Varicocele and Infertility

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INTRODUCTION

Approximately 8% of men in reproductive age seek medical assistance for fertility-related problems. Of these, 1–10% patients carry conditions that compromise the reproductive potential, and varicocele accounts for 35% of the cases.[1] In a group of 2,875 infertile couples attending our tertiary center for male reproduction, a varicocele was identified in 21.9% of the male partners.

The first reports of the existence of varicose veins surrounding the testis are dated to the 1st century AD; however, the association of varicocele and infertility was only suspected at the end of the 19th century when surgical occlusion of dilated veins was shown to improve semen quality.[2] Tulloch, in 1952, was the first to report that bilateral varicocele repair in a male with azoospermia resulted in an increase in sperm concentration and in a spontaneous pregnancy.[3] In 1965, MacLeod first reported that most semen specimens obtained from infertile men with varicocele had decreased sperm count, decreased motility, and increased abnormal forms.[4]

Varicocele is a condition involving the dilation of the veins of the pampiniform plexus that drain the testicles. Normally, the backward blood flow is prevented by small 1-way valves. Valve abnormalities or vein compression by adjacent structures can cause vein dilation. The pathophysiology of varicocele and its impact on the male reproductive potential have been debated for the last 50 years. Varicocele is still one of the most controversial issues in the field of male infertility, especially regarding why, when, and to whom treatment should be applied. Varicocele repair is considered the treatment of choice for varicocele-associated infertility, but its effectiveness has been discussed for several years. Although the ultimate endpoint for the treatment of male factor infertility is a live birth, efforts to maximize the couple's fertility potential by improving testicular function should be the main purpose of varicocele treatment. This chapter discusses the controversies and consensus of varicocele-associated infertility and provides the best practice guidelines for the clinical management of infertile patients with varicocele.

ETIOPATHOGENESIS

Varicoceles are identified in approximately 7% and 10–25% of prepuberal and postpuberal males, respectively.[5,6] In older men, varicoceles can be identified in up to 43% of the individuals.[7] Prevalence of varicocele increases over time and it is estimated that a 10% rise in incidence occurs for each decade of life. It is identified in approximately 35% of men with primary and 80% of men with secondary infertility.[1,8] The higher frequency of varicoceles in both the elderly and in men with secondary infertility suggests that it is a progressive disease. Although the frequency of unilateral left sided-varicocele has historically been reported to be approximately 85–90%, recent data indicate that bilateral palpable varicocele may be found in more than 50% of the affected subjects.[5]

The etiology of varicocele formation is likely to be multifactorial. The right internal spermatic vein inserts directly into the inferior

vena cava at an acute angle while the left one inserts into the left renal vein at a right angle. It is also suggested that a partial obstruction of the left spermatic vein exists due to the compression of the left renal vein between the aorta and the upper mesenteric artery (the 'nutcracker' phenomenon). An increase in the hydrostatic pressure of the left spermatic vein may be transferred to the venous plexus of the spermatic cord causing its dilation.[9] Moreover, primary insufficiency of the internal spermatic and subsequent malfunction of the external spermatic and cremasteric veins valves may lead to regression of blood.[10,11] A 5-fold increase in the hydrostatic pressure of the spermatic veins has been observed in men with varicocele as compared to controls.[12] Microscopic evaluation of the spermatic vein fragments revealed alterations in the longitudinal muscle layers and a decrease in the number of nerve elements in the vessel wall.[13] These findings suggest a defective contractile mechanism of blood transport through the pampiniform plexus that may lead to a reversal of the pressure gradient and cause a hypoxic status.

Several theories aim to explain the impact of varicoceles on testicular function, but none of them can fully elucidate the variable effect of varicocele on human spermatogenesis and male fertility.[14] Proposed mechanisms include hypoxia and stasis, testicular venous hypertension, elevated testicular temperature, increase in spermatic vein catecholamine leading to testicular underperfusion, and increased oxidative stress.[15] It is believed that reflux of warm blood from the abdominal cavity to the varicose veins increases the scrotum temperature, but the mechanism by which temperature influences spermatogenesis is not clearly understood. Germ cell apoptosis and subsequent oligozoospermia, a common phenomenon in men with varicocele, can be attributed to increased scrotal temperature, increased intratesticular cadmium concentration, and reduced levels of androgens.[16,17] Increased concentration of regressed toxic metabolites inside the testicles (e.g., catecholamines from the kidney and adrenal glands) can cause chronic vasoconstriction of the intratesticular arterioles, contributing, along with impaired venous return caused by valve insufficiency, to persistent testicular underperfusion and subsequent dysfunction of the spermatic epithelium.[18] Biopsies of varicocele-affected testicles showed a decrease in E-cadherin and alfa–catenin in the Sertoli–Sertoli junction and a subsequent disruption of the blood-testis barrier that can contribute to the pathology and impairment in sperm production.[19] However, histopathologic findings typical of varicocele have not been observed.[20]

