P = 0.0004), allowing 57.6% of men become candidates for NP. For men in the NP group, mean TMSC increased from 36.26 ± 52.08 million to 81.80 ± 310.83 million (P = 0.05).

Although not directly investigated, the data from this study suggests that improved semen parameters should lead to reduced cost of ART as less invasive options become available. Of note, there were some men who downgraded from their initial classification after varicocele repair. However, after a comparison of upgrades and downgrades between men opting for varicocelectomy vs. men who did not, there was a statistically significant lower rate of men downgrading and higher rate of men upgrading in the treated group vs. the untreated group (P = 0.001). A few limitations discussed by the authors include it's retrospective nature and the acknowledgement that although the cutoff values used to categorize men for IUI and IVF are what's commonly used, these values are not perfect predictors of achieving pregnancy. Furthermore, the data for this study only assessed male infertility factors omitting female infertility factors. As such, the proposed findings need to be interpreted with caution when making recommendations for individual couples.

In 2017, Dubin et al., conducted a study to determine the role of varicocelectomy in men with TMSC < 2 million (categorized as severe oligospermia) previously ineligible for IUI to see if varicocele repair would improve TMSC enough to qualify these patients for IUI, in turn providing potential cost savings. A total of 17 men that met the inclusion criteria underwent varicocelectomy. Post-surgical repair, semen analysis was collected subsequently every 3 months. Cost effectiveness was calculated using reported costs. Of the 17 men that underwent a varicocelectomy, 14 had statistically significant improvement in TMSC with a mean change of 6.0 ± 8.5 million (P = 0.01) vs a mean of 0.44 ± 0.54 million prior to varicocele repair. 10 of the

14 men had TMSC > 2 million and of this, one man achieved spontaneous pregnancy and seven underwent a cycle of IUI; 2 of the 7 (28.6%) achieved clinical pregnancy with IUI with an estimated cost per pregnancy of $35,924 (Dubin et al., 2016). Using estimates for pregnancy rates from a different study, the authors estimated the cost per pregnancy after 1 cycle of IVF/ICSI following varicocele repair to be $93,203 and $45,795 for men with clinical varicocele who opted to go straight to IVF/ICSI without repair (Kirby et al., 2016).

The results of this study suggest that varicocelectomy increases TMSC in severely oligospermic men and therefore provides previously ineligible couples the opportunity to use the more cost effective IUI over the costlier IVF/ICSI. In discussing the limitations of this study, the authors point out that their sample size was substantially small with only 17 patients. In addition, they note that in the study by Kirby et al., for men with clinical varicocele, success rates for IVF/ICSI were also derived from a small sample to include only three studies and also a small number of IVF/ICI cycles. Furthermore, they note that their approach to determining costs was simplistic in that that they only focused on patients newly eligible to undergo IUI after varicocele repair. They chose this route due to the complexity of having to include infertility implications on both male and female factors.

Discussion

Varicocele continues to be the most common clinical finding in infertile males and is often the sole issue preventing conception in infertile couples. Although the exact mechanism in which it affects infertility remains unknown, numerous theories have been proposed that corroborate how it induces harmful effects on the testes over time. Currently, data suggests that varicocelectomy is successful in reversing the harmful effects of varicoceles and improving semen parameters. Data discussing effects of varicocelectomy on pregnancy rates, however,

remain controversial. While some report increased rates, others negate such findings or state that these increased rates were not significant compared to untreated groups. Hence, identifying the subset of infertile men who benefit most from a varicocelectomy remains a challenge. In hindsight, improved seminal parameters postsurgical repair of varicoceles have been shown to upgrade couples initially ineligible for less invasive forms of assisted reproductive techniques (i.e. IUI), to qualify for these procedures, thus reducing cost while helping couples achieve pregnancy.

In men with clinically diagnosed varicocele, does the method of varicocelectomy chosen improve fertility outcomes?

Surgical ligation is the more commonly used approach in varicocele repair (Concuzza et al., 2008; Johnson & Sandlow, 2017). It consists of suprapubic ligation, subinguinal ligation, inguinal ligation, retroperitoneal/open ligation and laparoscopic ligation. In this review, studies identified compared these various approaches based on improvements in semen parameters, pregnancy rates and their adverse effects.

