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INVITED REVIEW

Male Fertility

The evolution and refinements of varicocele surgery

Joel L Marmar

Varicoceles had been recognized in clinical practice for over a century. Originally, these procedures were utilized for the management of pain but, since 1952, the repairs had been mostly for the treatment of male infertility. However, the diagnosis and treatment of varicoceles were controversial, because the pathophysiology was not clear, the entry criteria of the studies varied among centers, and there were few randomized clinical trials. Nevertheless, clinicians continued developing techniques for the correction of varicoceles, basic scientists continued investigations on the pathophysiology of varicoceles, and new outcome data from prospective randomized trials have appeared in the world's literature. Therefore, this special edition of the *Asian Journal of Andrology* was proposed to report much of the new information related to varicoceles and, as a specific part of this project, the present article was developed as a comprehensive review of the evolution and refinements of the corrective procedures.

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INTRODUCTION

Varicoceles have been recognized as clinical entities for more than a century but, in the early years, the treatment was exclusively for the management of pain. After 1952, these lesions were viewed differently because Tulloch reported that varicoceles may affect male fertility.[1] He performed a varicocelectomy on a man with azoospermia, sperm appeared in the ejaculate over time, and the patient achieved a pregnancy. In 1955, Tulloch reported his series of varicolectomies on 30 infertile men.[2] Three had azoospermia, but the others had varying sperm densities. Although the study design was crude evaluated by today's standards, the author concluded, "From the results obtained, it seems justifiable where a varicocele is associated with subfertility, the varicocele should be cured."

From 1970 to 2000, varicocelectomies gained worldwide interest for the treatment of male infertility. Several innovative procedures to correct varicoceles began to appear in the world's literature, and comprehensive review articles were published on the subject of varicocelectomies.[3,4] As a result of the growing worldwide interest, the number of varicocelectomies was increased in clinical practice, and the data of the National Survey of Ambulatory Surgery estimated that 67% of the patients undergoing ambulatory surgery for male infertility had a diagnosis of varicocele.[5] The number of procedures were increased further when the interventional radiologists began to treat varicoceles.

Controversy stimulates varicocele research

This clinical activity was not without controversy. Statisticians and reproductive endocrinologists were skeptical of the use of varicocelectomies for the treatment of male infertility for several reasons. They noted that the entry criteria for surgery varied among centers, the analysis of semen and pregnancy data often used inappropriate statistical methods, and almost all of the studies were retrospective. Since there were few prospective randomized trials, the Cochrane Collaborative presented negative reviews and, in 2009,[6] they concluded, "Insufficient evidence exists that treatment of varicocele in men from couples with otherwise unexplained subfertility does improve the couple's spontaneous pregnancy chances." The Reproductive Endocrinologists (REs) also weighed in on the role of varicocelectomies for the treatment of male infertility because they cited better results with IVF.[7]

Nevertheless, reproductive scientists continued to study the pathophysiology of varicoceles as source material for the investigation of male infertility. The early studies focused on the role of retrograde venous blood flow because of the increased heat that it produced within the testes which may affect developing sperm and Leydig cells. Others suggested that there was a retrograde accumulation of adrenal metabolites in the testes, as well. In time, the varicocele research evolved to the study of molecular and genetic information in both animal models and humans.[8–12] Although informative, these reports did not completely explain the basis for the clinical diversity that was associated with varicoceles. For example, why did some men with varicoceles remain fertile? How could a left-sided varicocele cause bilateral effects to both testes? However, new information has become available and helped explain these puzzling issues.

These new data identified molecular markers in men with varicoceles that were similar to responses that occurred in all cases of varicose veins. Recent articles suggest that the retrograde flow may transmit pressure to the walls of varicose veins which release products associated with oxidative stress.[13] In a study among adolescents with varicoceles, Romeo and Santoro[14] were the first to document that Reactive Oxygen Species (ROS) and Nitrous Oxide (N_2O) were released into the spermatic veins. Since these products in excess may damage sperm mitochondria, sperm cytology, and DNA, some

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investigators suggested that these products may represent the basis for the cause of infertility among men with varicoceles. Other investigators demonstrated that repeated measurements of the markers for oxidative stress were less variable than values noted on repeat semen analyses,[15] and still others have suggested that these markers should be considered in the work up of all infertile men.[16]

The new data

Following varicocele correction, Gabriel *et al.* reported that sperm DNA damage may decrease significantly as the sperm concentrations and pregnancy rates increased.[17] In the same time, an increase in the publications of prospective randomized trials appeared in the worldwide literature. Collectively, these data began to challenge the critics of varicocelectomies, and the Cochrane Collaborative re-evaluated its position.[18] In 2012, they reviewed 10 prospective randomized trials including 894 men and, based on these new data, they concluded, "Treatment of varicocele in infertile men with a clinically manifest varicocele and poor semen quality may be of benefit." In addition, they reported that the Number Needed to Treat (NNT) indicated that for every 7 men treated by varicocelectomy, there was 1 additional pregnancy. Independently, Comhaire and Decleer provided data from a multi-center study.[19] They reported that following varicocele repair the NNT was 6.3, and when antioxidants were provided after a varicocelectomy, the NNT was reduced even further. In addition, other publications have proposed a role for varicocelectomies in the treatment several other clinical situations such as low testosterone, nonobstructive azoospermia, and IVF/ICSI outcomes, but these matters will be considered elsewhere within this special issue of the journal. Therefore, it is an exciting time to be discussing surgeries and procedures for the correction of varicoceles, and the present manuscript will focus on the evolution of these techniques and consider some refinements.

IN THE BEGINNING

The pain era

Rothman[20] presented a concise historical manuscript on varicocele management. He noted that the early investigators reported that about 16% of the male population had varicoceles which are similar to the incidence today, but the treatments at that time were for the management of scrotal pain. The therapies included scrotal support, acupuncture, application of a seton (direct puncture of the veins and placement of a nonabsorbable thread into the veins until the veins dried up), application of an external clamp to compress the veins over a few weeks and ligation with a suture that was passed percutaneously by a needle behind the compression clamp, and then tied anteriorly above the skin to obstruct the veins for up to 2 weeks. Although this latter approach seemed crude, it was the forerunner of techniques that would be reported for the correction of varicoceles.

The early 20th century

Ivanissevich[21] developed conventional surgery for the management of varicoceles based on anatomical studies of cadavers, and this surgery was still used for the treatment of scrotal pain. He evaluated the anatomy of the spermatic cords, status of blood flow, and musculature of the anterior abdominal wall and stated that a varicocele was caused by venous reflux due to inefficient venous valves. He proposed a simple way to access to the spermatic cord and stated, "For the surgeon who is just beginning, it is undoubtedly easier to open the canal." He identified the contents of the spermatic cord in the inguinal canal and ligated the large varicose veins as a group after excluding the testicular artery and vas. Although he recognized the importance of excluding the testicular artery from the ligature, there were some cases of testicular ischemia, hydrocele formation, and recurrences. Nevertheless, he utilized this procedure on 4955 patients over 40 years of practice.