Excessive oxidative stress (OS) is often seen in infertile men with varicocele.[21] High production of reactive oxygen species (ROS) in the reproductive tract impairs both the fluidity of the sperm plasma membrane and the integrity of deoxyribonucleic acid (DNA) in the sperm nucleus. Abnormal high levels of sperm DNA damage are associated with a decrease in several fertility markers including fertilization rate, embryo cleavage rate, implantation rate, pregnancy rate, and live birth rate.[21]

DIAGNOSIS

Currently, physical examination with the patient standing in a warm room is the preferred diagnostic method. Varicoceles diagnosed by this method are termed 'clinical' and may be graded according to the size. It is important to ask the patient to perform a Valsalva maneuver during examination. Large varicoceles (grade III) are varicose veins seen through the scrotal skin. Moderate (grade II) and small-sized varicoceles (grade I) are dilated veins palpable with/without the aid of the Valsalva maneuver, respectively.[22] Physical examination is limited by a sensibility and specificity of about 70% when compared to other diagnostic modalities.[23,24] Interobserver and intra-observer variability has been observed when diagnosing varicocele.

Physical examination may be inconclusive or equivocal in cases of low-grade varicocele and in men with a history of previous scrotal surgery, concomitant hydroceles or obesity. Imaging studies may be recommended when evaluating infertile men for varicocele when physical examination is inconclusive. When a varicocele is not palpable but a retrograde blood flow is detected by other diagnostic methods such as venography, Doppler examination, ultrasonography, scintigraphy and thermography, the varicocele is termed subclinical.[24,25]

The gold standard method to diagnose blood reflux into the veins of the pampiniform plexus is the percutaneous venography of the spermatic veins; however, it is not routinely used because of its invasiveness.[24,25] Among the non-invasive diagnostic modalities, color Doppler ultrasound (CDU) has been shown to be the best diagnostic tool. The commonly accepted CDU criterion for varicocele (vein diameter of ≥3 mm) has a sensitivity of about 50% and specificity of 90% compared to physical examination.[26] However, a scoring system, incorporating the venous diameter, the presence of a venous plexus and the change of flow on Valsalva maneuver, yields a sensitivity and specificity >85% when compared to physical examination[26] or venography. A pencil-probe Doppler (9 MHz) stethoscope is an inexpensive tool that may aid in the diagnosis of the varicocele. The patient is examined in the upright position, and a venous 'rush' representing blood reflux is heard with/without the Valsalva maneuver. Although simple and easily performed in the office, Hirsh et al demonstrated that more than 50% of men without clinical varicoceles exhibited a Valsalva-maneuver Doppler-positive reflux.[27] Despite that, Doppler examination has been advocated as a useful tool to examine the contralateral spermatic cord to determine if a subclinical varicocele exists when a clinical varicocele is found on the other side.[28] Unfortunately, none of these adjunctive diagnostic methods can differentiate between clinical and subclinical varicoceles. The significance of a positive test result using any of these adjuvant techniques in infertile men remains uncertain.

MANAGEMENT

Treatment of varicocele in infertile men aims to restore or improve testicular function. Best practice guidelines recommend that treatment should be offered for couples with documented infertility whose male partner has a clinically palpable varicocele and abnormal semen analysis. Additionally, an adult male presenting with palpable varicocele and abnormal semen analyses who is not currently attempting to achieve conception but has a desire for future fertility is also a candidate for varicocele repair.[29] The ideal treatment must combine low complication rates with the highest seminal improvement to either increase the chances of spontaneous conception or to optimize assisted conception outcomes.

