CLINICS

REVIEW

The role of varicocele treatment in the management of non-obstructive azoospermia

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The literature on male reproductive medicine is continually expanding, especially regarding the diagnosis and treatment of infertility due to non-obstructive azoospermia. The advent of in vitro fertilization with intracytoplasmic sperm injection has dramatically improved the treatment of male infertility due to non-obstructive azoospermia. Assisted reproduction using testicular spermatozoa has become a treatment of hope for men previously thought to be incapable of fathering a child due to testicular failure.
In addition, numerous studies on non-obstructive azoospermia have reported that varicocelectomy not only can induce spermatogenesis but can also increase the sperm retrieval rate; however, the value of varicocelectomy in patients with non-obstructive azoospermia still remains controversial. The purpose of this review is to present an overview of the current status of varicocele repair in men with non-obstructive azoospermia.

KEYWORDS: Varicocele; Varicocele Repair; Male Infertility; Non-Obstructive Azoospermia; Sperm Retrieval.

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INTRODUCTION

A varicocele is an abnormally dilated pampiniform plexus, which is the venous network that drains blood from the testicles. The varicocele prevalence in the general population is estimated to be 15%; however, the prevalence is 35% among men with primary infertility and 81% among men with secondary infertility (1,2). The detrimental effects of varicoceles on fertility and the benefit gained by their repair have been debated among andrologists for almost 60 years. Since Tulloch reported the first unassisted pregnancy following varicocele repair in an azoospermic man in 1952, the effect of varicocelectomy on male infertility has become a hotly debated topic (3).

Azoospermia renders spontaneous pregnancy nearly impossible. The only treatment option for men with non-obstructive azoospermia (NOA) who desire to be biological parents is testicular sperm extraction (TESE) with intracytoplasmic sperm injection (ICSI). One of the primary benefits of varicocelectomy in NOA patients is that it has the potential to produce motile sperm; however, the value of varicocelectomy in patients with NOA remains unclear. Nonetheless, cumulative data reveal that varicocelectomy can improve spermogram results (4-18). The present review article provides an overview (from varying perspectives) of the role of varicocelectomy in patients with NOA-related infertility, based on the most current data.

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THE RELATIONSHIP BETWEEN VARICOCELES AND INFERTILITY

Varicoceles are diagnosed primarily during physical examinations and are graded based on the Dubin system: grade 1, varicose veins in the scrotum are palpable with the Valsalva maneuver; grade 2, veins are palpable without the Valsalva maneuver; and grade 3, varicose veins are observed in the scrotum without any maneuver or manipulation. Varicoceles that are detected via physical examination are referred to as clinical varicoceles, whereas those that are >3 mm in diameter and observed only via Doppler ultrasound with the Valsalva maneuver are considered subclinical varicoceles. Most studies on varicoceles are based on the Dubin system classification; thus, interobserver variation in the diagnosis of grade poses an obvious problem.

The pathophysiology of varicocele-related infertility

Rather than address the classical theories of varicocele formation, the present review focuses on theories concerning the mechanisms by which dilated scrotal veins impair spermatogenesis and cause infertility. The literature primarily includes studies on the progressive toxic effects of varicoceles, namely elevated temperature, adrenal hormone reflux, gonadotoxic metabolite reflux, altered testicular blood flow, antisperm antibody formation, alterations in the hypothalamic-pituitary-gonadal axis, and oxidative stress. Because the detrimental effects of varicoceles on

spermatogenesis are apparently related to several factors that may act synergistically, it is difficult to explain the mechanism of action using only one theory.

In healthy males, the scrotal temperature is 2 ℃ lower than the core body temperature. A testicular temperature that is identical to the core body temperature is associated with a decrease in the sperm count and sperm quality. Although the exact mechanism by which the temperature influences spermatogenesis is not clearly known, the most commonly accepted theory is thermal damage to the DNA and proteins in the nucleus of spermatic tubule cells and/or Leydig cells (19,20). It has been reported that men with varicoceles and impaired sperm quality have elevated scrotal temperatures and that varicocelectomy leads to a normal scrotal temperature (19,21); however, these results are limited by the fact that the studies were not designed to address factors other than varicoceles that can affect scrotal temperature, such as external exposure to heat and daily postural changes.

The reflux of catecholamines and their metabolites from the adrenal gland into left-sided varicoceles is reported to cause vasoconstriction and reduced testicular function; however, these results have not been consistently observed (19). Venous hypertension, caused by the exertion of pressure on the gonadal venous valves by a hydrostatic column can cause chronic vasoconstriction of testicular arterioles, thereby reducing testicular function (22). This phenomenon leads to persistent hypoperfusion, stasis, hypoxia, and subsequent dysfunction of the spermatic epithelium (23). Additional research is necessary to determine if the reflux of renal or adrenal metabolites contributes to the mechanism of injury observed with varicoceles.

Antisperm antibody formation is another theory for explaining varicocele-related male infertility. Infertile men have higher levels of testicular autoantibodies in their serum than fertile men. Currently, based on animal experiments, artificial varicocele induction does not cause rupture of the blood-testis barrier and is not correlated with an increase in antibody levels (24). Moreover, based on direct immunobead assays, varicoceles in infertile men do not alter the autoantibody level (25). This theory has yet to accumulate sufficient evidence-based support.