In a meta-analysis by Schauer et al. (2012) comparing suprapubic, subinguinal and inguinal ligation for treatment of varicocele, all three treatments led to significantly improved semen parameters with a mean increase in sperm count of 10.85 x 10^6/mL (95 CI 3.16-18.54; P = 0.006), 7.17 x 10^6/mL (95% CI 3.73-10.61; P < 0.001) and 9.75 x 10^6/mL (95% CI 3.48-16.02; P 0.002), respectively; and a mean increase in sperm motility of 6.80% (95% CI 3.95-9.66; P < 0.00001), 9.44% (95% CI 3.72-15.16; P = 0.001) and 12.25% (95% CI 4.76-19.75; P = 0.001), respectively. Further support for subinguinal varicocelectomy was provided by Enatsu et al. (2014) where results from their assessment showed that the subinguinal approach led to a significant overall mean increase from 2.4 to 11.6 million/mL (P < 0.001) and from 32.8% to

42.2% (P = 0.0024) in sperm count and sperm motility, respectively. Bryniarski et al. (2017) in one of the few prospective studies assessing whether the subinguinal approach is superior to laparoscopic varicocelectomy showed that semen parameters were significantly improved in both groups (P < 0.001) with no significant difference in sperm concentration or hormonal levels. In another meta-analysis by Yuan et al. (2017), assessing the efficacy and safety of subinguinal, laparoscopic and open varicocelectomy, they found that both subinguinal and laparoscopic approaches led to more significant increases in semen parameters than open varicocelectomy (P = 0.008, P = 0.001, respectively) while there was no significant difference between the microsurgical and laparoscopic groups (P = 0.09). Moreover, the subinguinal approach showed a significantly greater increase in sperm motility than the open varicocelectomy group (P = 0.02); but no significant difference was found between subinguinal and laparoscopic groups (P = 0.49) or between the laparoscopic and open groups (P = 0.34).

Each of the studies already discussed also compared pregnancy rates amongst the different surgical techniques. Schauer et al. (2012) showed that inguinal, suprapubic and subinguinal varicocelectomy led to an overall significant increase in spontaneous pregnancy (P = 0.035) with the inguinal approach showing the most improvement. An issue with this assessment, however, is that only the studies on suprapubic varicocelectomy reported that only spontaneous pregnancies were included; the others on inguinal and suprapubic did not state how pregnancy was achieved. Bryniarski et al. (2017) showed that although the subinguinal ligation had higher pregnancy rates than laparoscopy, the difference was not statistically significant. The latter was corroborated by Yuan et al. (2017) who also found that although improved, the differences in pregnancy rates between subinguinal and laparoscopic approach were not

statistically significant (P = 0.25). However, subinguinal ligation did show a more significant increase in pregnancy rates than open varicocelectomy (P = 0.002).

Of the four studies, two also discussed side effects or complications post surgery. Bryniarski et al. (2017) reported five patients in the laparoscopic group developed hydrocele (13.5%), whereas epididymitis was noted in one (2.7%) of the patients from the microsurgical group one week after operation. Furthermore, recurrent varicocele was observed in three patients (8.1%) from the laparoscopic group while none was seen in the microsurgical group. Similarly, Yuan et al. (2017) also reported that the incidence of complications and varicocele recurrence post repair were significantly lower for the subinguinal group than the laparoscopic and open group (P < 0.0001 and P < 0.00001, respectively). However, between the laparoscopic and open group, the differences were not significant.

An extension of the Enatsu et al. (2014) study was to identify parameters associated with improved outcomes of varicocelectomy in severely oligospermic patients (sperm concentration < 5 x 10^6/mL). What they found was that amongst the patients with a sperm concentration > 2 million per ml, there was a greater improvement in semen parameters and spontaneous pregnancy (56.3% and 25%, respectively). Based on several studies, the current consensus is that men with sperm concentration < 5 x 10^6/mL skip varicocelectomy and instead consider immediate ART as an alternative due to low spontaneous pregnancies. However, this study suggests that there may be a sub-category of men with severe oligospermia that may indeed benefit from a varicocelectomy.

Overall, these findings suggest that amongst microsurgical, laparoscopy and open varicocelectomy, microsurgical (specifically subinguinal) and laparoscopy would be the better option as both seem to have similar efficacy in improving fertility outcomes. However, when

post-surgical complications are considered, the subinguinal approach is preferred as it is associated with less issues post surgery.