1949

Another surgical procedure was reported by Palomo[22] and was called the "Radical Cure of a Varicocele by a New Technique." He studied a small series of 40 men and noted that three arteries supplied the testis. He concluded that as long as only two arteries were ligated, the flow from the remaining artery would serve as a sufficient blood supply for the testis. The procedure was done under local anesthesia; the incision for this procedure was 4 cm long and it was 3 cm above the internal ring. The dissection was just above the internal inguinal ring where the large spermatic veins were easily visible. Although the artery and veins were ligated together, Palomo excluded the deferential and cremasteric arteries which he believed provided sufficient blood supply to the testis. Among his first 40 cases, there were no relapses or evidence of atrophy but the matter of hydrocele formation was not discussed.

VARICOCELE SURGERY FOR INFERTILE MEN

After 1952

Tulloch[1] was the first surgeon to repair a varicocele for the treatment of infertility. Tulloch was influenced by the comments of noted colleagues. For example, Russell[23] stated that there was no doubt that the incidence of varicocele is higher in men with poor quality seminal fluid and the varicocele may have an effect on infertility, and Hotchkiss[24] stated that the temperature effect of the varicocele may influence the nutrition of the germinal epithelium and upset maturation of spermatozoa. He recommended varicocelectomy for prophylactic therapy.

Tulloch's initial report described an infertile man with a varicocele and azoospermia who achieved return of sperm to the ejaculate after a varicocelectomy.[1] Tulloch utilized the Robb procedure[25] which approached the spermatic veins 5 cm above the internal inguinal ring. At this site, the dilated veins were fewer in number and the arterial blood supply to the testis was avoidable. In addition, Robb demonstrated that secondary venous drainage was preserved after the repair because he observed some venous flow by means of the direct injection of dye into the remaining veins. These observations provided anatomical proof that reasonable arterial flow and venous drainage were preserved which encouraged others to consider the development of newer surgical methods for the treatment of varicoceles.

After 1970

Both Dubin and Amelar were the students of Robert Hotchkiss, and they authored several manuscripts related to varicoceles and male infertility. Among their manuscripts, they proposed a diagnostic grading system for clinical practice.[26] The patients were examined upright, and a Grade III varicocele was visible and palpable, Grade II was palpable, and Grade I was palpable with a concurrent Valsalva maneuver. They commented that all infertile men should be examined in this way, because a small palpable varicocele was as damaging as a large one.

In 1975, Dubin and Amelar[27] published their experience with varicocele surgery on 504 men who had not produced a pregnancy for at least 1 year. Before the surgery, all men had at least two semen analyses and those with azoospermia were excluded. The surgery was a modification of the Ivanissevich procedure (**Figure 1**).

In addition, Dubin and Amelar[28] were the first to recognize the importance of lymphatic preservation. When they summarized their 25-year experience on 986 men, 30 had postoperative hydroceles (3.0%)

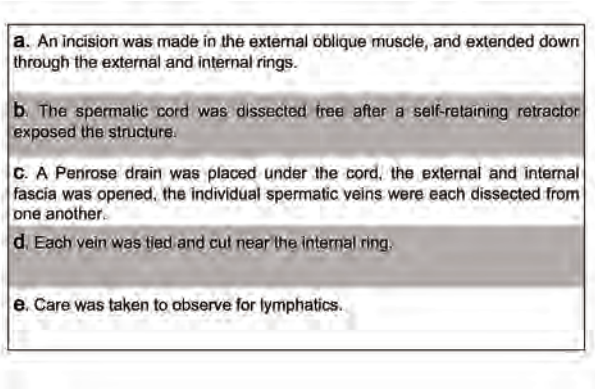

Figure 1: A modified Ivanissevich procedure (Dubin and Amelar[27]).

but only five required hydrocelectomies. At the same time, Szabo and Kessler[29] reported results on 111 internal spermatic ligations with the Palomo procedure and there were eight hydroceles (7.2%). Since the occurrence of hydroceles were not uncommon after the surgical techniques that were popular at that time, some surgical refinements seemed necessary.

INTERVENTIONAL RADIOLOGY

1966

The phenomenon of retrograde blood flow was permanently recorded preoperatively when Ahlberg *et al.*[30] used selective venography for diagnostic purposes and accurately documented the retrograde flow associated with varicoceles. In 1976, Comhaire and Kunnen[31] suggested that venography was not only available for the diagnosis of disturbed venous flow but also could be used therapeutically.

1978

Lima *et al.*[32] performed catheterization of the internal spermatic veins and then produced sclerosis of these structures with 5–10 ml of 75% hypertonic glucose solution. They repeated the glucose injection until the vein caliber was markedly reduced, and then they completed the procedure by adding 2 ml of monoethanolamine oleate. Although they were concerned about possible thrombus migration into the lung, this complication did not occur in their series. As an alternative, Kunnen[33] introduced percutaneous embolization with a tissue adhesive, 2-isobutyl-cyano acrylate (Bucrylate). The refluxing veins were identified by venography and then they were filled with Bucrylate that hardened in place to eliminate the retrograde flow. Comhaire and Kunnen[34] reported data on 97 infertile men with varicoceles who were treated with Bucrylate embolization. They noted that the varicocele size was not predictive of outcome, but the successes were greater among the men with the better preoperative semen data, and their overall pregnancy rate was 50.5%. However, this technique lost popularity when Fernandez Aparicio *et al.*[35] reported that the percutaneous delivery tube could become adherent to the hardened material within the vein which required immediate open surgery to correct the problem.

1981

Varicoceles were predominantly on the left side but, in 25% of the cases, there may be a varicocele on the right, as well. In the early days of percutaneous catheterization, it was often difficult to catheterize the right side but Gonzales *et al.*[36] introduced trans-jugular catheterization to embolize the right internal spermatic vein more efficiently. In a separate report, Formanek *et al.*[37] was successful with catheterization of the right spermatic vein in 17 of 24 patients but, over time, the technology improved for percutaneous embolization and it became un-necessary to use the trans-jugular approach. For example, Marshman[38] described a delivery guide wire for entry into the internal spermatic veins followed by embolization with small steel coils. The wire was an improvement because it could be steered into the veins under fluoroscopy, but these coils were of concern because some migrated into the lung.