Another debatable pathophysiological theory of varicocele-related infertility is that varicoceles negatively affect the hypothalamic-pituitary-gonadal axis. Some patients with varicoceles were reported to have low testosterone levels and sperm quality, which were reversed via varicocelectomy (26,27). The mechanism of effect of varicoceles on the hypothalamic-pituitary-gonadal axis is related to Leydig cell injury and an increase in the heat-associated malfunction of intratesticular enzymes acting on spermatogenesis (28). Additionally, it has been suggested that a low testosterone level negatively affects sperm maturation and increases apoptosis. In contrast, some studies report that there is no association between varicocelectomy and an increase in testosterone levels or sperm quality (29,30). The major criticism of these studies that examined the varicocele/hypothalamic-pituitary-gonadal axis theory is that blood samples used for testosterone measurement were obtained peripherally, which is not the most reliable sampling method (28). The contemporary andrology literature lacks research on intratesticular testosterone levels.

Oxidative stress secondary to elevated scrotal temperatures and the formation of reactive oxygen species (ROS) is another important theory for explaining the negative effects of varicoceles on testicular function; this explanation is gaining more support over time (31,32). In addition to other gonadotoxic factors associated with varicoceles, ROS also oxidize fatty acids in spermatozoa membranes and cause DNA damage and fragmentation of the sperm (33). There are several theories regarding the pathophysiological mechanism of the accumulation of ROS in tissues, the most widely accepted of which is the elevated venous pressure theory. Increases in venous pressure decrease testicular blood flow and cause hypoxia, which in turn leads to the accumulation of ROS (28). Several studies have revealed that infertile men with varicoceles have higher levels of seminal oxidative stress markers (e.g., ROS, lipid peroxidation, oxidative DNA damage) than fertile men and infertile men without varicoceles (27,34-36). Total antioxidant capacity (TAC) measurements are reportedly low in men with varicoceles compared with fertile controls (37). Agarwal et al. identified 23 human studies on the role of oxidative stress in varicocele-associated infertility and selected four that measured similar types of reactive oxygen species (ROS) using similar methods (37). This meta-analysis confirmed that ROS-induced oxidative stress, lipid peroxidation, and a low TAC may play a role in the etiology of varicocele-related infertility. Sperm DNA fragmentation is greater in infertile men with varicoceles than in fertile men without varicoceles, which was similarly observed in adolescents with bilateral varicoceles (38-40). Blummer et al. reported impaired mitochondrial activity and DNA fragmentation in the spermatozoa of men with varicoceles (41). The levels of oxidative stress biomarkers decrease following varicocelectomy, suggesting that, in men with a varicocele, oxidative stress in the seminal fluid is primarily caused by the varicocele itself (27). Additionally, after varicocele repair, an increase in the semen antioxidant capacity is observed (42). Several prospective and retrospective studies on the effect of varicocelectomy on sperm DNA damage have demonstrated that varicocele repair is associated with reduced sperm DNA damage (43-46). However, no randomized controlled trial has been conducted regarding the role of varicocelectomy in sperm DNA integrity.

The effects of varicocele repair on infertility

The current data in the medical literature concerning the effect of varicocelectomy on infertility are so inconsistent that a definitive interpretation of the findings is difficult, primarily due to differences in the treatment and outcome parameters. Whereas interventional radiologists percutaneously treat varicoceles using sclerotherapy or angioembolization, andrologists use open or endoscopic surgery. Open surgery can be performed via inguinal, subinguinal, or retroperitoneal approaches, with or without microscopic assistance. Retroperitoneal laparoscopic surgery is being replaced by inguinal robot-assisted procedures at some centers. A recent comparative review that included over 5,000 patients concluded that open, microsurgical, inguinal, or sub-inguinal varicocelectomy techniques resulted in higher spontaneous pregnancy rates (44.75%; range 33.8-51.5%) with lower recurrence and hydrocele-formation rates (2.07 and 0.72%, respectively) compared with laparoscopic, radiological embolization, and macroscopic inguinal or retroperitoneal varicocelectomy techniques (47).

The infertility-related treatment endpoints that are commonly analyzed following varicocele repair are semen parameters (i.e., concentration, motility, and/or morphology), sperm DNA integrity, and pregnancy rate (PR). Most published studies consider semen parameters (specifically the sperm density, motility, and morphology) to be the primary outcome parameters of varicocele repair.

Repair of clinical varicoceles

Clinical varicoceles are among the most extensively studied urological issues; however, the findings have been inconsistent, perhaps due to differences in the study designs. The first randomized controlled trial (RCT) to report that varicocele repair did not improve fertility was conducted by Nilsson et al. (48). The study randomized 96 infertile patients with visible left-sided varicoceles to receive high ligation (51 patients) or no treatment (46 patients), followed by 36-74 months of follow-up. The patients underwent semen analysis and a pregnancy inquiry every six months. The semen analysis findings and the reported pregnancy rates did not indicate that the varicocele repairs were effective. The report was criticized because some of the patients had normal sperm parameters preoperatively, and the sperm analysis findings were not stratified by the postoperative month. Another prospective RCT, which included 96 patients who were followed-up for four years, also reported that varicocele repairs did not positively affect the semen parameters or pregnancy rates (49). The pregnancy rate in the untreated group (22/41, or 53.7%) was higher than that in the group receiving treatment (13/38, or 34.2%). However, 26 of the 38 men who were randomized to treatment underwent open surgery, and 12 were treated with sclerotization or embolization. The use of multiple treatment methods associated with different success rates is a major limitation of the study. A multicenter, prospective RCT investigating varicocele treatment that was performed in Germany examined the effect of sclerotization of dilated veins on pregnancy rates (50). The researchers reported that there was no increase in pregnancy rates in the treatment group. The conception rate was 30% within 12 months after sclerotization among the treated patients and 16.2% among the untreated patients ($p = 0.189$). Although the number of cases necessary to achieve the study's goal was calculated to be 460, only 67 patients were randomized at the end of the three-year follow-up period. Therefore, poor recruitment and follow-up were the main limitations of the investigation.