In men with oligospermia vs azoospermia with a varicocele, does varicocelectomy before ART improve fertility outcomes?

The studies assessed in this review provide support for the efficacy of undergoing a varicocelectomy before IVF/ICSI in men with oligospermia. Esteves et al., (2010) showed that there was a significant increase in achieving pregnancy and live birth in treated versus untreated groups (OR 1.82 95% CI 1.62-3.15; P = 0.03 and OR 1.87 95% CI 1.08-3.25; P = 0.03, respectively). These findings were later challenged by Pasqualotto et al., 2012 who stated that although the treated group did have an increased pregnancy rate with IVF/ICSI in comparison to the untreated group, these findings were not significant (30.9% versus 31.1%; P = 0.9806, respectively). However, Pasqualotto et al.'s study failed to address two issues that may have skewed their data: (1) They only considered males with grade III varicocele compared to Esteves et al. which evaluated all three grades; (2) there was a significant difference between time to conceive in the treated versus the untreated group (P<0.001). It's plausible that couples requiring a longer time (treated group) had other issues contributing to the difficulty in getting pregnant (i.e. maternal age) that if eliminated may show results more favorable to the treated group. Gokce et al., (2013) later conducted a bigger study where they provided support for the findings by Esteves et al. (2010). They showed that varicocelectomy with IVF/ICSI led to significantly increased pregnancy rates (OR 2.02, 95% CI 1.25-3.87; P = 0.032) and live birth rates (OR 2.12, 95% CI 1.26-3.97; P = 0.026). Furthermore, in a meta-analysis by Esteves et al. (2016), that included all three of the aforementioned studies and one by Shiraishi et al., they concluded that pregnancy rates were significantly higher in couples that underwent a varicocele repair before

IVF/ICSI versus those that did not (OR 1.59, 95% CI 1.19-2.12; P < 0.05; I^2 = 25%). Additionally, a statistically significant increase in live birth rates was also reported by three of the four studies (OR 2.17, 95% CI 1.55-3.06; P < 0.05; I^2 = 0%). A summary of pregnancy outcomes from these studies is shown in *Table 1.*

Table 1

Pregnancy outcomes following IVF/ICSI for oligospermic men with treated and untreated varicoceles

	Treated varicocele			Untreated varicocele			Statistically significant?
Study	**Pregnancies**	**Couples**	**Pregnancy rate**	**Pregnancies**	**Couples**	**Pregnancy rate**	**P<0.05**
Esteves et al. (2010)	48	80	60.0%	73	162	45.0%	Yes
Pasqualotto et al. (2012)	52	169	30.9%	25	79	31.1%	No
Gokce et al. (2013)	105	168	62.5%	65	139	47.1%	Yes

Note. IVF = in Vitro fertilization, ICSI = intracytoplasmic sperm injection.

Unlike men with oligospermia, men with nonobstructive azoospermia (NOA) present with a more severe condition and accounts for 10% of infertile men (Esteves, Miyaoka, Roque & Agarwal, 2016). Of this 10%, varicocele is found in approximately 5% (Esteves, Miyaoka, Roque & Agarwal, 2016). However, with advances in ART, such as testicular sperm extraction (TESE) and ICSI combined with varicocelectomy, urologist are now able to offer fertility treatment to couples whose male partner has NOA. The studies discussed evaluated the effectiveness of a varicocele repair before TESE and IVF/ICSI. Areas assessed included sperm retrieval rate, pregnancy rates and the presence of sperm in ejaculate postsurgical repair (1 study). Inci et al., (2009) showed that men who underwent a varicocele repair had significantly greater sperm retrieval rate than men who did not (OR 2.63, 95% CI 1.05-6.60; P = 0.036). Subsequently, these men went on to achieve pregnancy at a higher rate (31.4%) than men who did not undergo surgery (22.2%), however, this increase was not significant. These findings were

corroborated in a similar study by Haydardedeoglu et al., (2010), where they also noted a significantly increased sperm retrieval rate in men in the treated group versus men in the untreated group. However, unlike in the Inci et al. study, this also translated to a significant increase in pregnancy rates (74.2% vs 52.3%; $P < 0.05$) and live birth rates (64.5% vs 41.5%; $P < 0.05$) in the treated versus untreated group. *Table 2* provides a summary of pregnancy outcomes from these two studies. In a meta-analysis by Esteves et al., (2016), three of the studies that evaluated sperm retrieval also showed a statistically significant increase in the treated group versus the untreated group (OR 2.65, 95% CI: 1.69-4.14; $P < 0.001$; $I^2 = 0$). Two of the three also evaluated pregnancy rates where they showed that pregnancy rates and live birth rates were also higher, albeit not significantly amongst men in the treated group versus the untreated group (OR 2.19, 95% CI: 0.99-4.83; $P = 0.05$; $I^2 = 0$ and OR, 2.07, 95% CI: 0.92-4.65; $P = 0.08$; $I^2 = 0$, respectively).

