CHAPTER 8

TREATMENT APPROACH IN ADOLESCENT VARICOCELE PATIENTS

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INTRODUCTION

In addition to symptoms such as scrotal pain, varicocele can cause subfertility as a result of stagnation in testicular development, atrophy and deterioration of sperm values. It is a common disease in the adolescent age group in parallel to the age of the child. When a careful physical examination is performed, the frequency of detection of bilateral varicocele is higher than expected (1). While left varicocele is seen in 90% of cases, bilateral varicocele is detected in approximately 10% of cases. Most of the varicocele cases in childhood and adolescent age group are asymptomatic. They are usually detected incidentally by physical examination or noticed by families. When a careful physical examination is performed in cases with varicocele, volume loss can be detected in the testis on the affected side. It is the most common pathology that can lead to surgically correctable male infertility in this age group (1, 2).

Measuring testicular volume is important in terms of the necessity of varicocele treatment and monitoring of after varicocelectomy. Testicular volume can be measured by ultrasonography as well as various types of orchidometers *(Prader, Takahara)*. Prader orchidometry is sufficient for practical use to measure testicular volumes (3).

When deciding on the treatment of adolescent varicoceles, the volume loss of 20% or more than 2 mL in the affected testis, softening of the testis, deterioration in sperm parameters, bilateral palpable varicocele, and the presence of symptomatic varicocele are taken into account (4).

Treatment options in adolescent cases with varicocele can be elaborated as: open surgery *(high retroperitoneal, inguinal, subinguinal),* laparoscopic surgery and radiological methods *(sclerotherapy or embolization)*. However, current treatment methods are inguinal or subinguinal approaches. The aim of varicocelectomy is to connect all internal spermatic vein branches and external spermatic vein

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branches (5). During this procedure, the vas deferens, lymph vessels and arteries should be preserved. In conventional varicocelectomy performed without the use of a microscope or optical magnifying glass, the inability to see and ligate the small internal spermatic vein branches is the most common cause of recurrence. In addition, another important reason in recurrent varicocele is shunt formation via external spermatic vein. In the treatment of varicocele with extraperitoneal, laparoscopic or radiological methods, inguinal or subinguinal approach should be preferred, since this vein cannot be reached (5, 6).

In order to prevent complications such as recurrence, arterial injury and postoperative hydrocele in varicoceles in children and adolescents, varicocelectomy is recommended to be performed with a microscope or using a loop (7).

In conclusion, varicocele is a disease that causes progressive testicular damage and its incidence increases with age. In children and adolescents with varicocele, microscopic or inguinal or subinguinal varicocelectomy with an optical magnifier is a safe treatment option with very low recurrence and complication rates (7).

INCIDENCE

Varicocele is one of the most common and correctable causes of male infertility. It was first described by Celcus in the 1st century. In Anatolia, Şerafeddin Sabuncuoğlu named varicocele as *"devali"* in his book titled *Surgicalyyetü'l Haniyye*, which he wrote in 1483, and described the disease as the bending of testicular veins and taking a shape similar to a bunch of grapes. He also described the surgical treatment of the disease in the same book (8).

Varicocele is a pathology characterized by dilatation of the veins forming the pampiniform plexus in the funiculus spermaticus. In addition to symptoms such as scrotal pain, it is a progressive pathology characterized by regression in testicular development, atrophy and deterioration in sperm parameters and may cause male infertility. It has been reported that varicocele is seen at a rate of 10-15% in the general population, and these rates increase to 19-41% in primary infertile cases and up to 53-80% among secondary infertile cases (9).

While the incidence is 1% in the pediatric age group under the age of 10, the prevalence of varicocele increases with age after the age of 13 years, reaching up to 14.1% between the ages of 15 – 19. This rate is very close to 15%, which is the incidence of varicocele in the general population (10). Adolescent varicocele is usually asymptomatic and detected during routine physical examination, and therefore its incidence may be higher than published data. Adolescent varicocele still remains one of the most interesting and controversial topics in pediatric urology (9).

PHYSIOPATHOLOGY OF VARICOCELE

Varicocele is observed on the left side in 90% of cases, hence bilateral involvement may be detected in 10%. Although the incidence of right-sided varicocele is quite low, renal masses and retroperitoneal masses that may cause obstruction in the spermatic vein or vena cava should always be considered in the presence of right-sided varicocele. Due to the anatomical features of the right and left spermatic veins and their different embryological origins, right side varicocele is extremely rare (11).

