Chapter 5
Treatment Modalities

In this chapter, we discuss the therapeutic modalities that have been applied to the treatment of varicocele, including medical therapy, surgical repair and embolization technique.

Medical Therapy

Nonsurgical treatment modalities for varicocele-related infertility have been poorly studied. Use of antioxidants, anti-inflammatory and gonadotropin therapy has been attempted with conflicting results, as shown in Table 5.1.

Antioxidants and Anti-Inflammatory Agents

Oral antioxidants for varicocele-related infertility, either as a therapeutic alternative or as an adjuvant treatment to varicocele repair have been recently examined.

In a rat model of varicocele, the use of a NOS inhibitor (aminoguanidine) resulted in an increase in semen parameters and reduction in sperm DNA fragmentation [209, 210]. Vitamin E has been also shown to significantly reduce seminal ROS levels in experimental rat varicocele model [211]. In humans, daily oral administration of pentoxifylline, zinc, and folic acid for 3 months improved sperm morphology for at least 4 weeks after the end of treatment [212]. However, this evidence comes from small non-controlled series with poor methodology. In another study, Cavalleni et al. [213] studied the effects of a 6-month course of the oral antioxidants L-carnitine (1 g/day) and acetyl-L-carnitine (2 g/day) given with the anti-inflammatory cinnoxicam (30 mg suppository given every 4 days) in oligozoospermic infertile men with or without varicocele. The researchers found that both men with low-grade varicocele and idiopathic oligoasthenoteratozoospermia responded better to the combination than those who were prescribed placebo or just the antioxidants. In
Table 5.1 Non-surgical modalities for treatment of infertile males with varicocele

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Antioxidant</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controlled trials</td>
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<tr>
<td>Cavallini et al. (2004) [213]</td>
<td>$n=62$ men with varicocele and 39 men with oligozoospermia treated compared with 71 men with varicocele and 47 men with oligozoospermia as controls (no treatment)</td>
<td>l-Carnitine (2 g/day) and acetyl-l-carnitine (1 g/day) for 6 months</td>
<td>Non-significant improvement in semen parameters in men with varicocele grade I and II, but significant improvement in pregnancy rate ($P&lt;0.01$)</td>
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<tr>
<td>Cavallini et al. (2004) [213]</td>
<td>$n=62$ men with varicocele and 44 men with oligozoospermia treated compared with 71 men with varicocele and 47 men with oligozoospermia as controls (no treatment)</td>
<td>l-Carnitine (2 g/day), acetyll-carnitine (1 g/day) and cinnoxicam suppository (30 mg) every 4 days for 6 months</td>
<td>Significant improvement in semen parameters in men with varicocele grade I and II at 3 and 6 months of therapy ($P&lt;0.05$) and significant improvement in pregnancy rate ($P&lt;0.01$)</td>
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<tr>
<td>Zampieri et al. (2010) [216]</td>
<td>$n=73$ men with subclinical left-sided varicocele compared with 95 men with subclinical varicocele as controls (no treatment)</td>
<td>$O$-$\beta$-Hydroxyethyl-rutoside (1 g/day in a on/off 3-month cycle for 1 year)</td>
<td>41% of patients in the treatment group had resolution of vein reflux within 3 years ($P&lt;0.05$)</td>
</tr>
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<td>Söylemez et al. (2012) [240]</td>
<td>$n=20$ normozoospermic men with varicocele and pain compared with 20 normozoospermic men with varicocele and pain as controls (no treatment)</td>
<td>Micronized purified flavonoid fraction (1 g/day for 6 months)</td>
<td>Relief of varicocele-associated pain in 30% of men; improved sperm motility at 6 months ($P=0.038$) and color Doppler parameters at 1, 3 and 6 months ($P&lt;0.01$)</td>
</tr>
<tr>
<td>Cavallini et al. (2003) [214]</td>
<td>Oligozoospermic men with varicocele were divided into three groups Group 1: grade I ($n=30$), grade II ($n=4$), grade III ($n=5$) received surgery Group 2: grade I ($n=43$), grade II ($n=10$), grade III ($n=8$) received cinnoxicam Group 3: grade III ($n=40$), grade II ($n=8$), grade III ($n=6$) received placebo</td>
<td>Cinnoxicam suppository (30 mg every 4 days for 1 year)</td>
<td>Cinnoxicam significantly improved sperm quality after 2 and 4 months ($P&lt;0.01$) in men with grade I varicocele compared with pretreatment parameters and placebo group Cinnoxicam therapy was associated with higher sperm concentration than was seen after surgery in men with grade I varicocele, but similar improvements in sperm motility and morphology to the surgery group Stopping therapy resulted a decline to the baseline values</td>
</tr>
<tr>
<td>Medical Therapy</td>
<td>Paradiso Galatiioto et al. [218] (2008)</td>
<td>N-acetylcysteine (600 mg), vitamin C (3 mg/kg/day), vitamin E (0.2 mg/kg/day), vitamin A (0.06 IU/kg/day), thiamine (0.4 mg/kg/day), riboflavin (0.1 mg/kg/day), piridoxin (0.2 mg/kg/day), nicotinamide (1 mg/kg/day), pantothenate (0.2 mg/kg/day), biotin (0.04 mg/kg/day), cyanocobalamin (0.1 mg/kg/day), ergocalciferol (8 IU/kg/day), calcium (1 mg/kg/day), magnesium (0.35 mg/kg/day), phosphate (0.45 mg/kg/day), iron (0.2 mg/kg/day), manganese (0.01 mg/kg/day), copper (0.02 mg/kg/day) and zinc (0.01 mg/kg/day) for 90 days</td>
<td>Improved sperm count in 30% of men ($P=0.009$)</td>
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<td><strong>Uncontrolled trials</strong></td>
<td>Kiliç et al. (2005) [217]</td>
<td>Micronized purified flavonoid fraction (1 g/day for 6 months)</td>
<td>Relief of varicocele-associated pain in 87.5% of men; improved spermogram and color Doppler parameters ($P&lt;0.001$)</td>
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<td>Takihara et al. (1987) [219]</td>
<td>Zinc sulphate (440 mg daily for 60 days to 2 years)</td>
<td>Significant increase in sperm motility at 2 and 12 months of therapy ($P&lt;0.05$)</td>
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<td></td>
<td>Yan et al. (2004) (220)</td>
<td>Jingling (dose NR)§</td>
<td>Semen parameters and pregnancy rate improved in 76.6% of men ($P&lt;0.01$); superoxide dismutase and zinc levels increased; cadmium levels reduced ($P&lt;0.01$)</td>
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</table>
a subsequent study by the same group, a 1 year course of cinnoxicam, improved the semen quality of men with low-grade varicocele [214]. Taken together, these results support the rationale of impaired fertility caused by elevated oxidative stress in men with varicocele, and the beneficial effect of improving the antioxidant defense system by exogenous antioxidant administration.