Table 2

Pregnancy outcomes following IVF/ICSI for non-obstructed azoospermic men with treated and untreated varicoceles

	Treated varicocele			**Untreated varicocele**			**Statistically significant?**
Study	**Pregnancies**	**Couples**	**Pregnancy rate**	**Pregnancies**	**Couples**	**Pregnancy rate**	**P<0.05**
Inci et al. (2009)	21	66	31.4%	7	30	22.2%	No
Haydardedeoglu et al. (2012)	23	31	74.2%	34	65	52.3%	Yes

In an extension of the latter study, they also assessed the presence of sperm in the ejaculates postsurgical repair. This included 15 studies with a total of 344 patients of which 151 (43.9%) had sperm in ejaculates post varicocele repair. Pregnancy outcomes with postsurgical ejaculated sperm with or without IVF/ICSI was found to be 18.9% and 13% respectively. Whether this is significant is unknown as not all studies included these results, as such comparison wasn't possible. This limited data makes it difficult to affirm conclusively that there

is increased fertility potential in treated individuals with ejaculate in their semen postsurgical repair.

As shown, there are conflicting data regarding pregnancy and live birth rates following varicocelectomy in men with NOA. Albeit there are increased rates, some studies state this is significant, while others state otherwise. As such, more prospective studies need to be conducted to make a stronger conclusion. Lastly, couples should be warned about the length of time between surgical repair of varicocele and TESE/ICSI/IVF. Per the Inci et al. and Haydardedeoglu et al. studies, the observed time to successful pregnancy ranged from a mean of 2 to 3.5 years and those who failed to get pregnant had a mean wait time of six years between procedures. Therefore, maternal age and individual preferences need to be addressed when taking into consideration the wait time.

Although the above studies regarding efficacy of varicocelectomy in men with oligospermia versus NOA were all retrospective, they were adequately powered to provide recommendations regarding treatment for each group. Nonetheless, prospective studies are needed to evaluate conclusively, the subgroups of men that may benefit most from undergoing a varicocelectomy to include factors such as male age, duration of infertility, female age, grade of varicocele, and semen parameters.

In men with clinically diagnosed varicocele, is it cost effective to undergo a varicocelectomy before ART?

Although varicocelectomy can improve IVF/ICSI outcomes, whether this procedure is cost effective depends on the degree of abnormality found in semen analysis. There is sufficient evidence showing an increase in pregnancy rates after varicocele repair in men with

oligospermic semen parameters (Esteves, Oliveira, & Bertolla, 2010; Gokce et al., 2013; Esteves, Rogue & Agarwal, 2016).

Samplaski et al. (2017) assessed the ability of varicocele repair to improve semen parameters enough to allow couples needing IVF or IUI to upgrade to less invasive ART. The principle parameter used to evaluate efficacy was TMSC. The 373 men in this study were then divided into three groups based on baseline TMSC: IVF group (TMSC <5 million), IUI group, (TMSC between 5-9 million) and the natural pregnancy group (TMSC > 9 million). Overall, semen parameters significantly improved post varicocele repair in all TMSC groups ($P = 0.007$) with the most pronounced increase seen with the IVF group. The improved parameters subsequently allowed 53% of men to upgrade from IVF candidacy to IUI or natural pregnancy. Although cost wasn't assessed directly, the data does suggest that varicocelectomy does lead to improvements in semen parameters that provide access to less invasive more cost-effective ART options.