Although the etiology of varicocele is still unknown, many theories have been proposed. It has been reported that the incidence of varicocele in first degree relatives of cases was found to be around 53%, and this rate was considerably higher than the normal population (12). The pathophysiology of adolescent varicocele may be multifactorial. In the etiology of varicocele, it is generally thought that anatomical features, hydrostatic pressure increase in venous structures causes venous reflux formation and accordingly, there is dilatation of the veins in plexus pampiniformis in the spermatic cord. There are different opinions regarding the factors that can cause the above-mentioned increase in venous hydrostatic pressure. These can be listed as follows (13 – 15):

- The nutcracker phenomenon known as partial obstruction of the testicular vein due to the compression of the left renal vein between the superior mesenteric artery and the aorta has been described. Studies have reported the proximal type of this phenomenon, which results in the left renal vein extending between the anterior of the aorta and the posterior of the superior mesenteric artery, with an overall incidence of 0.7%, and the distal type, which is in the form of compression of the left common iliac vein secondary to compression of the left common iliac artery, with an incidence of 0.5% (13 – 15).
- A condition that causes reflux of venous blood due to insufficient valves in the gonadal veins and the absence of competent venous valves. Anatomical studies and retrograde venography revealed that there is no valve at the junction of the left renal vein and the left spermatic vein. On the other hand, the presence of venous valves in 75% of the cases with varicocele and the presence of varicocele despite the absence of valves in the remainder has made this view controversial (13 – 15).
- One of the most frequently mentioned theories in the literature and classical text books is that the right testicular vein enters the inferior vena cava obliquely, whereas the left testicular vein opens directly to the left renal vein at a right angle. All these features cause dilatation and tortuosity by causing an increase in venous pressure in testicular veins (13 – 15).

It is known that the presence of varicocele has negative effects on spermatogenesis. Testicular vascular changes resulting in hyperthermia, changes in testicular blood flow and venous pressure, reflux of renal-adrenal products, change in testis nutrition or interstitial fluid formation, hormonal dysfunction, autoimmunity, acrosome reaction defect, increased oxidative stress, apoptosis and toxic elements such as cadmium can are held responsible. Although the mechanism of varicocele and deterioration in testicular functions has not been fully revealed, it is emphasized that the heat factor and venous reflux are the two most important factors that play a role in the pathophysiology (15).

The undesirable effects of varicocele may occur as testicular growth failure, semen abnormalities, Leydig cell dysfunction and histological changes such as tubular thickening, fibrosis, decreased spermatogenesis, maturation arrest (15)

DIAGNOSIS & CLINICAL SYMPTOMS

Varicocele is often asymptomatic and rarely causes pain in the adolescent age group. It may be noticed by the patient himself, his parents, or by the physician during a routine physical examination. The gold standard in the diagnosis of varicocelectomy is physical examination. In a warm environment, the patient should be examined in both lying and standing positions, and also by performing the Valsalva maneuver in the same positions. However, in the presence of conditions that complicate physical examination *(patients with testicles located above the scrotum, patients with small scrotal sac, anatomical features that cause difficulty in physical examination, presence of cremaster hyperreflexia, examination difficulty due to environment-patient structure)*, color Doppler ultrasonography may be necessary (16).

Physical examination is performed with palpation of the spermatic cord before and after the Valsalva maneuver. The spermatic veins are filled much better when the Valsalva maneuver is performed while the patient is standing. For this reason, the patient must be examined on an outpatient basis in order to detect low-grade varicoceles on physical examination. According to physical examination findings, the grading system published by *Dubin and Amelar in 1970* is still in use today (17).

- *Grade 0:* Also called sub-clinical varicocele. It includes varicoceles that cannot be detected by clinical examination and can be detected by radiological diagnostic methods such as scrotal Doppler ultrasonography or venography (17).
- *Grade 1.* It describes small dilated veins that can be palpated only with the Valsalva maneuver (17).

- *Grade 2.* Varicocele, palpable at rest or with normal breathing, without Valsalva. Defines moderately dilated veins (17).
- *Grade 3.* Varicocele, visible at rest or without the need for palpation with normal breathing. It describes highly enlarged veins (17).