Currently, varicoceles are treated either by surgery (open with/without magnification and laparoscopy) or percutaneous embolization of the internal spermatic vein. Although the techniques vary, the basic concept is the occlusion of the dilated veins of the pampiniform plexus. The high retroperitoneal (Palomo), radiologic, and laparoscopic approaches are performed for internal spermatic vein ligation, while the inguinal (Ivanissevich) and subinguinal approaches also allow the ligation of the external spermatic and cremasteric veins that may contribute to the varicocele (Table 1).

Percutaneous embolization is successfully accomplished in approximately 90% of the attempts. It is associated with faster recovery and minimal pain as compared to the standard surgical approaches, but with higher recurrence rates (Table 1). Embolization requires interventional radiologic expertise and has potentially serious complications such as vascular perforation, coil migration, and thrombosis of pampiniform plexus.[30–33] Nonetheless, percutaneous embolization may

Table 1.
Treatment Options for Varicocele Repair in Infertile Men. Vein Ligation Sites and Postoperative Recurrence, Hydrocele Formation and Spontaneous Pregnancy Rates among Different Techniques

Technique	Internal spermatic vein ligation	External spermatic vein ligation	Recurrence rate	Hydrocele formation rate	Spontaneous pregnancy rate
Retroperitoneal High-Ligation (Palomo)	Yes	No	7–35%	6–10%	25–55%
Laparoscopic	Yes	No	2–7%	0–9%	14–42%
Embolization	Yes	No	2–24%	NR	20–40%
Macroscopic Inguinal (Ivanissevich)	Yes	Yes	0–37%	7%	34–39%
Microscopic inguinal or subinguinal	Yes	Yes	0–0.3%	0–1.6%	33–56%

NR: not reported.
Values are expressed as range.

have a role in the treatment of persistent or recurrent varicoceles previously treated by surgery.[34]

Laparoscopic varicocelectomy provides higher magnification with low incidence of hydrocele formation. However, external spermatic veins, the second cause of varicocele recurrence, cannot be ligated, leading to a recurrence rate of approximately 5%.[30] Laparoscopic approach requires extensive training and the cost of instrumentation is high. It is more invasive than an open microsurgical approach, requiring general anesthesia and placement of a urethral catheter.[35,36] Complications include intestinal and vascular injuries that occur in approximately 8% of the cases.[30]

Open surgical varicocele repair is often performed using a retroperitoneal, inguinal or subinguinal approach. High ligation of the internal spermatic vein can be easily performed via the retroperitoneal approach, but it is associated with high recurrence and hydrocele formation rates. Inguinal and subinguinal approaches offer the advantage of also allowing the ligation of the external spermatic veins. Internal and external spermatic veins can be identified via inguinal/subinguinal approaches macroscopically, but the use of magnification facilitates identification and preservation of internal spermatic artery and lymphatics, which may prevent testicular atrophy and hydrocele formation, respectively.[37]

Microsurgical varicocelectomy can be performed via an inguinal/subinguinal approach with similar results, and reported recurrence and hydrocele formation are below 2%. The main advantage of the subinguinal over the inguinal approach is that the former obviates the need to open the aponeurosis of the external oblique, which usually results in more postoperative pain and a longer time before the patient can return to work. It is believed that subinguinal microsurgical varicocelectomy requires more microsurgery skills because it is associated with a greater number of arteries and internal spermatic veins with smaller diameter as compared to the inguinal approach.[30] However, histomorphological studies were unable to find differences in number and wall thickness of

spermatic cord veins and arteries between the subinguinal and inguinal levels.[38]

A recent systematic review including 4,473 individuals was performed to define the best treatment modality of palpable varicocele in infertile men.[30] The authors concluded that open microsurgical inguinal/subinguinal varicocelectomy techniques resulted in higher spontaneous pregnancy rates and fewer recurrences and postoperative complications than laparoscopic, radiologic embolization and macroscopic inguinal or retroperitoneal varicocelectomy techniques in infertile men.