Studies reporting a positive effect of varicocelectomy on fertility have similar drawbacks, which are primarily related to study design and execution. Performing meta-analyses of RCTs is challenging because of the wide variation in study designs, methodologies, and populations. The following are some examples of larger-scale RCTs: A Japanese study compared 141 patients who underwent high ligation and 83 patients who did not receive treatment (51). The researchers reported a significant improvement in the concentration and motility of the sperm and higher pregnancy rates in the surgically treated group. Madgar et al. studied 45 couples in which the male partner was infertile (with oligozoospermia) and in which clinical varicoceles were the only observable factor causing infertility (52). In total, 25 of the men underwent high ligation, and their partners had a 60% pregnancy rate one year post surgery, whereas the non-treatment group had a pregnancy rate of 10%. The men in the non-treatment group underwent high ligation one year later, and the one- and two-year post-surgery pregnancy rates were 44 and 22%, respectively. In a recent RCT comparing subinguinal microsurgical varicocelectomy (n = 73) with observation (n = 72), Abdel-Meguid et al. found that the pregnancy rate was significantly higher in the treatment group (32.9% vs. 13.9%, OR 3.04, 95% CI = 1.33-6.95) (18). All of the semen parameters significantly improved in the treatment arm ($p<0.0001$), while none of these parameters changed significantly in the control arm (sperm concentration [$p = 0.18$], progressive motility [$p = 0.29$], and normal morphology [$p = 0.05$]).

The Cochrane Review (2004) analyzed randomized clinical trials investigating the effects of surgery and embolization for varicoceles in subfertile men (53). The combined Peto OR favoring treatment over no-treatment was 1.10 (95% CI = 0.73-1.68), indicating no benefit of varicocele treatment over observational management in subfertile couples in which a varicocele in the male partner is the only abnormal finding. This meta-analysis concluded that surgical and radiological treatment of varicoceles in men with otherwise unexplained infertility could not be recommended; however, the meta-analysis was criticized because it included studies of men with normal semen parameters and subclinical varicoceles. Ficarra et al. published a meta-analysis including only three randomized clinical trials that did not include patients with normal spermogram findings or those with subclinical varicoceles (50,52,54). The researchers reported that these studies were methodologically deficient and heterogeneous and that pooling them does not result in a high-quality meta-analysis. Marmar et al. conducted a meta-analysis that included only randomized controlled studies of men with palpable varicoceles and abnormal semen parameters and found significantly increased odds of pregnancy after varicocele treatment (OR: 2.87; 95% CI = 1.33-6.20) (55). The Cochrane Review was subsequently updated in 2009, reporting that the treatment of varicoceles in men with no other cause of infertility does not increase the possibility of conception (56). Eight studies were included in the meta-analysis, which examined a total of 607 men. However, trials that included men with subclinical varicoceles and men with normal semen analyses were included in the treatment arms. When the analysis was limited to include only the studies of men who had abnormal semen parameters with clinical varicoceles, the OR suggested a possible benefit of varicocele treatment, although the statistical power was reduced (OR: 2.08; 95% CI = 0.60-4.25) (57). A recent meta-analysis, which was published in 2011, concluded that varicocelectomy improves seminal parameters and reduces sperm DNA damage and seminal oxidative stress in subfertile men with clinical varicoceles; however, there is insufficient evidence to demonstrate a beneficial effect of varicocele repair on spontaneous pregnancy rates (58). Nevertheless, the American Urological Association (AUA) and the American Society of Reproductive Medicine (ASRM) still recommend varicocele repair for patients with palpable varicoceles and at least one abnormal semen parameter (59,60).

The effect of varicocele repair in azoospermic patients

NOA significantly reduces a man's potential for fertility. Historically, spermatogenesis has been induced and stimulated in some men following varicocele repair. Tulloch was the first to report a spontaneous post-varicocelectomy pregnancy in a couple with an azoospermic male (3). Since

then, varicocelectomy has become the most frequently performed surgery for the treatment of male infertility.

Azoospermia or severe oligospermia occurs in 4-13% of men with clinical varicoceles (28). Matthews et al. studied a cohort of 78 infertile men; 22 were azoospermic and 56 were oligoasthenospermic (13). All of the patients underwent microvaricocelectomy. Post-operative semen analyses revealed that 55% of the azoospermic patients and 82% of the oligoasthenospermic patients had motile sperm. The pregnancy rate in the azoospermic group was 14% (versus 38% in the oligoasthenospermic group), and two spontaneous pregnancies occurred in the azoospermic group. The researchers also reported that the presence of testicular atrophy at the initial examination has no prognostic value for fertility; however, the study was limited by the lack of a control group.