Percutaneous venography was also used to diagnose and manage varicocelectomy failures. For example, Morag *et al.*[39] demonstrated persistent refluxing veins in 21 of 40 patients who had high surgical ligations, and they occluded the persistently refluxing veins with steel coils. As an alternative, Walsh and White[40] performed percutaneous renal vein catheterization and occlusion with balloons of various sizes that could be deflated and repositioned. White *et al.*[41] reported successful balloon occlusions of 52 varicoceles among 50 outpatients with only 1 recurrence at 8 months, but Kaufman *et al.*[42] studied recurrences in cases after both balloon and surgical occlusions. Among the failed balloon cases, recurrences occurred because parallel collaterals were not occluded whereas among the surgical failures some deep pelvic veins were untied. In a separate publication, Murray *et al.*[43] diagnosed and treated 44 recurrent varicoceles in 37 patients. Among 18 failed balloon occlusion procedures, the recurrences were treated with surgery. After 26 failed surgical procedures, 10 (38.5%) were high or mid-level, 15 (57.7%) were low inguinal, but none were trans-scrotal. These cases were corrected by balloon occlusion. None required repeat inguinal or scrotal surgery.

MICROSURGERY

1979

Modern microsurgery was introduced in 1970's primarily to improve the outcome of vasectomy reversals, but it was suggested that this equipment may benefit for varicocele surgery, as well. Silber[44] reported a patient who sustained ligation of the internal spermatic arteries during a varicocelectomy, and he recommended the use of occular loupes when dissecting the cord structures. In a separate review, Woznitzer and Roth[45] reported a surprising number of arteries within the specimens removed at the time of varicocele repair. They suggested that an operating microscope, microsurgical instruments, and a Doppler ultrasound probe could be used for a varicocelectomy to observe lymphatics and avoid injury to the internal spermatic arteries.

1985

Marmar *et al.*[46] presented the first microsurgical varicocelectomy with an operating microscope and microsurgical instruments. Based on the experience gained from performing vasectomy reversals, the operating room staff was familiar with the setup, and they were able to rapidly prepare the room for the varicocelectomy. With the availability of the microsurgical equipment, Marmar introduced several innovations (**Figure 2**).

1992

Goldstein *et al.*[47] modified the microsurgical, sub-inguinal varicocelectomy in several ways. They performed 640 varicocelectomies in 429 men. These surgeons had proven skills with microsurgery, and they used the sub-inguinal approach, but they took a more aggressive approach with arterial dissection and venous ligation, and they delivered the testis as part of the procedure (**Figure 3**). Their failure rate was 0.6% of all procedures, and the pregnancy rate per couple was 43% within 6 months. Although other surgeons delivered the testis during a varicocelectomy, Ramasamy and Schlegel[48] compared

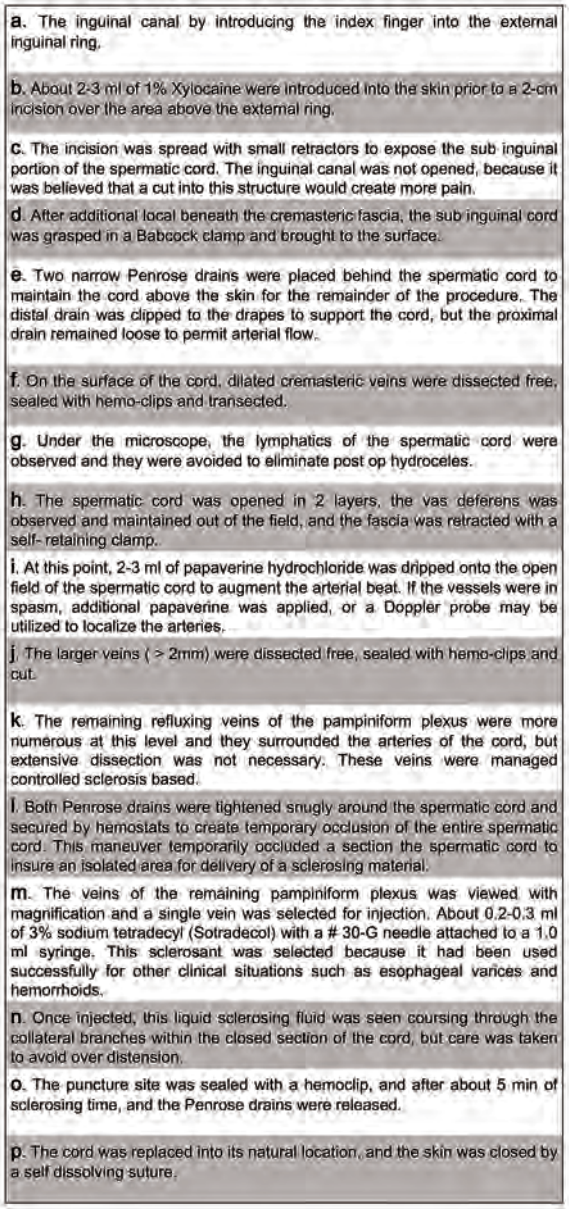

Figure 2: Sub-inguinal microsurgical varicocelectomy (Marmar *et al.*[46]).

the results of microsurgical inguinal varicocelectomy with testis delivery (55 patients) and without testis delivery (110 patients). At 1 year, the pregnancy rate was 40.0% for those with delivery and 55.0% for those without delivery. The differences were not statistically significant, but anecdotally they observed that delivering the testis resulted in more trauma, a longer operating time and inflammatory changes in the scrotum.

1994

Marmar and Kim[49] updated their series that included 606 procedures on 466 patients. There was only one permanent hydrocele. The recurrence of a palpable varicocele was 0.82% based on the total number procedures that were performed on these men. The 1-year pregnancy rate for 186 postvaricocelectomy patients was 35.6% versus 15.8% for 19 men with varicoceles who were treated medically, and

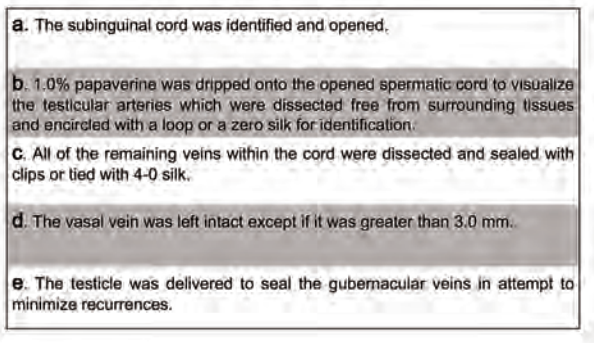

Figure 3: Microsurgical varicocelectomy with delivery of the testicle (Goldstein *et al.*[47]).

these differences were statically significant. The readers are encouraged to read this report for the discussion on the statistical methods that were used for analysis of the semen data. One other fact to note is that none of the steps of the original procedure have changed since it was introduced in 1985.