Overall, varicocelectomy studies report significant improvements in one or more semen parameters in approximately 65% of men.[39] The mean time for semen improvement and spontaneous pregnancy after surgery is approximately 5 months and 7 months, respectively.[35] However, it is still unknown why fertility potential is not always improved after varicocelectomy. Studies evaluating predictors for successful varicocele repair would aid in the identification of the best candidates for treatment, but to date few reports exist and results are conflicting.[30,39–46] From the existing data, it seems that infertile men either with higher pre-operative semen parameters or undergoing varicocele repair for large varicoceles are more likely to show postoperative semen parameters improvement.[39,41] It was also shown that men who achieved a postoperative total motile sperm count greater than 20 million were more likely to initiate a pregnancy either spontaneously or via intrauterine insemination.[42] On the other hand, reduced pre-operative testicular volume, elevated serum follicle-stimulating hormone (FSH) levels, diminished testosterone concentrations, subclinical varicocele, as well as the presence of Y chromosome microdeletions seem to be negative predictors for fertility improvement after surgery.[43–48] In the presence of bilateral palpable varicocele, the consensus is to perform surgery on both sides at the same operative time.[49]

CONTROVERSAL ISSUES

Treatment of Subclinical Varicocele

Subclinical varicocele refers to the presence of retrograde blood flow that cannot be detected by physical examination of the spermatic cord during Valsalva maneuver, and requires adjunctive tests for diagnosis, such as Doppler examination, color Doppler ultrasound (CDU), scrotal thermography, isotope imaging or venography.

Currently, existing evidence does not support the recommendation for treating infertile men with subclinical varicocele.[29,48,50] The management of infertile men with a unilateral clinical varicocele and a subclinical one at the contralateral side, on the other hand, may pose a different dilemma. Zheng et al compared the efficacy of bilateral and left unilateral varicocelectomy in a group of 104 infertile men with left clinical and right subclinical varicoceles, and found that bilateral varicocelectomy had no benefit over the left clinical varicocelectomy.[51] In their study, however, a retroperitoneal approach was used for vein ligation, which was shown to be associated with high recurrence rate.[30] Elbendary et al, in a recent prospective trial, studied a group of 145 infertile men with clinical left and subclinical right varicoceles.[52] Patients were randomized to undergo either unilateral inguinal repair of clinical varicocele or bilateral repair of both clinical and subclinical ones. Although a significant improvement in sperm parameters was observed in both groups, the magnitude of change in sperm count and motility and the spontaneous pregnancy rates were significantly higher in the group of men who had bilateral varicocele repair. Their findings are in agreement with earlier studies suggesting that bilateral varicocelectomy is more effective than unilateral for such patients.[53,54] It is also postulated that altered blood flow after unilateral clinical varicocelectomy may unmask an underlying contralateral venous anomaly that may result in a clinically manifested varicocele.[28,53]

Varicocele and Azoospermia

Varicoceles are found in approximately 5% of men with azoospermia, but it is still debatable whether varicoceles can cause or contribute to azoospermia.[55] There has been a renewed interest in varicocele repair in azoospermic men resulting from the introduction of intracytoplasmic sperm injection (ICSI). Success rates varied and no predictors of success have been definitively identified because of the small numbers in the case series.[55–62] A recent meta-analysis examined the impact of varicocele repair to recover spermatogenesis in non-obstructive azoospermia (NOA) men.[63] A total of 233 infertile men with clinical varicocele and NOA were analyzed in a mean postoperative follow-up of 13 months. Motile sperm was found on postoperative ejaculate in 39% of men. Pregnancies were achieved in approximately 26% of men with sperm in the ejaculate, 60% unassisted, and 40% with the assistance of in vitro fertilization (IVF). Postoperative mean sperm density and motility were 1.6 million and 20%, respectively. Levels of serum FSH and testosterone, testis size, patient age, varicocele grade, and surgical technique did not appear to affect outcomes, but the limited number of patients precluded conclusions. Histopathology was the only predictor of success. Postoperatively appearance of sperm in the ejaculates was significantly higher in patients with biopsy-proven hypospermatogenesis (HS) or maturation arrest (MA) than Sertoli-cell only (SCO) (odds-ratio 9.4; 95% confidence interval 3.2–27.3). Combined success was 48% with HS or MA compared to 11% with SCO.