Chinese medicine exhibiting antioxidant activity has also been explored as therapeutic alternatives to surgery in animal and human studies. *Qiangjing*, a herbal medicine that was administered to rats with experimental varicocele, was found to increase glutathione peroxidase and reduce malondialdehyde in the epididymal fluid [215]. Semi-synthetic forms of bioflavonoid—a plant pigment that imparts color to flowers and displays anti-inflammatory and antioxidant properties—have also been used in men with varicocele. In one study, Zampieri et al. [216] administered 1000 mg/day of *O*-beta-hydroxyethylrutoside in a cyclical 3-month on/off therapy for 1 year to 36 infertile men with subclinical left-sided varicocele. The authors observed a slowed progression of varicocele in treated patients compared with 95 patients with subclinical varicocele who did not receive the bioflavonoid. The patients in the untreated group failed to demonstrate any protective effects against testicular growth arrest. Kiliç et al. [217] used micronized flavonoid supplements to relieve pain in normozoospermic men with varicocele and found that sperm motility was markedly improved.

Few human studies have compared antioxidant or anti-inflammatory therapy either alone of combined with surgical varicocele repair, as shown in Table 5.1. In one study, Cavallini et al. [214] showed superiority of varicocele repair in comparison with non-steroidal anti-inflammatory cinnoxicam (30 mg, suppositories used every 4 days for 12 months) to improve semen quality, especially when applied to high-grade varicoceles. In one study by Paradiso Galatioto et al. [218], the association of N-acetyl cyteine (NAC) 600 mg to a combination of vitamins and minerals (Vitamin C 3 mg/kg/day, vitamin E 0.2 mg/kg/day, vitamin A 0.06 IU/kg/day, thiamine 0.4 mg/kg/day, riboxavin 0.1 mg/kg/day, piridoxin 0.2 mg/kg/day, nicotinamide 1 mg/kg/day, pantothenate 0.2 mg/kg/day, biotin 0.04 mg/kg/day, cyanocobalamin 0.1 mg/kg/day, ergocalciferol 8 IU/kg/day, calcium 1 mg/kg/day, magnesium 0.35 mg/kg/day, phosphate 0.45 mg/kg/day, iron 0.2 mg/kg/day, manganese 0.01 mg/kg/day, copper 0.02 mg/kg/day, zinc 0.01 mg/kg/day) was able to improve sperm count in men with persistent oligozoospermia following varicocele embolization, but no effects were observed on pregnancy rates at 1-year follow-up. Contrary results were achieved by Takihara et al. [219] in a uncontrolled study with zinc sulphate therapy (440 mg for 60 days). The authors of this aforementioned study reported that not only sperm motility but also pregnancy rates were improved after varicocelectomy. Similarly, Yan et al. [220] reported increases in both seminal parameters, including reduction of oxidative stress, and pregnancy rates in 30 infertile men who received the Chinese medicine *Jingling*, which is a herbal derived substance exhibiting antioxidant effects, after surgical varicocele repair.