When microsurgery is contemplated on either inguinal or sub-inguinal spermatic cord, the surgeon should become familiar with the specific anatomy. For example, Hopps *et al.*[50] reported the vascular anatomy on 48 consecutive patients who had sub-inguinal cord surgery and compared their findings to those of Jarow *et al.*[51] who reported the anatomy of the cord in the inguinal canal. During the sub-inguinal surgery, there is no need to open the inguinal canal, and Gontero *et al.*[52] reported statistically significant lower intra-operative visual analog pain scores (VAS) with the sub-inguinal approach. However, Hopps *et al.*[50] stated that the sub-inguinal approach more difficult because the primary branch point for the testicular artery occurs in the inguinal canal and, as a result, there are more arterial branches covered by more small veins. Marmar and Kim[49] did not expose the arterial branches because they occluded the smaller remaining venous branches by controlled sclerosis. Pasqualotto *et al.*[53] dissected the small venous breaches and reported better outcomes for sperm densities and pregnancies based on the number of ligations of adherent veins. In either case, the surgeons must fully understand the anatomy to avoid vascular injuries.

1997 - microsurgery for adolescents with varicoceles

Lipshultz and Corriere[54] suggested that varicocele ligations at an early age may prevent a progressive decline in testicular size, and Kass *et al.*[55] examined testicular biopsies among adolescent boys with varicoceles to confirm retarded testicular growth. Therefore, the presence of testicular hypotrophy and varicocele has become the basis for varicocelectomy in adolescents. In a prospective study on adolescents, Paduch and Niedzielski[56] reported a 26% increase in volume of the left testicle after a modified Palomo procedure which supports the role for this surgical repair among adolescents. However, Kass and Marcol[57] reported an overall 11.0% failure rate after the nonarterial sparing Palomo procedure, and 16% failure rate among adolescents with the a modified Ivanissevich inguinal procedure. In addition, Ferber and Kass[58] reported a 29% rate for hydroceles with the Palomo procedure among adolescents. Therefore, other surgical methods were considered for adolescents.

Lemack *et al.*[59] utilized a microsurgical repair on 30 adolescents with varicoceles, and they had no failures. In addition, it is interesting to note that this group included five boys who had failed with a

nonmicrosurgical varicocelectomy. In a separate report, Schiff *et al.*[60] performed 97 sub-inguinal microsurgical varicolectomies on 74 adolescents and they reported 1 hydrocele. Although these techniques require microsurgical skills, Mirilas and Mentessidou[61] reported that they offered good results with low morbidity, but all surgeons are advised to carefully study the complex vasculature of the spermatic cord and testis to obtain favorable results.

ANTEGRADE SCLEROSIS

When considering the evolution of varicocele surgery, the Tauber procedure deserves a detailed discussion. This technique was first described in 1988, but Tauber and Johnsen[62] did not report the technique in the English version until 1994 when it became known as "antegrade scrotal sclerotherapy." They performed open surgery to expose the spermatic cord and select a single vein for sclerosis in an antegrade manner, and the steps of the procedure are shown in **Figure 4**. Their study group included 218 patients with varicoceles and the reasons for surgery included scrotal pain, poor semen analyses, and varicoceles progression. The follow-up revealed no postoperative varicocele in 91% of the cases and, among the infertile group, 42% of the cases conceived within 6–30 months.

Despite these favorable results, there have been a few notable complications associated with these procedures. For example, Goll *et al.*[63] reported the loss of a testicle due to a hemorrhagic infarct after antegrade sclerotherapy. In a separate study, Salerno *et al.*[64] documented that an anomalous anastomoses may occur between the left internal spermatic and visceral veins, and they suggested venographic studies before sclerosis to minimize recurrences, but there were other implications. In a patient with a venous anomaly, Vincini *et al.*[65] reported a large bowel infarct following antegrade sclerotherapy that required colonic resection and a colostomy. As a result, in a review of 5254 cases, Tauber *et al.*[66] recommended preliminary phlebography to identify venous anomalies before antegrade sclerosis.

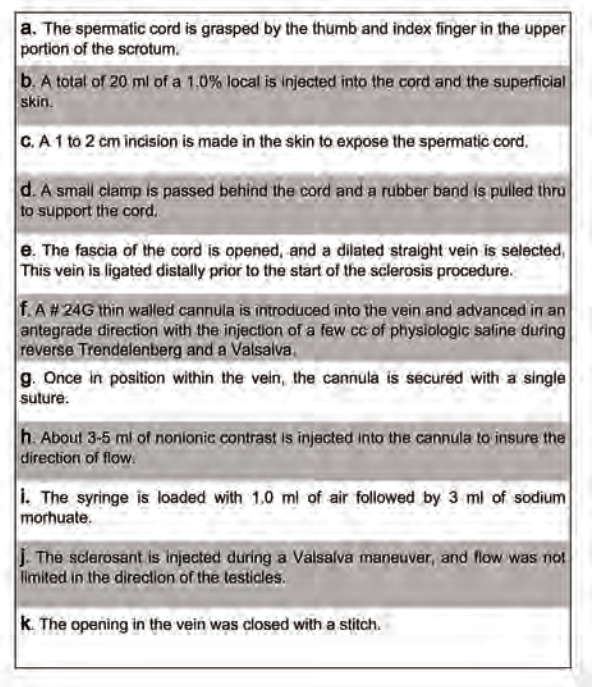

Figure 4: Antegrade sclerotherapy (Tauber and Johnsen[62]).

Antegrade scrotal sclerotherapy for adolescents with varicoceles

In 2001, Mazzoni *et al.*[67] reported sclerotherapy for adolescents because of its simplicity, low cost, and lack of hydrocele formation. They compared 45 adolescent varicocelectomies done with the Palomo procedure versus 44 Tauber procedures. The Palomo procedures had two failures (4.4%) and two postoperative hydroceles (4.4%). In contrast, the Tauber procedures had two failures (4.5%) but no hydroceles. However, Zaupa *et al.*[68] followed 84 children after antegrade scrotal sclerotherapy, 6 (7.0%) had recurrences, no hydroceles, but 3 (3.0%) had more serious complications including two with wound infections, one with a scrotal hematoma and focal testicular necrosis. Therefore, the parents of the children with varicoceles must be informed of these complications before consenting to these procedures. The reality of these complications has stimulated other investigators to seek modifications.

Colpi *et al.*[69] utilized a sub-inguinal approach combined with sclerotherapy alone for occlusion of the venous vessels by a modification of the Marmar and Kim[49] (**Figure 5**). The study group consisted of 307 men aged 17–51 years. Therefore, this modification was applicable to adolescents as well as adults. There were some cases of postoperative penile swelling, but there were no hydroceles or atrophic testes. In a separate report, Carmignani *et al.*[70] introduced sclerotherapy of the pampiniform plexus with a modified Marmar technique in children and adolescents. They evaluated 25 patients between 9 and 18 years (mean 14.4). There were no recurrences and only one hydrocele. The authors concluded that this modification was safe, easy to perform, and applicable to the treatment of children and adolescents. Further, their modification did not require extensive venous dissection, and the modification was less invasive than the laparoscopic procedures that have been popularized for young patients, which will be the topic of the next section.