During physical examination, testicular volume and vas deferens should be checked. The most important parameter in the physical examination of children and adolescents with varicocele is the correct evaluation of testicular volume and consistencies. In standard practice, the volume of the right testis is compared with that of the left testis and is generally similar. The most commonly used formula to reveal asymmetry in the left testis; *[(Right testis volume – left testis volume) \ right testis volume] x 100*, which gives the ultrasonic volume difference in cm^3. A decrease in testicular volumes or softening of testicular consistency is a sign that spermatogenesis may be severely affected. During this examination, testicular volume can be determined by orchidometry *(Prader, Rochester or Takahara)* or calculated using the formula *[length x width x thickness x 0.52]* by ultrasound. In addition, it is stated that there is no more than 0.5 cm difference between the long axes of both testicles in the normal population. Although ultrasonography is found to be more sensitive in determining the volume difference between testicles, it is more practical to use orchidometry (18 – 21).

The routine use of color Doppler ultrasound for the diagnosis of varicocele is not recommended. However, scrotal ultrasonography is recommended in the presence of specific conditions such as obesity and surgical interventions with a short cord. It has been shown that during the measurement of vein diameters in ultrasonography, a vein diameter of at least 2.7 mm and above can be significant, and values of 3.6 mm and above will significantly increase the sensitivity and specificity for clinical varicocele (22). In color Doppler ultrasonography, the diagnosis of varicocele is made by detecting reflux in the internal spermatic vein. In this examination, the velocity of blood flow towards the probe is technically coded in red and the velocity of flow away from the probe is coded in blue (20).

It should be known that reflux during the valsalva maneuver is very important in the examination. In previous studies, reflux was found in 83% of the patients with clinical varicocele on the left and 59% on the right. However, the presence of reflux during valsalva was in 42% of the cases in the Doppler examination performed in healthy men (23). This suggests the absence or insufficiency of the valves in the veins. In the examination, it is stated that reflux can be short-term, medium-term or long-term reflux lasting more than 2 seconds. In the past, color Doppler ultrasound was used in adolescents with obvious left varicocele or abnormal sperm parameters to determine whether bilateral treatment was

needed. However, the diagnosis and treatment of subclinical varicocele is still a controversial issue, and the common view is that subclinical varicocele does not require treatment (24).

In adolescents with varicocele, the presence of follicle-stimulating hormone *(FSH)* and luteinizing hormone *(LH)* responses to stimulation with gonadotropin-releasing hormone *(GnRH)* is used as a reliable test in demonstrating testicular damage. It has been reported that histopathological changes were found in the testicles of patients with a positive test (25).

TREATMENT GUIDELINES & SURGERY METHODS

In adolescents, although fertility potential should be preserved, this situation is not known at the time of application. Since 80% of adult men with varicocele can be fertile, it is very important to be very selective in the surgical treatment of adolescent varicocele, to determine the group that will respond to the treatment and to avoid unnecessary surgeries. One should bear in mind that not every case with varicocele is a candidate for treatment. The European Association of Urology *(EAU)* and the American Association of Urology *(AUA)* guidelines have established the limits of treatment indications in varicocele based on the results of studies conducted in the past years (26 – 28). If these indications are not taken into account, high rates of benefit from the treatment should not be expected.

Indications for treatment of varicocele according to EAU and AUA guidelines are (26, 28):

- Presence of palpable varicocele.
- The couple has known infertility.
- The female partner's fertility is normal.
- Presence of abnormal semen parameters.

Apart from the aforementioned and indispensable factors, the following additional factors should always be considered. These factors are (26 – 28):

- Presence of adolescent varicocele and testicular hypotrophy.
- Coexistence of non-obstructive azoospermia and palpable varicocele.
- Presence of genetic infertility.
- Presence of pain.

Moreover, with the evaluation of many studies, the following opinions come to the fore regarding in which cases better results in terms of semen analysis and pregnancy can be obtained after varicocelectomy operation (29 – 30).

- Presence of Grade 3 varicocele.
- Absence of testicular atrophy.
- Normal FSH serum levels.
- Positive GnRH test.
- Patients with a total motile sperm count > 5 million.
- Cases with sperm motility >60%.
- Normal FSH / testosterone, low inhibin B levels in semen.
- Presence of normal genetic tests.
- Short infertility period.
- No molecular defect detected.