Despite the potential advantages of oral antioxidant/anti-inflammatory agents to varicocele patients, a definitive conclusion of its indication cannot be drawn at the present time. Most published studies have inadequate design and lack controls,
which prompts an urgent need for well-designed trials. For the time being, it is sound to assume that antioxidant therapy will continue to be prescribed by urologists treating men with infertility issues with and without varicocele, despite the lack of firm evidence supporting its routine prescription [221].

**Surgical Treatment**

The principle of surgical treatment is the interruption of the spermatic vein continuity, thus shielding the testis from the harmful effect of venous reflux or high volume venous blood flow, and therefore restore or improve testicular function.

**Patient Selection**

Current recommendations suggest that treatment should be offered for couples with documented infertility whose male partner has a clinically palpable varicocele and abnormal semen analysis. Given the diagnosis of such condition is mainly clinical, a detailed medical history and physical examination must be taken, and prognostic factors identified. Physical examination with the patient standing in a warm room is the preferred diagnostic method, as discussed in Chap. 4. When physical examination is either inconclusive or equivocal, such as in cases of low-grade varicocele and in men with a history of previous scrotal surgery, concomitant hydrocele or obesity, imaging studies may be recommended [184, 222].

Pre-operative workup should include hormone profile testing particularly, follicle stimulating hormone (FSH) and testosterone level. Testicular volume should be assessed using a measurement instrument such as the Prader orchidometer or a pachymeter [4]. At least two semen analyses must be obtained and evaluated according to the World Health Organization guidelines [223].

Infertile men undergoing varicocele repair for large varicoceles are more likely to show—sperm parameters improvement [224]. On the other hand, reduced pre-operative testicular volume, elevated serum FSH levels, diminished testosterone concentrations and subclinical varicocele are negative predictors for fertility improvement after surgery [89, 203, 225–229].

Men with clinical varicoceles presenting with azoospermia may be candidates for surgical repair. In such cases, genetic evaluation including Giemsa karyotyping and polymerase chain Yq microdeletion screening for AZFa, AZFb and AZFc regions are recommended. A testis biopsy (open or percutaneous) may be obtained to assess testicular histology, which has been shown to be the only valid prognostic factor for restoration of spermatogenesis [230, 231]. The benefit of varicocelectomy in azoospermic men with genetic abnormalities is doubtful and should be carefully balanced. The same caution is valid for patients with atrophic testes and/or history of cryptorchidism, testicular trauma, orchitis, systemic or hormonal dysfunc-
tion because varicocele in such cases may not be the cause of infertility but merely coincidental.

As for all restorative surgical procedures in male infertility, the evaluation of the female partner’s reproductive potential is recommended before an intervention is indicated, and the alternatives to varicocele repair fully disclosed.

**Surgical Techniques**

The aim of surgical treatment of varicocele to infertile men is to offer the highest improvement in the male fertility status with low complication rates. Because the estimation of natural pregnancy after treatment is difficult to ascertain due to a variety of factors, including the lack of a uniform post-treatment follow-up interval and female factor parameters such as age and reproductive health, the ultimate treatment goal is to improve the male fertility potential regardless of the method to be used for conception (unassisted or 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.

**Anesthesia**

Anesthesia for varicocelectomy may be carried out using local, regional or general type, according solely with the surgeon and patient’s preferences. It is our preference to perform microsurgical subinguinal varicocele repair using short-acting propofol intravenous anesthesia associated with the blockage of the spermatic cord using 10 mL of a 2% lidocaine hydrochloride in an outpatient basis [230, 232].