Beginning four months after varicocele-repair surgery, Kim et al. examined 28 men with azoospermia and bilateral or unilateral varicoceles (11). Of the 28 men, 12 (43%) had sperm in their ejaculates, with a mean sperm count of $1.2 \pm 3.6 \times 10^6$/ml at 24 months of follow-up. They reported two pregnancies following assisted reproductive technology (ART) treatment; however, there were no spontaneous pregnancies. In another case-control study that evaluated the treatment outcomes and benefits of varicocelectomy in men with NOA and severe oligospermia, spermatogenesis was induced, and 0.2 million motile sperm were produced by two of the six men with NOA (9). It was also reported that 28.6% of virtual azoospermia patients had motile sperm counts above five million following microsurgical varicocele repair, and spontaneous pregnancy occurred in three (21.4%) patients (10). The researchers also reported that 28.6% of patients with virtual azoospermia were spared ICSI procedures as an initial therapeutic option and were given the opportunity to conceive children without bypassing the usual process of natural selection. Gat et al. observed a significant improvement in the concentration, motility, and morphology of sperm in 56.2% of azoospermic men following internal spermatic vein embolization (8). The mean sperm concentration increased to $3.81 \pm 1.69 \times 10^6$/ml after embolization. The authors concluded that if azoospermia is not too long-standing, the treatment of varicoceles may significantly improve spermatogenesis or renew sperm production. In addition, adequate treatment may spare 50% of azoospermic patients from TESE in preparation for ICSI.

In a recently published prospective noncontrolled study, Taha A. Abdel-Meguid reported the recovery of motile sperm in the ejaculate of 10 of 31 (32.3%) men with NOA and clinically palpable varicoceles following subinguinal microsurgical varicocelectomy (61).

Since 1952, numerous reports of changes in the sperm parameters and pregnancy rates in patients with NOA after varicocele repair have been published. Based on these reports, 21-56% of men have motile sperm and 0-15% of their partners have spontaneous pregnancies following varicocele repair; however, none of these studies included a control group (Table 1) (4-18). On one hand, control groups are not considered to be necessary because the control group is expected to remain azoospermic for the duration of any study; on the other hand, NOA patients can exhibit the spontaneous return of spermatozoa in their ejaculate, indicating the necessity for a control group (62). In contrast, some studies indicate that men with clinical varicoceles that are associated with NOA rarely have an adequate number of sperm in their ejaculate after undergoing varicocele repair to avoid TESE (16). Schlegel and Kaufmann reported that seven of 31 patients (22%) produce sperm, as measured by a post-varicocelectomy semen analysis at an average follow-up of 14.7 months, and only 9.6% have sufficient motile sperm in the ejaculate to enable the use of ICSI and avoid TESE.

However, positive changes in the semen parameters following varicocele repair do not last forever. Some researchers recommend the cryopreservation of semen samples that contain motile sperm because azoospermia may recur (12,14). Pasqualotto et al. treated 27 azoospermic men with microsurgical repair (14). Semen samples obtained six months post-surgery revealed that nine patients had sperm in their semen; however, a 12-month post-surgery semen sample analysis revealed that five patients (55.6%) were again azoospermic, which the researchers posited may be a temporary effect due to the induction of spermatogenesis. They also stated the possibility that the men had intermittent sperm production and that the findings were thus unrelated to the surgery.

Most of the above-mentioned studies were small, retrospective, uncontrolled case series that examined pre- and post-varicocele-repair sperm parameters and reported only short-term outcomes. As such, there is a need for evidence obtained from well-designed randomized or non-randomized controlled trials and from meta-analyses of primary studies to enhance the objectivity and validity of the findings. A recent meta-analysis examined the ability of varicocele repair to improve the semen parameters and pregnancy rates in patients with NOA, focusing on factors that may predict treatment success (63). The analysis included only English-language reports on surgical varicocelectomy or internal spermatic vein embolization in men with NOA. Studies that included patients with obstructive azoospermia, severe oligospermia, and cryptozospermia, as well as investigations including patients with subclinical varicoceles, individual case reports, and studies with a follow-up of <4 months, were excluded from the analysis. There were no prospective or randomized trials investigating the treatment of men with NOA. Eleven studies on varicocele repair in men with NOA (a total of 233 patients) were included in the meta-analysis. Following varicocele repair, motile sperm were observed in the semen of 91 of the 233 (39.1%) men, and there were 14 (6%) spontaneous pregnancies and 10 pregnancies with the assistance of in vitro fertilization (IVF). The post-operative sperm density was $1.6 \times 10^6 \pm 1.2 \times 10^6$ per milliliter and the mean sperm motility was $20.1 \pm 18.5\%$. In total, 11 (4.6%) post-surgical patients with motile sperm in their semen relapsed into azoospermia within two-six months after treatment. As reported by the researchers, the primary limitation of the meta-analysis was the lack of prospective studies and RCTs on varicocele repair in men with NOA; all of the included studies were retrospective and non-randomized. Additionally, only 20 small-scale reports were included, and the pregnancy rates in this meta-analysis could have been higher if studies with longer follow-up periods had been included.