LAPAROSCOPIC VARICOCELECTOMY

Laparoscopies were first used for the diagnosis of intra-abdominal pathology but, over time, most hospital had laparoscopic instruments that were used for a variety of procedures. In the beginning, some complications had been reported during laparoscopic procedures. For example, Soulie *et al.*[71] reported the complications with 350 laparoscopic procedures related to urologic diagnoses. These included 0.3% mortality rate, a 1.1% conversion rate to an open case, and a

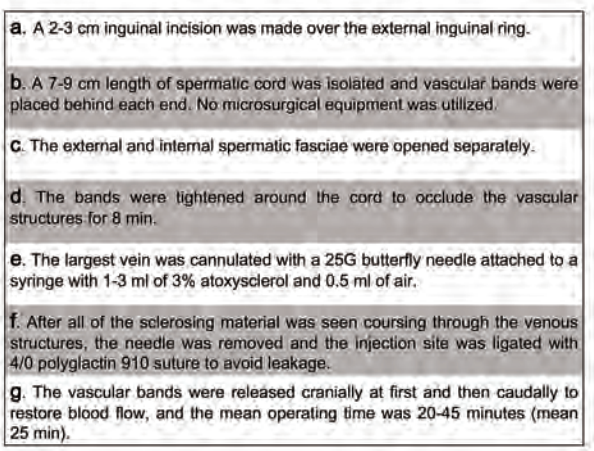

Figure 5: Complete sclerotherapy of the temporarily occluded spermatic cord (Colpi *et al.*[69]).

2.6% injury rate to the vasculature or visceral organs. There was a 2.8% postoperative complication rate including thromboembolism and wound infections at the trocar sites. However, the complication rate decreased from 9.0% for the first 100 cases to 4.0% for the next 250 procedures.

As the complication rate for laparoscopy decreased over time, it was not un-expected that clinicians would perform laparoscopic varicocelectomies. Hagood *et al.*[72] reported laparoscopic varicolectomies on 10 patients. The operative repairs were proximal to the internal ring and four were bilateral. They reported that the laparoscopic camera provided a microscopic view, the arteries were easily observed after a papaverine drip, and the internal spermatic veins were not difficult to clip and divide. Postoperatively, one patient had shoulder pain and three had a pneumoscrotum that resolved in 1 day, but overall patients had less pain than other procedures and they were managed by acetaminophen with codeine for 2 days. Donavan and Winfield[73] had a similar experience with 14 laparoscopic varicocelectomies and, in addition, they reported improvement in the postoperative semen parameters, as well.

However, other investigators reported more notable complications. Ralph *et al.*[74] reported a vasal injury that required a vasovasostomy and Jarow *et al.*[75] reported a genitofemoral nerve injury. Esposito *et al.*[76] reported 19 complications among 211 children (9.0%) which included 14 hydroceles, 3 with scrotal emphysema, 2 with umbilical granulomas, and 5 with recurrences. Despite these complications of the early cases, Peters[77] reviewed the status of laparoscopy in pediatric urology and predicted that these procedures would become more efficient with experience and they would continue to increase in number.

Sautter *et al.*[78] reported a prospective randomized comparison of laparoscopy versus antegrade sclerotherapy, and they raised the question of costs. The disposables were 316 Euros for the laparoscopic procedures which were twice as high as the 160 Euros for sclerotherapy, but Friedersdorff *et al.*[79] recently reported laparo-endoscopic single-site varicocelectomies with reusable components. The costs were lower with these procedures, and the outcomes were similar to conventional laparoscopies.

Borruto *et al.*[80] presented a review of the literature and a meta-analysis that compared laparoscopic versus open varicocelectomy in children and adolescents. They retained 11 studies for statistical analysis. Overall, they concluded that there were no differences between the procedures for recurrence and postoperative hydrocele rates. However, among the laparoscopic group, the recurrences were higher for patients who had artery ligation, but the rate of hydrocele formation was less among patients who had dye injections before their procedures. The authors concluded that with specific planning, the results of laparoscopic surgery are comparable to other surgical procedures, but the laparoscopic approach has the advantage to simultaneously treat bilateral varicoceles.

REFINEMENTS

The procedures for the correction of varicoceles have been described in the preceding sections. They have been used widely in clinical practice with generally good results, but none are without risks and complications. In this section, the focus will be on ways to avoid some of the risks and manage the complications with innovative methods. In addition, several new uses for varicocelectomies will be considered.

Ways to avoid hydroceles

Oswald *et al.*[81] introduced the idea of preoperative dye injections into the subdartos space before 28 Palomo procedures in adolescents. They injected 2 ml of isosulphan blue, and the lymphatics were clearly stained in 24 of 28 patients. There were no hydroceles or recurrences among those who were stained successfully. Methylene blue was avoided because this dye may cause local tissue reactions. Ishibashi *et al.*[82] used Indigo carmine because there has been extensive experience with this dye in cases of lymphatic mapping and sentinel node identification in cases of breast cancer. If 1–2 lymphatic channels were preserved during a varicocelectomy, there were no postoperative hydroceles.

Ways to repair hydroceles

Since hydroceles require management when they occur after some varicocelectomies, new minimally invasive hydrocoelectomies may be applicable. For example, Onol *et al.*[83] reported that after a 15 mm transverse scrotal incision, the tunica vaginalis could be grasped and dissected without delivery of the testis. By means of traction on the tunic, the sac was dissected from the subcutaneous scrotal tissue and delivered sufficiently so that the base could be opened and drained of fluid. The edges of the sac were cauterized and dropped back into the scrotum followed by skin closure. Saber[84] presented a slight modification whereby a disc of the tunic was excised and over sewn before skin closure.

Dissection and ligation of the deep veins within the pampiniform plexus

Some reports suggested that the number of veins ligated may influence the outcome of varicocelectomies, but these extensive dissections and ligations may be risky. Shindel *et al.*[85] questioned whether the number of veins ligated truly affected semen outcomes. Nevertheless, for those who choose to perform these extensive dissections, Zhang *et al.*[86] introduced the use of transfixing microsutures for difficult to isolate periarticular veins.

Immediate repair of arterial injury during a varicocelectomy

Even with the aid of an operating microscope, Chan *et al.*[87] reported that arterial injuries may occur in about 0.9% of microsurgical varicocelectomies. However, Kumar *et al.*[88] noted that the torn artery may be repaired immediately by observing the bleeding during arterial pulsations and closure with three #11-0 nylon sutures.