Many studies have tried to reveal the clinical progression of adolescent varicocele and, most importantly, to determine the parameters that distinguish cases that will benefit from surgery (31 – 33). These studies have focused on the degree of varicocele, testicular hypotrophy, and more recently, changes in semen parameters (33). The importance of varicocele grade is controversial in the literature. It has been reported in previous studies that varicocele grade and volume difference are independent parameters (31), and there is no difference in semen parameters between grade 2 and grade 3 varicoceles. As a result of all these studies, a high degree of varicocele is not accepted as an indication for treatment today. Bilateral varicocelectomy is recommended for cases because the volume difference cannot be understood in bilateral high-grade varicoceles (34).

The difference in volume between the testicles is another parameter used for the indication of surgery. Until recently, 2 ml or more than 10% volume loss in the testis with varicocele was considered an absolute treatment indication (35). However, in the studies conducted in the last two years, it has been shown that if the volume difference is 20%, deterioration in semen parameters becomes obvious. While abnormal total motile sperm count was found in 59% of adolescents with a volume difference of more than 20%, abnormal motile sperm count was found in only 11% of the cases when the volume difference between the testicles was between 10 – 20% (36). In the light of these data, it is argued that surgical intervention is the most appropriate approach if there is a volume difference of more than 20% between the testicles and this difference persists for one year. In a recent study on the time required to wait for the spontaneous recovery of this difference in volume difference, it was reported that if the peak retrograde flow velocity in the varicocele vein is higher than 38 cm/s and the volume difference between the testicles is more than 20%, it is not necessary to wait for the decision of surgery (37).

In the light of all this information, the indications for adolescent varicocele treatment are as follows (38 – 40):

- Volume loss of more than 20% or 2 mL in the affected testis.
- Testicular softness.
- Deterioration in sperm parameters.
- Presence of bilateral palpable varicocele.
- Presence of symptomatic high-grade varicocele.
- Excessive FSH-LH response to GnRH stimulation.

In adolescents with a testicular volume difference of 20% or more, semen analysis should be performed, if possible, and abnormal semen parameters should be taken as a marker for clinical decision making. However, performing this analysis in children and adolescents involves psychological and ethical difficulties. However, semen analysis results are considered to be a more important parameter in the treatment decision than the volume difference between the testicles. Studies are ongoing to reveal a marker or finding that can be used as a prognostic factor earlier than testicular volume difference or abnormal semen parameters in the treatment of adolescent varicocele (41).

The aim of adolescent varicocele treatment is to preserve fertility. For this reason, the method to be applied should protect the testicular functions at an optimal level, treat the disease and its complications should be minimal (42). The treatment options for adolescent varicocele are similar to adults, based on ligation or occlusion of all internal spermatic vein branches and preservation of arteries and lymphatics. Complication rates such as varicocele recurrence, arterial injury and postoperative hydrocele formation should be the low, and the recovery in postoperative sperm parameters and pregnancy rates should be higher than for a successful treatment (43).

Although varicocele can be treated with open surgical *(high retroperitoneal, inguinal, subinguinal and scrotal),* laparoscopic and radiological *(sclerotherapy or embolization)* methods, the gold standard in the treatment is microscopic varicocelectomy. Although the laparoscopic approach is a method used in the treatment of varicocele, it carries the risk of serious complications such as intestinal and major vascular injuries, as well as the inability to visualize and ligate the external spermatic vein as a result. Although these complications are rare, they can be serious and may even require laparotomy. The high cost is another disadvantage of the laparoscopic treatment of varicocele (44).

Radiological occlusion-embolization *(with balloon or coil)* or sclerotherapy of the internal spermatic vein is another alternative in the treatment of varicocele.

The advantages of percutaneous embolization are that it causes less pain and earlier recovery in the postoperative period. However, it is a method that requires a lot of experience and the results of the treatment may vary depending on the experience of the treating physician. Although a balloon or coil is successfully placed in the internal spermatic vein venographically in 75-90% of the procedures, in some cases, the internal spermatic vein cannot be accessed due to technical reasons. For this reason, surgical treatment is required as a final result in some of the patients who are tried for radiological occlusion. Vascular perforation, coil or balloon migration, thrombosis of the pampiniform plexus, and contrast allergy are among the complications encountered. Exposure to radiation is another disadvantage. Today, it is accepted that the radiological treatment method can be an alternative mostly in recurrences after surgical treatment (45)