The effect of varicocele repair on the sperm retrieval rate

Although varicocele repair improves spermatogenesis in 39.1% of patients, TESE is inevitable due to inadequate numbers of sperm in some patients' ejaculates and to

Table 1 - Literature review of varicocele repair performed in men with NOA

Reference	No. of patients	Follow-up (months)	Patient age (years)	Procedure/ approach	Bilateral repair (%)	Pre-op mean± SD FSH (mIU/ml)	Histopathology	Return of motile sperm to the ejaculate	Post-op sperm density (mean x10^6/ml)	Post-op sperm motility (%)	Spontaneous pregnancy rate	Pregnancies with ART	Relapse rate
Matthews, 1998 (13)	22	10.3	35	Microsurgery	77	19.6±4.5	N/A	12/22 (55%)	2.20	55	3/22 (15%)	3	N/A
Kim, 1999 (11)	28	15	35	Varicocelectomy/ inguinal	71	20.0±16.0	SCO: 3 MA: 13 HS: 18	SCO: MA: 5 HS: 9 Overall: 14/28 (50%)	1.20	19	2/28 (7%)	2	N/A
Kadioglu, 2001 (10)	24	13.4	30	Microsurgery/ inguinal	71	12.3±7.1	SCO: 7 MA: 14 HS: 3	SCO: 3 MA: 1 HS: 1 Overall: 5/24 (21%)	0.04	14	0/24 (0%)	N/A	N/A
Schlegel, 2004 (16)	31	14.7	N/A	N/A	94	N/A	N/A	7/31 (22%)	N/A	N/A	0/31 (0%)	N/A	4/7 (57%)
Cakan, 2004 (4)	13	9	29	Varicocelectomy/ inguinal	15	35±2.8	SCO: 5 MA: 3 HS: 5	SCO: 0 MA: 0 HS: 3 Overall: 3/13 (23%)	0.7	11	0/13 (0%)	N/A	0/13 (0%)
Esteves, 2005 (7)	17	18.9	32	Microsurgery/ inguinal	65	14.6	SCO: 6 MA: 5 HS: 6	SCO: 0 MA: 3 HS: 5 Overall: 8/17 (47%)	0.8	N/A	1/17 (6%)	N/A	N/A
Gat, 2005 (8)	32	12	34	Percutaneous embolization	88	N/A	N/A	18/32 (56%)	3.8	1	4/18 (12%)	5	7/18 (39%)
Poulakis, 2006 (15)	14	24.8	33	Anterograde sclerotherapy	87	17.8±4.8	SCO:3 MA: 5 HS:4	7/14 (50%)	3.1	2	2/14 (14%)	N/A	N/A
Pasqualotto, 2006 (14)	27	12	30	Microsurgery/ subinguinal	56	17.0±12.4	SCO:10 MA: 8 HS: 9	SCO: 4 MA: 3 HS: 2 Overall: 9/27 (33%)	0.87	19	SCO: 0 MA: 1 HS: 0 Overall: 1/9 (11%)	N/A	SCO: 4 MA: 1 HS: 2 Overall: 7/9 (78%)
Lee, 2007 (12)	19	7.4	32	Microsurgical/ inguinal	36	20.8±12.3	SCO: 10 MA: 6 HS: 3	SCO: 1 MA: 4 HS: 2 Overall: 7/19 (36%)	0.36	47	SCO: 0 MA: 0 HS: 1 Overall: 1/19 (5%)	N/A	2/7 (29%)
Ishikawa, 2008 (9)	6	±6	N/A	Microsurgical/ inguinal	33	14.6±10.5		2/6 (33%)	0.2	N/A	0/6 (0%)	N/A	
Cocuzza, 2009 (5)	10	9	29	Microsurgery/ subinguinal	100	21±15.2	SCO: 4 MA: 4 HS: 2	SCO: 1 MA: 0 HS: 2 Overall: 3/10 (30%)	SCO: 0 MA: 12.2 HS: 2.25 Overall: 5.5	SCO :0 MA: 40 HS: 35 Overall: 37	N/A	N/A	N/A
Youssef, 2009 (17)	79 (51 complete, 28 virtual azoospermia)	7.4	32	High ligation	73.4	16.56±8.32	SCO: 22 MA: 26 HS: 23 Normal: 8	SCO: 2 MA: 6 HS: 13 Normal: 6 Complete: 14/51 (28%) Virtual: 13(46%)	SCO: 0.65 MA: 4.6 HS: 2.77 Normal:5.21 Overall: 3.56	SCO: 33 MA: 49 HS: 41 Normal: 41 Overall: 42	SCO: 0 MA: 2 HS: 2 Normal: 2 Complete: 2/51 (4%) Virtual: 4/28(14%) Overall: 6/79 (7.6%)	N/A	N/A
Abdel-Meguid, 2012 (61)	31	19.3	35	Microsurgery/ subinguinal	61.3	18.1±7.3	SCO: 10 MA: 8 HS: 13	SCO: 0 MA: 3 HS: 7 Overall: 10 (32.3%)	2.3±1.7	15	N/A	N/A	SCO: 0 MA: 1 HS: 1 Overall: 2/10 (20%)

azoospermia relapse following the recovery of spermatogenesis in other patients (14,16,63). There are few studies on the effect of varicocele repair on the results of TESE. In a retrospective study, Schlegel and Kaufmann evaluated the sperm retrieval rates in varicocele repair and non-repair groups, dividing them into subgroups based on histopathological abnormalities (16). In patients with the Sertoli cell-only (SCO) pattern, the sperm retrieval rate by TESE was 26% with repair and 38% without repair; in subjects with the maturation-arrest pattern, the retrieval rate was 53% with repair and 47% without repair; and in patients with the hypospermatogenesis pattern, the rate was 96% with repair and 96% without repair. The total sperm retrieval rate was 60% in 68 patients who underwent varicocelectomy and same (60%) in 70 patients with untreated varicoceles. Patients with subclinical varicoceles were also included in the analysis, which may explain why the sperm retrieval rates were not affected by a history of varicocelectomy, as treatment for subclinical varicoceles is of questionable benefit (64,65).