Simplification of laparoscopic varicocelectomies

The conventional approach for laparoscopic varicocelectomies utilized several ports, but recent modifications were introduced to simplify the procedure, especially for children. Kaouk and Palmer[89] reported the use of a single umbilical port in three children with no complications, failures, and postoperative hydroceles. Youssef and Abdalla[90] presented an expanded randomized trial that included 80 patients, and they compared the single incision trans-umbilical laparoscopic varicocelectomy (SIL-V) to the conventional laparoscopic technique (CLT-V). Following the SIL-V, there was a high rate of cosmetic satisfaction and significantly lower visual analog pain scores (VASs).

New device for percutaneous occlusion of varicoceles

A newly patented vascular occlusive devise was introduced and known as the Endo-luminal Occlusive System (EOS). It consisted of a Nitinol base attached an open sleeve of PTFE, and the system was reported to be rapid, more controllable, and less expensive than other systems. Although this devise is applicable to both arteries and veins, the first clinical trial after FDA approval was on six men with varicoceles (Venbrux *et al.*[91]) and they reported that the product provided 100% occlusion in the vessels that were studied.

Robotic-assisted varicocele surgery

In 2008, Corcione *et al.*[92] were the first to use a robotic-assisted platform in association with a laparoscopic varicocelectomy. Shu *et al.*[93] performed the first 8 robotic-assisted sub-inguinal varicocelectomies and compared these data to eight patients who had conventional microsurgical procedures. The operating times were the same, and neither group had complications. Recently, Parekattil and Gudeloglu[94] published a comprehensive review of robotic assistance for andrology. They commented that the operative microscope revolutionized microsurgery in 1970's whereas robotic assistance may represent the start of the second revolution. However, they pointed out that the growth of robotic assistance has been limited by high equipment and insurance costs. Therefore, the question remains whether robotic-assisted varicocelectomies can compete with standard microsurgical procedures, especially with the introduction of new magnification systems that could provide surgeons the ability to work at variable focal lengths and with High-definition Television screens for operative clarity. Parekattil and Gudeloglu[94] have incorporated such an imaging system (VITCOM) onto the 5th arm of their robotic platform, but others have used this equipment alone for various microsurgical procedures. No doubt, improved technology will continue to advance microsurgery, but the costs and outcome data will determine the eventual role for robotic surgery versus conventional microsurgery for the management of varicoceles.

CONCLUSIONS

The diagnosis and treatment of varicoceles have come a long way since the time they were corrected for the management of pain, alone. Over many decades, men and animal models with varicoceles have been a major resource for the study of male infertility. Now, the studies of varicoceles have entered the molecular era, and new data based on these molecular findings have led the way toward a better understanding of the pathophysiology of these venous lesions. The evolution of varicocele surgery and the refinements have been creative, effective, and rewarding, as well. In conclusion, it is hoped that the material in this special issue (including the present manuscript) will stimulate even more research that will lead to fresh ideas in future regarding the management of male infertility and other conditions related to varicoceles.

REFERENCES

1 Tulloch WS. Consideration of sterility: subfertility in the male. *Edinb Med J* 1952; 59: 29.
2 Tulloch WS. Varicocele in subfertility. Results of treatment. *Br Med J* 1955; 2: 356–8.
3 Baazeem A, Belsile E, Ciampi A, Dohle G, Jarvi K, *et al*. Varicocele and male factor infertility treatment: a new meta-analysis and review of the role of varicocele repair. *Eur Urol* 2011; 60: 796–808.
4 Diegido P, Jhaveri JK, Ghannam S, Pinkhasov R, Shabsigh R, *et al*. Review of current varicocelectomy techniques and their outcomes. *BJU Int* 2011; 108: 1157–72.
5 Meacham RB, Joycbase GF, Wise M, Kparker A, Niederberger C. Male infertility. *J Urol* 2007; 177: 2058–66.
6 Evers JL, Collins JA, Vandekerckhov P. Surgery or embolization for varicocele in subfertile men. *Cochrane Database Syst Rev* 2009; 1: CD000479.
7 Csokmay JM, DeCherney AH. Discriminate use of varicocelectomy in light of advances in assisted reproductive techniques. In: Carrell DT, Racowsky C, Schlegel PN, Van Voorhis BJ, editors. Biennial Review of Infertility. Vol. 1. New York: Humana Press; 2012. p. 249–57.
8 Turner TT. The study of varicocele through the use of animal models. *Hum Reprod Update* 2001; 7: 78–84.
9 Fretz PC, Sandlow JL. Varicocele: current concepts in pathophysiology, diagnosis, and treatment. *Urol Clin North Am* 2002; 29: 921–37.
10 Agarwal A, Hamada A, Esteves SC. Insight into oxidative stress in varicocele-associated male infertility: part 1. *Nat Rev Urol* 2012; 9: 678–90.