**Techniques**

Both open (with or without magnification) and laparoscopic approaches are the surgical methods for varicocele treatment. The high retroperitoneal and laparoscopic approaches are performed for internal spermatic vein ligation while the inguinal and subinguinal approaches allow the ligation of the internal and external spermatic and cremasteric veins that may contribute to the varicocele [34, 232].

*Open Retroperitoneal* High open retroperitoneal varicocele ligation involves incision medial to the anterior superior iliac spine at the level of the internal inguinal ring, as shown in Fig. 5.1. The external oblique muscle is split, the internal oblique muscle is retracted and the peritoneum is teased away. Exposure of the internal spermatic artery and vein is carried out retroperitoneally near the ureter. At this level, only one or two internal spermatic veins are seen, but the internal spermatic artery may not be easy to identify. The veins are ligated near to the point of drainage into the left renal vein. As shown in Fig. 2.1a, neither the parallel inguinal and retro-
peritoneal collateral veins that exit the testis and bypass the retroperitoneal area of ligation nor the cremasteric vein can be identified in the retroperitoneal approach. It is believed that these collaterals cause recurrence of varicocele, as noted by the high recurrence rate after retroperitoneal open varicocele ligation. The surgical approach on the right side may be more difficult because the right testicular vein drains in the inferior vena cava, as shown in Fig. 2.1b.

Laparoscopic Laparoscopic varicocelectomy is essentially a retroperitoneal approach using high magnification. The spermatic artery and the lymphatics are easily identified and spared. The collateral veins can also be clipped or coagulated. However, the external pudendal vein, a common cause of varicocele recurrence, is not accessible (see Fig. 2.1a). This shortcoming of laparoscopic varicocelectomy leads to a recurrence rate of approximately 5% [233]. Laparoscopy varicocele repair is more invasive, costly and it is associated with higher complication rates than open procedures [233–235].

Inguinal and Subinguinal The classic approach in inguinal varicocelectomy involves an incision over the inguinal canal, opening of the external oblique aponeurosis and isolation of the spermatic cord, as shown in Fig. 5.1. The internal spermatic veins are dissected and ligated. An attempt is made to identify and spare the testicular artery and lymphatics. The external spermatic veins running parallel to the spermatic cord or perforating the floor of the inguinal canal are identified and ligated. Although the internal and external spermatic veins can be identified

**Fig. 5.1** Incision sites used for subinguinal, inguinal and retroperitoneal open surgical varicocele repair. In the subinguinal approach, a transverse incision is made just below the level of the external inguinal ring. An oblique incision is made along the axis between the anterior superior iliac spine and the pubic tubercle for the inguinal approach. In the retroperitoneal approach, a transverse incision is made medial to the anterior superior iliac spine. (Reprint with permission from Esteves [232])
macroscopically, the use of magnification facilitates identification and preservation of internal spermatic artery and lymphatics, which may prevent testicular atrophy and hydrocele formation, respectively [236]. Microsurgical varicocelectomy either using inguinal or subinguinal approaches has been considered the best method for varicocele repair [34, 232, 237]. Nevertheless, these procedures requires more skill as compared to other surgical modalities because a higher number of internal spermatic vein channels and smaller-diameter arteries are seen at the level of the inguinal canal. As such, it is important for the urologist who opts to treat varicocele using microsurgery to obtain appropriate training. It is also important to have adequate microsurgical instruments and a binocular operating microscope with foot-control zoom magnification because loupe-magnification is insufficient for proper identification of testicular arteries and lymphatics. 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. Our preferred method is the testicular artery and lymphatic-sparing subinguinal microsurgical repair, as shown in Fig. 5.2 [34, 230, 232, 237, 238]. Briefly, a 2.5 cm skin incision is made over the

![Microsurgical Subinguinal Varicocele Repair](image-url)

**Fig. 5.2** Illustration depicting a left subinguinal microsurgical varicocelectomy. A 2 cm transversal skin incision is made immediately below the external inguinal ring. The muscle layers and the inguinal canal are not violated. The spermatic cord is exteriorized and the cremasteric veins are identified and ligated (a). In panel B, the spermatic cord was dissected to allow the identification of the testicular artery (blue vesselloop), dilated varicose veins (red vesselloops), and lymphatics (blue cotton sutures). While testicular artery and lymphatic channels are preserved, dilated veins are ligated with non-absorbable sutures and transected (c). (Adapted with permission from Esteves and Miyaoka R. Surgical Treatment for Male Infertility. In: Parekattil SJ, Agarwal A (Eds). Male Infertility: Contemporary Clinical Approaches, Andrology, ART & Antioxidants. Springer, New York, 1st ed. 2012, pp. 55–78)
external inguinal ring. The subcutaneous tissue is separated until the spermatic cord is exposed. The cord is elevated with a Babcock clamp and the posterior cremasteric veins are ligated and transected. A Penrose drain is placed behind the cord without tension. The cremasteric fascia is then opened to expose the cord structures and the dissection proceeds using the operating microscope with magnification ranging from 6 to 16×. Dilated cremasteric veins within the fascia are ligated and transected. Lymphatics and arteries are visually identified and preserved. Whenever needed, the cord structures are sprayed with papaverine hydrochloride to increase the arterial beat and ease identification of testicular arteries. Alternatively, an intraoperative vascular Doppler flow detector can be used to identify and spare arteries [239]. All dilated veins of the spermatic cord are identified, tagged with vessel loops, then ligated using non-absorbable sutures and transected. Vasal veins are ligated only if they exceed 2 mm in diameter. Sclerosis of small veins is not used.