One of our earlier studies (conducted at Hacettepe University Hospital, Ankara, Turkey), which compared the sperm retrieval rate based on micro-TESE and ICSI outcomes in 96 patients with NOA (including 66 patients who previously underwent successful varicocelectomy for clinical varicoceles and 30 patients who had unrepaired varicoceles), demonstrated that varicocele repair significantly increases the sperm retrieval rate in patients with clinical varicoceles and NOA (53% versus 30%, OR = 2.63, 95% CI = 1.05-6.60, $p = 0.036$) (66). In that study, we also compared 2PN fertilization rate, the high-quality embryo rate, the mean number of transferred embryos, and the clinical pregnancy rate; however, the parameters were similar in the treated and untreated groups. Haydardedeoglu et al. also compared the sperm retrieval rates and ICSI outcomes in treated and untreated varicocele groups and found that the sperm retrieval rate was higher in the varicocele repair group (60.81 and 38.46%, respectively, $p = 0.01$) (67). They also reported that the clinical pregnancy rate and the live-birth rate were significantly higher in the varicocelectomy group (74.2% versus 52.3% and 64.5% versus 41.5%, respectively, $p<0.05$). Notably, patients with spermatozoa, as measured by post-operative semen analyses, were excluded from these two studies. Although this exclusion represents a bias in favor of the non-treatment groups, the sperm retrieval rate in the varicocele repair groups was still higher than that in the non-treatment groups.

The role of testicular histopathology

The utility of testicular biopsy findings in predicting which patients are most likely to exhibit improved semen parameters after varicocele repair has been studied. Reportedly, patients with late-stage maturation arrest and hypospermatogenesis are more likely to exhibit improved semen parameters and pregnancy rates (7,10-12). Kim et al. observed sperm in 12 of 28 men with azoospermia following varicocele repair (11). When they divided the group based on the biopsy results, nine men with severe hypospermatogenesis and five with maturation arrest at the spermatid stage exhibited improved sperm densities. No improvement was noted in three men with the SCO pattern or in three others with maturation arrest at the spermatocyte stage; furthermore, no spontaneous pregnancies occurred. One couple used fresh ejaculate for ICSI, and another couple underwent TESE with ICSI.

Kadioglu et al. detected motile sperm in the ejaculate of five of 24 patients who underwent microsurgical varicocele repair (10). Based on the histopathological findings, the motile sperm rates in the patients with the SCO pattern, maturation arrest at the spermatocyte stage, maturation arrest at the spermatid stage, the SCO pattern with focal spermatogenesis, and hypospermatogenesis were 0 (0/5), 0 (0/6), 37.5 (3/8), 50 (1/2), and 33.3% (1/3), respectively. Esteves and Glina reported that eight of 17 azoospermic patients had sperm in their ejaculate following microsurgical subinguinal repair. In total, five of six patients with hypospermatogenesis and three of five patients with maturation arrest had sperm in their ejaculate, but none of the six SCO syndrome patients had sperm in their ejaculate (7). Lee et al. analyzed their patients' semen three months after microsurgical inguinal varicocelectomy, and the presence of sperm based on the histopathological pattern was as follows: hypospermatogenesis, two of three patients; maturation arrest, four of six patients; and SCO pattern, one of ten patients (12). One couple in the hypospermatogenesis group had a spontaneous pregnancy. In the study of Abdel-Meguid, sperm were recovered in patients with HS (seven of 13, 53.8%) and late MA (three of six, 50%), whereas no sperm could be recovered from the ejaculate of patients with early MA or SCO.

Research findings on the potential for inducing spermatogenesis following varicocele repair in azoospermic men with the SCO pattern are inconsistent. Pasqualotto et al. reviewed the medical records of 27 azoospermic men who underwent testis biopsy and microsurgical repair of clinical varicoceles (14). The microsurgical repair was bilateral in 15 patients and unilateral in 12 patients, and it was performed using a subinguinal approach. Each patient underwent an open, diagnostic testicular biopsy during the varicocele repair, which was performed under general anesthesia. Biopsies were performed on both testes. Germ cell aplasia was identified in 10 of the patients, hypospermatogenesis was identified in nine patients, and early maturation arrest was identified in eight patients. Induction of spermatogenesis was achieved in nine of the patients (33.3%), six of whom had bilateral varicoceles (40%, 6/15) and three of whom had unilateral varicoceles (25%, 3/12). Four (40%) of the nine patients exhibited the SCO pattern, three (33%) had maturation arrest, and two (22%) had hypospermatogenesis. The researchers concluded that, because a single testis biopsy showing germ cell aplasia may not indicate the overall testis histology, varicocele repair must be considered for all men with azoospermia and a palpable varicocele, regardless of their testicular histopathology.