When comparing cost effectiveness of varicocelectomy in men with severe oligospermia previously ineligible for IUI, Dubin et al. (2016) showed that of the 17 men who underwent a varicocelectomy, 14 had significantly improved semen parameters ($P = 0.01$) post surgery. 10 of the 14 men with total motile semen count (TMSC) > 2 million now qualified for IUI. Of the seven that opted to undergo one cycle of IUI, two (28.6%) achieved pregnancy. Subsequently, they calculated the cost per pregnancy with 1 cycle of IUI post surgery to be $35,92 compared to $93,203 and $45,795 for men with clinical varicocele who opted for IVF/ICSI post surgery or immediate IVF/ICSI without surgical repair of varicocele, respectively (Kirby et al., 2016). Lastly, it's important to note that although IUI is more cost effective than immediate IVF/ICSI

and IVF/ICSI after varicocelectomy, it's incidence of pregnancy is lower (29% vs 49% vs 42%, respectively).

Penson et al. (2002) also conducted a study comparing cost-effectiveness of four strategies related to varicocele induced infertility: observation, varicocele repair followed by IVF if the couple failed to conceive within a year post repair, gonadotropin stimulation and IUI followed by IVF if IUI failed and immediate IVF without repair. Immediate IVF proved to be least cost-effective coupled with the least effective (live birth rates). In addition, IVF followed by varicocelectomy was the slightly less expensive and a more effective option when compared to IUI ($22,114 with 73% effectivity vs $22,122 with 72% effectivity, respectively). Although observation was the least expensive overall, it resulted in the least effectivity with only 14%.

Conversely, the role of varicocele repair in men with NOA is not as clear. Lee et al. (2009) performed a cost analysis where they compared TESE with IVF/ICSI versus varicocelectomy with IVF/ICSI. Their findings demonstrated that directly proceeding to TESE was more cost effective than undergoing a varicocelectomy ($69,731 versus $75,576) when direct and indirect costs were considered. Furthermore, the authors state that varicocelectomy in men with NOA will only favor immediate TESE when it results in ≥ 40% spontaneous pregnancy rate or when the rate of successful delivery after IVF/ICSI is < 10%. Implications of this study can be extended to the meta-analysis by Esteves et al. (2016) where they document that varicocelectomy in men with NOA does not significantly increase pregnancy or live birth rates. As such, from a financial perspective, immediate TESE is superior.

Per these studies reviewed, varicocelectomy can exclude the need for multiple cycles of ART due to improvements in liver birth rates after ART while offering a cost-effective option.

However, in men with a varicocele and NOA induced infertility, proceeding directly to TESE then IVF may be more beneficial.

Applicability to Clinical Practice/Policy

Although a varicocele is the most treatable cause of male infertility, treatment via varicocelectomy isn't necessary an option for every male. Per the American Society for Reproductive Medicine, recommendations for varicocelectomy should be offered to men attempting to conceive only when all of following are met: a palpable varicocele, there is documented infertility, the man has one or more abnormal semen parameter and the female partner has normal fertility or potentially correctable infertility (Report on varicocele and infertility, 2014). An extension of this recommendation was also made to include men with a palpable varicocele and abnormal semen parameters not currently attempting to conceive; young men with a varicocele and normal semen analyses due to potential risk for future testicular dysfunction; adolescent males with evidence of reduced ipsilateral testicular size or abnormal semen parameters and; pain associated varicoceles. Of note, for men with a palpable varicocele and normal semen parameters, the current recommendation is not to treat.

As with any recommendation, these are merely guidelines and should be followed on a case by case basis. Research presented in this study shows that varicocelectomy has a greater benefit for men with clinical varicocele and oligospermia compared to men with non-obstructive azoospermia. As such, the latter may benefit more from direct testicular extraction than IVF/ICSI. Nevertheless, there are certain circumstances where treatment of varicocele in men with NOA should be considered. As already discussed, evidence has shown that in some men with NOA, varicocele repair has led to slight improvement of sperm numbers in the ejaculate, thus eliminating the need for testicular extraction before IVF/ICSI.

Other considerations include maternal age; advancement in age reduces the success of IVF/ICSI. Therefore, delaying IVF/ICSI in place of a varicocelectomy may be inadvisable. Number of children desired is another; if only one child is desired, ART may be better especially in men with NOA, whereas if multiple children are desired, varicocelectomy may be of benefit in increasing the chances of spontaneous pregnancy. In regard to cost, current literature supports the recommendation of repair before ART for oligospermic or severely oligospermic patients and as a cost effective measure, but shows that in men with NOA, immediate testicular extraction is a better option.

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