11 Benoff S, Marmar JL, Hurley IR. Molecular and other predictors for infertility in patients with varicoceles. *Front Biosci* 2009; 14: 3641–72.
12 Eisenberg ML, Lipshultz LI. Varicocele-induced infertility: newer insights into its pathway. *Indian J Urol* 2011; 27: 56–64.
13 Krzysciak W, Kozka M. Generation of reactive oxygen species by a sufficient, insufficient and varicose vein wall. *Acta Biochem Pol* 2011; 58: 89–94.
14 Romeo C, Santoro G. Free radicals in adolescent testis. *Oxid Med Cell Longev* 2014; 2014: 912878.
15 Smit M, Dohle GR, Hop WC, Wildhagen MF, Weber RF, *et al*. Clinical correlates of the biological variation of sperm DNA fragmentation in infertile men attending an andrology outpatient clinic. *Int J Androl* 2007; 30: 48–55.
16 Deepinder F, Cocuzza M, Agarwal A. Should seminal oxidative stress measurement be offered routinely to men presenting for infertility evaluation? *Endocr Pract* 2008; 14: 484–91.
17 St Gabriel M, Chan SW, Alhathal N, Chen JZ, Zini A. Influence of microsurgical varicocelectomy on human sperm mitochondrial DNA copy number: a pilot study. *J Assist Reprod Genet* 2012; 29: 759–64.
18 Kroese AC, de Lange NM, Collins JA, Evers JL. Varicocele surgery, new evidence. *Hum Reprod Update* 2013; 19: 317.
19 Comhaire F, Decleer W. Comparing the effectiveness of infertility treatments by numbers needed to treat (NNT). *Andrologia* 2012; 44: 401–4.
20 Rothman CM. The varicocele-1800. *Urology* 1980; 15: 99–100.
21 Ivanissevich O. Left varicocele due to reflux; experience with 4,470 operative cases in fourty-two years. *J Int Coll Surg* 1960; 34: 742–55.
22 Palomo A. Radical cure of varicocele by a new technique: preliminary report. *J Urol* 1949; 61: 604–7.
23 Russell JK. Varicocele in groups of fertile and subfertile males. *Br Med J* 1954; 1: 1231.
24 Hotchkiss RS. Fertility in Men. Philadelphia: JP Lippincott; 1944.
25 Robb WA. Operative treatment of varicocele. *Br Med J* 1955; 2: 355–6.
26 Dubin L, Amelar R. Varicocele size and results of varicocelectomy in selected subfertile men with varicoceles. *Fertil Steril* 1970; 21: 606–9.
27 Dubin L, Amelar R. Varicocelectomy as therapy in male infertility: a study of 504 cases. *Fertil Steril* 1975; 26: 217–20.
28 Dubin L, Amelar RD. Varicocelectomy: 986 cases in a twelve-year study. *Urology* 1977; 10: 446–9.
29 Szabo R, Kessler R. Hydrocele following internal spermatic ligation: a retrospective study and review of the literature. *J Urol* 1984; 132: 924–5.
30 Ahlberg NE, Bartley O, Chidekel N, Fritjofsson A. Phlebography in varicocele scroti. *Acta Radiol Diagn* 1966; 4: 517–28.
31 Comhaire F, Kunnen M. Selective retrograde venography of the internal spermatic vein: a conclusine approach to the diagnosis of varicocele. *Andrologia* 1976; 8: 11–24.
32 Lima SS, Castro MP, Costa OF. A new method for the treatment of varicoceles. *Andrologia* 1978; 10: 103–6.
33 Kunnen M. New techniques for embolisation of the internal spermatic vein: intravenous tissue adhesive (author's transl). *Rofo* 1980; 133: 625–9.
34 Comhaire FH, Kunnen M. Factors affecting the probability of conception after treatment of subfertile men with varicocele by transcatheter embolization with bucrylate. *Fertil Steril* 1985; 43: 781–6.
35 Fernandez Aparicio T, Minana Lopez MB, Pamplona M, Aguirre F, Carrero F, *et al*. Complications of varicocele embolization: adhesion of intravascular catheter during infusion of bucrylate. *Actas Urol Esp* 1994; 18: 141–4.
36 Gonzales R, Narayan P, Formanek A, Amplatz K. Transvenous embolization of internal spermatic veins: nonoperative approach to treatment of varicoceles. *Urology* 1981; 17: 246–8.
37 Formanek A, Rusnak B, Zollikofer C, Castaneda-Zungia WR, Narayan P, *et al*. Embolization of the spermatic vein for treatment of infertility: a new approach. *Radiology* 1981; 139: 315–21.
38 Marshman JW. Evaluation of a new distal delivery guidewire for steel coils. *Eur J Radiol* 1982; 2: 250–3.
39 Morag B, Rubenstein ZJ, Madgar I, Lunenfeld B. The role of spermatic venography after surgical high ligation of the left spermatic veins: diagnosis and percutaneous occlusion. *Urol Radiol* 1985; 7: 32–4.
40 Walsh PC, White RI. Balloon occlusion of the internal spermatic vein for treatment of varicoceles. *JAMA* 1981; 246: 1701–2.
41 White RI Jr, Kaufman S, Barth HK, Kadir S, Smyth JW, *et al*. Occlusion of varicoceles with detachable balloons. *Radiology* 1981; 139: 327–34.
42 Kaufman SI, Kadir S, Barth KH, Smyth JW, Walsh PC, *et al*. Mechanisms of recurrent varicocele after balloon occlusion or surgical ligation of the internal spermatic vein. *Radiology* 1983; 147: 435–40.
43 Murray RR Jr, Mitchell SE, Kadir S, Kaufman SL, Chang R, *et al*. Comparison of recurrent varicocele anatomy following surgery and percutaneous balloon occlusion. *J Urol* 1986; 135: 286–9.
44 Silber SJ, editor. Retroperitoneal and renal microsurgery. In: Microsurgery. Baltimore: Williams and Wilkins Company; 1979. p. 468–9.
45 Woznitzer M, Roth JA. Optical magnification and Doppler ultrasound probe for varicocelectomy. *Urology* 1983; 22: 24–6.
46 Marmar JL, DeBenedictis TJ, Praiss D. The management of varicoceles by