Even with the improvement in spermatogenesis in up to half of the NOA patients with a favorable testicular histopathology after varicocele repair, ICSI will be necessary for most couples to initiate a pregnancy.[55,63] However, the use of motile ejaculated sperm is preferred for ICSI, since their fertilizing ability is higher than that of sperm retrieved from the testis.[64] Nonetheless, continuing azoospermia after varicocele repair is still a potential problem and sperm extraction before ICSI will be inevitable for many individuals. Results of testicular sperm extraction (TESE) for men who remain azoospermic after varicocelectomy are scarce and conflicting.[65] Schlegel et al reported sperm retrieval rates of 60% per attempt using testicular microdissection (micro-TESE) in men with NOA and varicocele, regardless of whether previous varicocelectomy had been done.[65] It is questionable, however, if the inclusion of patients with subclinical varicocele biased their results since the benefit of treating subclinical varicocele is debatable. On the other hand, Inci et al, also using micro-TESE, reported a 2.6-fold increase in the chances of retrieving testicular sperm for ICSI after repair of clinical varicoceles.[66] Unfortunately, testicular histopathology results were not available in their study. Therefore, it cannot be excluded that higher retrieval rates were obtained after varicocelectomy because this group was biased by patients with favorable histopathology patterns for successful sperm retrieval, such as the ones exhibiting HS or MA.[67]

PERSONAL EXPERIENCE AND RECOMMENDATIONS

Varicocele remains one of the most debatable issues in the field of reproductive medicine. Due to the multifactorial origin of infertility, several factors may interact synergistically in the same individual, and the presence of a significant problem affecting the partner adds to the complexity of the problem. For example, many men with varicocele–associated infertility have lifestyle choices that include smoking, obesity, poor nutrition, use of gonadotoxic medication, and exposure to environmental toxins. These conditions are often associated with increased systemic or seminal oxidative stress and may have a negative synergistic effect in men with varicocele. Treatment of

varicocele alone in the presence of inadequate lifestyle choices is likely to solve only part of the problem. Lifestyle modifications may have an important beneficial impact on both systemic and reproductive health; therefore, when considering therapeutic measures to treat varicocele-associated infertility, counseling towards lifestyle modifications should be strongly encouraged. This strategy, along with the cause-specific treatment, is more likely to lead to a marked improvement in the male reproductive health as compared to repair of varicocele alone.

The treatment of varicocele in infertile men should aim to achieve the highest improvement in the male fertility status, with lower rates of complications such as recurrence or persistence, hydrocele formation, and testicular atrophy. Increase in the spontaneous pregnancy rates after the treatment of varicocele is difficult to ascertain due to a variety of factors that includes the lack of a uniform post-treatment follow-up interval and the female factor parameters, such as age and reproductive health. Therefore, the ultimate treatment goal should be the improvement in the chances of conception, either unassisted/assisted. The ideal surgical technique should aim for ligation of all internal and external spermatic and cremasteric veins, with preservation of spermatic arteries and lymphatics. This can only be achieved by the inguinal/subinguinal microsurgical approaches.

In our practice, when a clinically palpable varicocele is identified in one side, the contralateral cord is examined using a pencil-probe Doppler (9 MHz) stethoscope to determine if a subclinical varicocele exists. If so, it is treated at the same time as the co-existent clinical varicocele. This is based on the observation that altered blood flow after varicocelectomy may unmask an underlying venous anomaly and result in clinical varicocele formation.[28,53] Although loupe-magnification may be used to facilitate the ligation of the dilated varicose veins, it is insufficient for identification of both testicular arteries and lymphatics. Using this method, we found that instillation of papaverine was needed in most cases to aid in the identification of arterial pulsations (Table 2). Also, recurrence seems to be higher when loupe-magnification is used in association with the inguinal or subinguinal approach to repair varicoceles. An intraoperative pencil Doppler examination (9 MHz) can also be used to aid in the identification of the artery pulsations. In our hands, the subinguinal microsurgical varicocelectomy using the operating microscope is the method of choice to treat varicocele-associated infertility. The subinguinal approach provides excellent results, as shown in Table 2. The surgical intervention can be performed in an outpatient basis using i.v. anesthesia in association with spermatic cord blockade with lidocaine.[14,55] Although empirical, the early use of antioxidants is a common practice after varicocelectomy in our institution.

The urologist who opts to treat varicocele using microsurgery should obtain appropriate training. It is also important to have adequate microsurgical instruments and a binocular operating microscope with foot-control zoom magnification. Microsurgical varicocelectomy, either using inguinal/subinguinal approaches, requires more skill as compared to other surgical modalities because a higher number of internal spermatic vein channels and smaller-diameter artery are seen at the level of the inguinal canal. However, the routine use of microsurgery during varicocele repair may help the urologist to master his/her microsurgical skills, which will be of great benefit when performing more demanding and less frequent microsurgical procedures, such as vasovasostomies and vasoepididymostomies.