A meta-analysis that compared the outcomes of varicocele repair in men with NOA, based on histopathology, indicated that, compared with men with SCO, there is a higher probability for the successful induction of spermatogenesis in men with late maturation arrest or hypospermatogenesis (63). The rates of success in 156 patients, defined as sperm in the ejaculate or spontaneous pregnancy, were 42.1% in the patients with maturation arrest and 54.5% in those with hypospermatogenesis, which were significantly higher than that in subjects with the SCO pattern (11.3%) (patients with the SCO pattern vs. maturation arrest: $p<0.001$; patients with the SCO pattern vs. hypospermatogenesis: $p<0.001$). Patients with late maturation arrest

(n = 24) had a higher success rate (45.8%) than subjects with early maturation arrest (n = 11.0%) ($p = 0.007$). The validity of the results of this meta-analysis is limited by the small total study population (n = 156); however, the researchers concluded that testicular histopathology based on testicular biopsy could be used to determine whether patients with NOA may benefit from varicocele repair. Several factors should also be considered when interpreting the results. As the researchers stated, unilateral and bilateral testicular biopsies were performed in a heterogeneous manner, based on the preferences of each researcher. None of these eight studies reported a predominant or favorable histopathology or other types of histopathology, nor did the studies examine the number of seminiferous tubules per biopsy. Therefore, the results should be interpreted with caution, as a single testis biopsy is not representative of the entire organ. As such, azoospermic patients who exhibit the SCO pattern based on a single, large testis biopsy may exhibit improvements in semen quality following varicocelectomy. Another concern regarding the diagnostic testicular biopsy is its invasiveness and associated potential risks, such as inflammatory changes, hematoma, parenchymal fibrosis, and permanent devascularization of the testis, as well as the potential to remove foci of spermatogenesis in an already compromised testicle; therefore, there is no consensus regarding the indications for a diagnostic testicular biopsy before varicocele repair.

The effect of genetic anomalies on the outcome of varicocele repair

The presence of Y microdeletions or karyotype abnormalities is clinically significant. Karyotype abnormalities or Y chromosome deletions are observed in 16.6% of azoospermic men (68). The data from studies on Y chromosome microdeletions in men with varicoceles clearly indicate that genetic defects and varicoceles can coexist (69,70). Rao et al. compared chromosomal abnormalities and Y chromosome microdeletions in infertile men with varicoceles and idiopathic infertility (71). The frequencies of chromosomal defects in the individuals with varicoceles and idiopathic infertility were 19.3 and 8.76%, respectively, whereas the frequencies of Y chromosome microdeletions were 5.26 and 3.60%, respectively. This close association has made it necessary to investigate the effect of coexisting genetic anomalies on varicocele repair; however, only a few studies have addressed the results of varicocelectomy in infertile men with coexisting genetic infertility.

Cayan et al. reported the results of varicocelectomy in oligospermic infertile men who presented varicoceles either with or without genetic anomalies (72). Among the 19 patients who were included, five had a genetic anomaly (abnormal karyotype [n = 3] or Y chromosome microdeletions [n = 2]). In the genetic anomaly group, all five patients exhibited improvements in their semen quality following varicocele repair. A similar study evaluated the effect of Y chromosome microdeletions on the varicocele repair outcome in five patients who harbored a Yq microdeletion and in four who had no microdeletions (73). A post-operative semen analysis revealed that the five patients with Yq microdeletions exhibited no improvement in their semen parameters, whereas the semen parameters were significantly improved in the patients without microdeletions.

The Y chromosome plays a crucial role in the control of spermatogenesis. The site of Y chromosome deletion is a more important predictive factor for sperm retrieval than is a coincident varicocele (16). Similarly, in men with Klinefelter syndrome, a history of varicocele repair does not appear to change the outcome of TESE (16). Therefore, Y chromosome mapping and karyotype analyses are essential in the work-up of men with varicoceles and azoospermia and may be predictive of the varicocele repair outcomes. Additionally, couples should be aware of the genetic anomalies associated with karyotype abnormalities an Y chromossome deletions and should undergo genetic counseling to ascertain the risk of transmitting these mutations to their offspring.

The cost effectiveness of varicocele repair in NOA patients

Decision models have been constructed based on predefined assumptions and have been used to predict outcomes when multiple complex treatments are available. Several decision analysis models have been used to calculate the cost of pregnancy associated with initial surgical or initial ART treatment in men with infertility caused by varicoceles. In 1997, Schlegel published a cost-effectiveness analysis of the value of varicocele repair versus ART treatment in couples with varicocele-associated infertility (74). Only results from controlled trials of varicocelectomy were used. Varicocelectomy-associated costs were determined based on surgeon and anesthesiologist fees, as well as hospital-associated charges. All of the costs were obtained from published sources, including the Medicare Resource-Based Relative Value Scale (MRBRVS). Time off from work and the costs of treating complications (hydrocelectomy and exploration for bleeding) were estimated based on published studies on men who underwent varicocelectomy. The cost of a basic evaluation for the presence of a varicocele, including a comprehensive office consultation, follicle stimulating hormone (FSH) and testosterone blood tests, two semen analyses, and a follow-up visit, was also included in the analysis. The treatment of varicocele-associated male infertility using varicocelectomy was reported to be a cost-effective alternative to treatment with ART. The mean cost of a live birth following varicocelectomy and the mean cost of a live delivery following ICSI were calculated to be $26,268 (95% CI = $19,138-$44,656) and $89,091 (95% CI = $78,720-$99,462), respectively.