microdissection of the spermatic cord at the external inguinal ring. *Fertil Steril* 1985; 43: 583–8.
47 Goldstein M, Gilbert BR, Dicker AP, Dwosch J, Genecco C. Microsurgical inguinal varicocelectomy of the testis: an artery and lymphatic sparing technique. *J Urol* 1992; 148: 1808.
48 Ramasamy R, Schlegel PN. Microsurgical inguinal varicocelectomy with and without testicular delivery. *Urology* 2006; 68: 1323–6.
49 Marmar JL, Kim Y. Subinguinal microsurgical varicocelectomy: a technical critique and statistical analysis of semen and pregnancy data. *J Urol* 1994; 152: 1127–32.
50 Hopps CV, Lemer ML, Schlegel PN, Goldstein M. Intraoperative varicocele anatomy: a microscopic study of the inguinal versus subinguinal approach. *J Urol* 2003; 170: 2366–70.
51 Jarow JP, Ogle A, Kaspar J, Hopkins M. Testicular artery ramification within the inguinal canal. *J Urology* 1992; 147: 1290–2.
52 Gontero P, Pretti G, Fontana F, Zitella A, Marchioro G, *et al.* Inguinal versus subinguinal varicose vein ligation using magnifying loupe under local anesthesia: which technique is preferable in clinical practice? *Urology* 2005; 66: 1074–9.
53 Pasqualotto FF, Lucon AM, Moreirade Goes P, Sobriero BP, Hallak J, *et al.* Relationship between the number of veins ligated in a varicocelectomy with testicular volume, hormonal levels and semen parameters outcome. *J Assist Reprod Genet* 2005; 22: 245–9.
54 Lipshultz L, Corriere J. Progressive testicular atrophy in the varicocele patient. *J Urol* 1977; 117: 175–6.
55 Kass EJ, Chandra RS, Belman AB. Testicular histology in the adolescent with a varicocele. *Pediatrics* 1987; 79: 996–8.
56 Paduch DA, Niedzielski J. Repair versus observation I adolescent varicocele: a prospective study. *J Urol* 1997; 158: 1128–32.
57 Kass EJ, Marcol B. Results of varicocele surgery in adolescents: a comparison of techniques. *J Urol* 1992; 148: 694–6.
58 Ferber KM, Kass EJ. Varicocelectomy in adolescent boys: long-term experience with the Palomo procedure. *J Urol* 2008; 180 4 Suppl: 1657–9.
59 Lemack GE, Uzzo RG, Schlegel PN, Goldstein M. Microsurgical repair of the adolescent varicocele. *J Urol* 1998; 160: 179–81.
60 Schiff J, Kelly C, Goldstein M, Schlegel P, Poppas D. Managing varicoceles in children: results with microsurgical varicocelectomy. *BJU Int* 2005; 95: 399–402.
61 Mirilas P, Mentessidou A. Microsurgical subinguinal varicocelectomy in children, adolescents, and adults: surgical anatomy and justified technique. *J Androl* 2012; 33: 338–49.
62 Tauber H, Johnsen N. Antegrade scrotal sclerotherapy for the treatment of varicocele: Technique and late results. *J Urol* 1994; 151: 386–90.
63 Goll A, Schoeneich G, Haidl G, Burger R. Testicular loss due to hemorrhagic infarct in Tauber antegrade scrotal varicocele sclerotherapy. *Urologe A* 1997; 36: 449–51.
64 Salerno S, Cannizzaro F, LoCastro, A, Romano P, Bentivegna E, *et al.* Anastomosis between the left internal spermatic and splanchnic veins. Retrospective analysis of 305 patients. *Radiol Med* 2000; 99: 347–51.
65 Vincini P, Di Pierro GB, Grande P, Voria G, Antonnini G, *et al.* Large bowel infarct following antegrade scrotal sclerotherapy for varicocele. A case report. *Can Urol Assoc J* 2014; 8: 9–10.
66 Tauber R, Pfeiffer D, Burns T. Phlebography: why it is important to study radiological imaging of spermatic veins. *Arch Ital Urol Androl* 2003; 75: 62–7.
67 Mazzoni G, Spagnoli A, Luchetti MC, Villa M, Capiyanucci ML, *et al.* Adolescent varicocele: Tauber antegrade sclerotherapy versus Palomo repair. *Urology* 2001; 166: 1462–4.
68 Zaupa P, Mayr J, Hollwarth ME. Antegrade scrotal sclerotherapy for treating primary varicocele in children. *BJU Int* 2006; 97: 809–12.
69 Colpi GM, Carmignani L, Bozzini G, Picozzi S. Surgical subinguinal approach to varicocele combined with antegrade intraoperative sclerosis of venous vessels. *Surg Innov* 2012; 19: 252–7.
70 Carmignani L, Casellato S, Galasso G, Bozzini G, Spinelli M, *et al.* Sclerotherapy of the pampiniform plexus with modified Marmar technique in children and adolescents. *Urol Int* 2009; 82: 187–90.
71 Soulie M, Seguin P, Richeux L, Mouly P, Vazzoler N, *et al.* Urologic complications of laparoscopic surgery: experience with 350 procedures in a single center. *J Urol* 2001; 165: 1960–3.
72 Hagood PG, Meehan DJ, Worischek JH, Andrus CH, Parra RO. Laparoscopic varicocelectomy: preliminary report of a new technique. *J Urol* 1992; 147: 73–6.
73 Donavan JF, Winfield HN. Laparoscopic varix ligation. *J Urol* 1992; 147: 77–81.
74 Ralph DJ, Timoney AG, Parker C, Pryor JP. Laparoscopic varicocele ligation. *Br J Urol* 1993; 72: 230–3.
75 Jarow JP, Assimos DG, Pittaway DE. Effectiveness of laparoscopic varicocelectomy. *Urology* 1993; 42: 544–7.
76 Esposito C, Valla JS, Najmaldin A, Shier F, Mattioli G, *et al.* Incidence and management of hydrocele following varicocele surgery in children. *J Urol* 2004; 171: 1271–3.
77 Peters CA. Laparoscopy in pediatric urology. *Urology* 1993; 41: 33–7.
78 Sautter T, Sulser T, Suter H, Gretener D, Hauri D. Treatment of varicocele: A prospective randomized comparison of laparoscopy versus antegrade sclerotherapy. *Eur Urol* 2002; 41: 398–40.
79 Friedersdorff F, Aghdassi SJ, Werthemann P, Cash H, Goranova I, *et al.* Laparoendoscopic single-site (LESS) varicocelectomy with reusable components: comparison with the conventional laparoscopic technique. *Surg Endosc* 2013; 27: 3646–52.
80 Borruto FA, Impellizzen P, Antonuccio P, Scalfari G, Arena F, *et al.* Laparoscopic vs open varicocelectomy in children and adolescents: review of the recent literature and meta-analysis. *J Pediat Surg* 2010; 45: 2464–9.
81 Oswald J, Korner I, Riccabona M. The use of isosulphan blue to identify lymphatic vessels in high retroperitoneal ligation of adolescent varicocele – Avoiding postoperative hydrocele. *BJU Int* 2001; 87: 502–4.
82 Ishibashi H, Mori H, Yada K, Shimada M, Sogami T, *et al.* Indigo carmine dye-assisted lymphatic-sparing laparoscopic Palomo varicocelectomy in children. *J Med Investig* 2014; 61: 151–5.
83 Onol SY, Ilbey YO, Onel FF, Ozbek E, Arslan B, *et al.* A novel pull through technique for the surgical management of idiopathic hydrocele. *J Urol* 2009; 181: 1201–5.
84 Saber A. New minimally access hydrocelectomy. *Urology* 2011; 77: 487–90.
85 Shindel AW, Yan Y, Naughton CK. Does the number and size of veins ligated at left-sided microsurgical subinguinal varicocelectomy affect semen analysis outcomes? *Urology* 2007; 69: 1176–80.
86 Zhang Y, Yang X, Wu X, Zhang H, Chen S, *et al.* Microsurgical varicocelectomy with transfixing of the difficult-to-isolate periarterial vein using microsutures. *Urology* 2015; 85: 948–52.
87 Chan PT, Wright EJ, Goldstein M. Incidence and postoperative outcomes of accidental ligation of the testicular artery during microsurgical varicocelectomy. *J Urol* 2005; 173: 482–4.
88 Kumar R, Dash SC, Thulkar S, Gupta NP. Repair of testicular artery injury during microsurgical varicocelectomy. *J Urol* 2003; 169: 615–6.
89 Kaouk JH, Palmer JS. Single –port laparoscopic surgery: initial experience in children for varicocelectomy. *BJU Int* 2008; 102: 97–9.
90 Youssef T, Abdalla E. Single incision transumbilical laparoscopic varicocelectomy versus the conventional laparoscopic technique: a randomized clinical study. *Int J Surg* 2015; 18: 178–83.
91 Venbrux AC, Rudakov L, Plass A, Emmert MY, Ebner A. A new occlusive device: application of the ArtVentive endoluminal occlusion system (EOS) – The first in human clinical trial. *Cardiovasc Intervent Radiol* 2014; 37: 85–93.
92 Corcione F, Esposito C, Cuccurullo D, Settembre A, Miranda N, *et al.* Advantages andlimits of robot-assisted laparoscopic surgery: preliminary experience. *Surg Endosc* 2005; 19: 117–9.
93 Shu T, Taghechian S, Wang R. Initial experience with robot-assisted varicocelectomy. *Asian J Androl* 2008; 10: 146–8.
94 Parekattil SJ, Gudeloglu A. Robotic assisted andrological surgery. *Asian J Androl* 2013; 15; 67–74.