**Postoperative Follow-Up**

Postoperative care usually includes local dressing and scrotal supporter for 48–72 h and 1 week, respectively. Scrotal ice packing is always recommended to control local edema for the first 48 postoperative hours. Patients are counseled to restrain from physical activity and sexual intercourse for 2–3 weeks. Oral analgesics usually suffice to control postoperative pain. Postoperative follow-up aims to evaluate improvement in semen parameters, complications and pregnancy outcome. Semen analysis should be performed every 3 months until the semen parameters stabilize or pregnancy occurs.

Results of surgical varicocele repair. In a recent systematic review comparing different surgical modalities to treat varicocele for male infertility [233], it was concluded that open microsurgical inguinal or subinguinal varicocelectomy techniques resulted in higher rate of natural pregnancy and fewer recurrences and postoperative complications than laparoscopic, radiologic embolization and macroscopic inguinal or retroperitoneal varicocelectomy techniques, as shown in Table 5.2. Hydrocele formation is the most common complication of varicocelectomy, with the incidence ranging from 0 to 10%. The lowest and highest reported hydrocele formation rates are seen with the microsurgical and high retroperitoneal methods, respectively. Recurrence rates, which range from 0 to 35%, are also technique-dependent. Acciden-

**Table 5.2** Comparison of post-operative recurrence, hydrocele formation and natural pregnancy rates among the surgical modalities for treatment of infertile males with varicocele

<table>
<thead>
<tr>
<th>Technique</th>
<th>Recurrence (%)</th>
<th>Hydrocele formation (%)</th>
<th>Natural pregnancy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Open retroperitoneal</td>
<td>7–35</td>
<td>6–10</td>
<td>25–55</td>
</tr>
<tr>
<td>Laparoscopic</td>
<td>2–7</td>
<td>0–9</td>
<td>14–42</td>
</tr>
<tr>
<td>Macroscopic inguinal</td>
<td>0–37</td>
<td>7</td>
<td>34–39</td>
</tr>
<tr>
<td>Microscopic (inguinal or subinguinal)</td>
<td>0–0.3</td>
<td>0–1.6</td>
<td>33–56</td>
</tr>
</tbody>
</table>

Values are expressed as a range
tal testicular artery ligation during microsurgical varicocelectomy has been reported to be about 1%, and it may cause testicular atrophy. It has been recently demonstrated that use of intraoperative vascular Doppler during microsurgical varicocelectomy allowed more arterial branches to be preserved and more internal spermatic veins to be ligated [239].

**Key Points**

- Medical therapy, including antioxidants and anti-inflammatory agents have been utilized to treat symptomatic men with varicocele and infertility in men with varicocele with variable success. A definitive conclusion of its indication cannot be drawn at the present time because most published studies have inadequate design and lack controls.
- Varicoceles are surgically treated either by open (with or without magnification) or laparoscopic approaches. The principle of the surgery is the occlusion of the dilated veins of the pampiniform plexus. The high retroperitoneal and laparoscopic approaches are performed for internal spermatic vein ligation while the inguinal and subinguinal approaches allow the ligation of the internal and external spermatic and cremasteric veins that may contribute to the varicocele.
- Open microsurgical inguinal or subinguinal varicocelectomy techniques result in higher rate of natural pregnancy and fewer recurrences and postoperative complications than laparoscopic, radiologic embolization and macroscopic inguinal or retroperitoneal varicocelectomy techniques.
- The aim of surgical treatment of varicocele in infertility is to offer a chance to completely or partially restore the male fertility status with lower complication rates. The ultimate treatment goal is to increase the likelihood of establishing a pregnancy irrespective of the method of conception, i.e., natural or assisted.