Another decision analysis study of the cost of treatment of male infertility compared the cost-effectiveness of varicocelectomy and ART treatment in patients with varicoceles (75). The cost per pregnancy and the pregnancy rate in each study arm were calculated and compared. Overall, the initial surgical repair of varicoceles was more cost-effective than ART was; however, intrauterine insemination (IUI) yielded a lower cost per pregnancy than varicocelectomy in men with a preoperative total motile sperm count (TMC) between 10 and 20 million sperm ($9,000 versus $11,333, respectively). In men with low sperm counts (TMC <10 million) who qualified for sperm retrieval/ICSI but not IUI, a varicocelectomy was more cost-effective than sperm retrieval/ICSI when the post-operative pregnancy rate was greater than the 14% threshold. In men with high sperm counts (TMC>10 million) who qualified for IUI but not sperm retrieval/ICSI, a varicocelectomy was more cost-effective than IUI only when the pregnancy rate was greater than the 45% threshold.

Although these studies examined the cost-effectiveness of varicocele repair and ART, they were not specific to varicocele-associated NOA patients. A recent analysis specifically investigated the cost-effectiveness of ART for varicocele-associated NOA (76). In this study, the cost per live birth associated with varicocelectomy and microsurgical TESE was calculated and examined over time. The authors estimated the contribution of direct-cost elements and the impact of indirect costs, such as time off work while recovering from male-related and IVF-related interventions; maternal complications, including ovarian hyperstimulation syndrome (OHSS), pelvic hemorrhage, infection, stroke, myocardial infarction, and ovarian cancer; complications from male interventions, including interventions for bleeding, infection, and testicular atrophy, as well as those associated with anesthesia-related complications; and multiple-gestation pregnancies associated with IVF/ICSI. In contrast to previous studies, this decision analysis model was based on outcome data from the Society for Assisted Reproductive Technology (SART) database, the peer-reviewed literature, the MRBRVS, and high-volume IVF centers in the US, and the model revealed that microsurgical TESE is more cost-effective than varicocelectomy for the treatment of varicocele-related NOA when indirect costs are considered. The costs of varicocelectomy and TESE were calculated to be $79,576 and $69,731, respectively. Varicocelectomy was more cost-effective than TESE when the rate of spontaneous pregnancy after varicocelectomy was >40% or when the live birth rate following IVF/ICSI was <10%; however, several factors were not considered in the analysis. As the researchers reported, it is possible that some of the patients in the TESE group also had obstructive azoospermia or oligospermia, which may have caused an upward bias in the live delivery rate. Moreover, the live birth rate associated with the use of freshly ejaculated sperm following varicocele repair and the live birth rate associated with the use of sperm retrieved via TESE following unsuccessful varicocele repair should have been included in the analysis because varicocelectomy increases the sperm retrieval rate (66,67,76). The analysis included only four studies of varicocele repair in men with NOA, resulting in a lower rate of viable sperm in the post-operative ejaculates (10%) and a lower spontaneous pregnancy rate (2.8%) than those reported in a recent meta-analysis (63). The researchers also did not consider the reimbursements offered by most insurance companies for varicocele repair, the various costs based on geography, the limited availability of IVF/ICSI, and the cost of complications related to IVF/ICSI (63). Nevertheless, consideration of the cost-effectiveness of treatment options should not necessarily be the primary concern for a clinician who is treating infertile couples. Cost-effectiveness analyses should be considered in relation to institution-specific data, thus yielding institution-specific results.

EXPERT COMMENTARY

Varicoceles are very common in infertile males and exhibit a progressive pathology. Although the precise pathophysiology remains unknown, varicocele repair can successfully reverse the negative effects of varicoceles on testicular function. Although the role of varicocele repair in NOA patients has been evaluated in several studies, the value of varicocelectomy in these cases remains unclear.

Varicocelectomy not only results in the induction of spermatogenesis, rendering testicular sperm extraction/retrieval unnecessary but also increases the micro-TESE sperm-retrieval rate in men who remain azoospermic following varicocele repair. However, because of the possibility of azoospermia relapse following an initial post-varicocelectomy improvement in the semen quality, patients should be informed of the option for sperm cryopreservation.

The testicular histopathology may predict the success of varicocele repair. The value of varicocele repair in men with azoospermia and the SCO pattern is questionable. In patients with NOA, the testicular histology is often heterogeneous, so a single testis biopsy may not indicate the overall testis histology. Therefore, azoospermic patients with the SCO pattern based on a single large testis biopsy may exhibit improvements in their semen quality following varicocelectomy.

There is a strong association between genetic defects and varicocele-related infertility in men. Because it is possible that these defects can be transmitted to offspring, Y chromosome mapping and karyotype analysis are crucial for the evaluation of men with varicocele-related infertility. Informing surgical candidates about underlying genetic abnormalities and the potential for a poor response to surgery would be extremely helpful in their decision-making process. Additionally, if a genetic abnormality is identified, the couple should undergo genetic counseling.

In contrast to earlier reports, a recent cost-effectiveness analysis has revealed that the use of varicocelectomy for the specific treatment of varicocele-associated male infertility is not more cost-effective than assisted reproduction using ICSI; however, cost-effectiveness should not necessarily be the primary concern for clinicians who treat infertile couples. Additionally, an analysis of cost-effectiveness should be conducted in an institution-specific manner.

Although several studies have evaluated the role of varicoceles in NOA, these investigations were poorly designed studies that lacked controls; therefore, properly designed and carefully randomized controlled trials are necessary to precisely assess the impact of varicocelectomy on fertility outcomes in NOA patients. Nonetheless, in light of the currently available data, varicocele repair should be considered before TESE/ICSI in all azoospermic men who have clinically palpable varicoceles.

AUTHOR CONTRIBUTIONS

Inci K and Gunay LM reviewed the current literature in detail and wrote this manuscript. Both authors approved the final version of the text.

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