Shunt formation via external spermatic vein is thought to be one of the causes of recurrence after varicocele treatment. Low level ligation *(inguinal/ subinguinal)* methods should be preferred, since the external spermatic vein cannot be reached by extraperitoneal or laparoscopic way, which is one of the varicocelectomy methods. In conventional varicocelectomies performed without using a microscope or optical magnifying glass, the inability to ligate small internal spermatic vein branches due to the inability to see is the most important reason for recurrence in the treatment of varicocele. In addition, one of the most important reasons for the use of loop or microscope is the preservation of the spermatic artery by visualization. Although microscope and loop are utilized as optical magnifiers to achieve these goals, there is a consensus that microscope is more advantageous than loop in providing ideal varicocelectomy conditions (36, 37). *Espec*ially in subinguinal varicocelectomy, it is more difficult to apply this method, which requires experience, since the number of veins are high and the artery is more difficult to protect. Less proximal vein ligation, lower risk of arterial injury, and less experience in microsurgery are the advantages of the inguinal method (46).

Complications

Although the rate of complications vary according to the method applied and the physician/surgeon who applies it, the important complications of varicocele treatment are hydrocele, testicular atrophy and recurrence. These risks should be explained to the patient before varicocele treatment. Hydrocele secondary to ligation of testicular lymphatics is the most common complication of varicocelectomy. Although its incidence varies between 3-33%, it is around 7-9% on average (47).

The use of an optical magnifier such as a microscope significantly reduces the occurrence of hydrocele. With different surgical approaches, recurrence after varicocelectomy is reported to be 0-45%. Venographic studies show that recurrent varicoceles occur due to periarterial, parallel inguinal, midretroperitoneal, gubernacular, and rarely transscrotal collateral veins. The use of a microscope or optical magnifier allows the detection of small-diameter internal spermatic veins that may later dilate and cause recurrence. While varicocele recurrence is around 15% in methods in which varicocelectomy is performed with the naked eye, it is reported to be around 1% in varicocelectomy series in which microscope or optical magnifying glass is used (48 – 50).

Testicular atrophy and/or impaired spermatogenesis, which are other important complications of varicocelectomy, often develop due to testicular artery injury or ligation. However, atrophy after arterial ligation is less common due to the presence of cremasteric and vasal arteries (51).

FOLLOW – UP

In patients with no testicular volume loss and asymptomatic varicocele, annual physical examination and follow-up is an appropriate method. In addition to the annual physical examination, an annual spermiogram is recommended according to age. Surgery is the most appropriate approach in the early period in patients with decreased testicular volume during follow-up. Considering the possible post-surgical complications such as recurrence, hydrocele development, and testicular arthrosis, annual physical examination and control are recommended. The improvement in semen parameters can be followed by performing a spermiogram at the 6th month after surgery in age-appropriate patients (52).

PREDICTIVE FACTORS ON VARICOSELE TREATMENT

Many clinical parameters have been evaluated in previous literature to predict the results of varicocele treatment, but none of them have been derived with the use of multivariate analysis. Although success varies from case to case, cases with the following findings benefit more from varicocele treatment (53 – 55):

- Advanced varicocele
- Normal/near normal testicular volumes
- Normal FSH/testosterone, low inhibin B
- Total motile sperm count > 5 million
- Normal genetic tests
- Short infertility period
- No detection of molecular disorders

CONCLUSION

Varicocele in adolescence is one of the most important surgically correctable causes of testicular atrophy. Therefore, testicular volumes of patients with adolescent varicocele should be closely monitored with serial ultrasound measurement and examination. After puberty, spermiogram follow-up also makes important contributions to ultrasound measurements. Varicocele is a disease whose incidence increases with puberty in adolescents and its incidence varies between 14-20%. 20% of affected adolescents have fertility problems. A 20% reduction in testicular size or a reduction of more than 2 ml on the side with varicocele is considered testicular atrophy and is an indication for surgery. Today, there is strong evidence that timely surgical treatment will prevent testicular atrophy and infertility caused by adolescent varicocele.

Today, surgery is the gold standard among treatment methods. The use of a microscope or optical magnifier during surgery is the main factor in increasing treatment efficacy and reducing complication rates. Although surgical treatment is at the forefront, the results of embolization with angiography are comparable in experienced hands.

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