Even though spontaneous pregnancy remains the litmus test for evaluating varicocele treatment success, many patients with varicocele related-infertility will require assisted reproductive technology (ART) due to the severity of sperm abnormalities and/or the presence of a significant problem affecting

Table 2.
Results of Microsurgical Subinguinal Varicocelectomies in a Group of 485 Men with Varicocele and Infertility

Type of magnification	Loupe	Operating microscope
No. of procedures	101	384
Male age in years; Mean (range)	32.4 (24.0–63.0)	34.5 (24.0–52.0)
Varicocele side; N (%)		
Unilateral	51 (50.4)	184 (47.9)
Bilateral	50 (49.6)	200 (52.1)
Varicocele grade[†]; N (%)		
Grade I	14 (13.9)	73 (19.0)
Grade II	48 (47.5)	199 (51.8)
Grade III	39 (38.6)	112 (29.2)
Endocrine profile; mean ± SD		
Serum FSH (mUI/mL)	5.7 ± 8.8	6.1 ± 7.8
Serum testosterone (ng/dL)	523.8 ± 547.1	575.3 ± 677.2
Mean operative time; minutes (range)		
Unilateral	78.6 (50–90)	89.2 (60–105)
Bilateral	101.1 (80–150)	112.9 (90–150)
No. of veins ligated; mean (range)		
Left side	4.8 (2–7)	6.1 (2–9)
Right side	4.2 (2–6)	5.1 (2–7)
Vein diameter in millimeters; mean (range)		
Left side	3.2 (1–6)	3.1 (1–6)
Right side	2.8 (1–4)	2.5 (1–5)
Testicular artery identified; %	84.1*	97.6
Improvement in seminal parameters[‡]; %	60.4	68.5
Recurrence rate; N (%)	3 (2.9)	4 (1.0)
Hydrocele formation rate; N (%)	1 (1.0)	0 (0.0)
Other complications; N (%)	2 (1.9)[§]	1 (0.2)[¶]
Clinical pregnancy; N	85[a]	270[a]
Spontaneous; N (%)	20/69 (28.9)	58/172 (33.7)
Assisted reproduction; N (%)	4/16 (25.0)[b]	56/98 (57.1)[c]

[†]The largest varicocele grade is reported in cases of bilateral varicocele.
*Instillation of papaverine for identification of artery pulsation was necessary in 85% of the cases.
[‡]≥15% improvement from baseline pre-operative values in at least one of the semen parameters (sperm count, progressive motility, strict morphology), in a minimum of three postoperative semen analyses.
[§]Testicular hematoma (1 case); testicular atrophy (1 case).
[¶]Testicular hematoma.
[a]Reported number of patients who were assessed for pregnancy.
[b]Intra-uterine insemination (IUI; n = 12; in vitro fertilization/intracytoplasmic sperm injection (IVF-ICSI; n = 4).
[c]IUI (n = 18); IVF-ICSI (n = 80).

the female partner. The indication of varicocele repair prior to IVF/ICSI is unusual, but in certain circumstances varicocele treatment should be considered. Men with NOA with favorable testicular histopathology may restore sperm to the ejaculate after repair of clinical varicoceles.[55] Sperm restoration, although minimal, yields the possibility of IVF/ICSI without the need of sperm retrieval techniques (SRT). It has been shown that for patients who are still azoospermic after varicocelectomy, SRT success rates using testicular microdissection sperm extraction, and as a result the couple's chance for pregnancy, may be increased.[66] Varicocelectomy has also a potential to obviate the need for ART or to down stage the level of ART needed to bypass male factor infertility.[68] Recently, our group has shown that treatment of clinical varicoceles may also improve the outcomes of assisted reproduction in couples with varicocele-related infertility.[69] We studied 242 infertile men with treated and untreated clinical varicoceles who underwent ICSI, and found significantly higher live birth rates after ICSI in the group of men who underwent microsurgical varicocele repair before ART (46.2%) as compared to the ones undergoing ICSI in the presence of a clinical varicocele (31.4%). In our study, the chances of achieving a live birth (odds ratio = 1.87; 95% confidence interval 1.08–3.25; p = 0.03) by ICSI were increased while the chance of miscarriage occurrence after obtaining a pregnancy by ICSI were reduced (odds ratio = 0.433; 95% confidence interval 0.22 to 0.84; p = 0.01) if the varicocele had been treated before assisted conception.

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