**Name of journal: World Journal of Meta-Analysis**

**ESPS Manuscript NO: 7787**

**Columns: REVIEW**

Varicocele: How this condition and its management affect men's health

Baazeem A. Varicocele and Men’s Health

Abdulaziz Baazeem

**Abdulaziz Baazeem,** Department of Surgery, Umm Al-Qura University, Makkah 24382, Saudi Arabia

**Author contributions:** Baazeem A solely contributed to this paper.

**Correspondence to: Dr. Abdulaziz Baazeem MD, FRCS(C), FECSM, Assistant Professor** of Urology, Department of Surgery, Umm Al-Qura University, PO Box 7607, Makkah 24382, Saudi Arabia. theurologist@gmail.com

**Telephone:** +966-1252-81189 **Fax:** +966-1252-70000-4125

**Received:** November 29, 2013 **Revised:** January 21, 2014

**Accepted: February 18, 2014**

**Published online:**

**Abstract**

Varicocele is a relatively common condition that can impact men’s health in various ways. Unfortunately, its prevalence and the availability of various different methods of repairing it might lead to the administration of unnecessary treatment. An understanding of the various ways that this condition can impact men’s health is necessary in order to manage it appropriately. At present, there is substantial evidence to support varicocele repair in men who present with infertility, abnormal semen parameters, clinical varicocele and a normal female partner (or one with a potentially correctable abnormality). Varicocele repair appears to improve seminal fluid quality and might improve pregnancy rates. It might also have a role in managing men with non-obstructive azoospermia. Varicocele can also be a cause of scrotal pain that is usually of a dull character. Varicocele repair is an effective method of managing this type of pain, especially once proper measures have been taken to exclude other possible causes of orchalgia. Conservative measures are generally not effective in managing varicocele-related scrotal pain. There is growing evidence to suggest that varicocele repair might have a role in improving the serum testosterone level in men with hypogonadism, especially in the subfertile population. Well-designed prospective studies are needed to support the utilization of varicocele repair in managing these patients as well as in preventing testicular dysfunction on a prophylactic basis.

© 2014 Baishideng Publishing Group Co., Limited. All rights reserved.

**Key words:** Varicocele; Varicocelectomy; Infertility; Azoospermia; Pain

**Core tip:** The prevalence of varicocele and the availability of various different methods of repairing it might lead to the administration of unnecessary treatment. An understanding of the various ways that this condition can impact men’s health is necessary in order to manage it appropriately. An overview of this disorder is given, together with different indications of treating it in adult men.

Baazeem A. Varicocele: How this condition and its management affect men's health.

**Available from: URL:**

**DOI:**

**INTRODUCTION**

A varicocele is a tortuous spermatic vein that is abnormally dilated. It is a relatively common condition. A clinical varicocele has been described to be palpable in around 15% of all men[1].However, in a more recent study, it was found to be present in 24.2% of healthy young men[2].Furthermore, its prevalence has been described to be as high as about 35% of men who present for assessment of infertility[3].Varicocele repair is currently considered to be the most commonly performed procedure to treat male infertility. This relatively high prevalence of varicocele, coupled with the availability of a multitude of relatively low-risk methods of repair might lead to over-treating it.[4] The aim of this review is to examine how varicocele can affect men’s health and the theories on how it exerts these effects. In addition, the potential outcomes of repairing varicocele for various indications will be assessed.

**Associations and etiology**

Varicocele occurs predominantly on the left side. Several factors have been proposed to explain this disproportion in laterality, including more frequent occurrence on the left side of absent or incompetent spermatic vein valves, a longer spermatic vein, retro-aortic left renal veins, the nut-cracker phenomenon (the compression of the left renal vein between the superior mesenteric artery and the aorta) as well as the insertion of the spermatic vein into the higher pressure left renal vein[5-8].

There appears to be an association between varicocele and conditions such as peripheral varicose veins and coronary artery ectasia, suggesting a diffuse vascular abnormality[9,10].Its prevalence appears to rise with advancing age, increasing by about 10% with each decade[11].The prevalence in the elderly was described to reach 42% in a study that involved men with a mean age of 60.7 years[12].A higher prevalence of varicocele has been described in first-degree relatives, suggesting a hereditary component as well[13,14].Varicocele also appears to be positively correlated with adolescent gynecomastia and inversely related to the Body Mass Index (BMI)[15, 16].

**DIAGNOSIS AND CLASSIFICATION**

Varicocele is typically diagnosed by physical examination. The classical description of it is that of a “bag of worms” when the patient is examined in the standing position, in a warm room. Varicoceles are usually classified according to the Dubin system[17]: Grade I: Palpable distension of intrascrotal veins only with the Valsalva maneuver; Grade II: Palpable, but not visible, distension of the intrascrotal veins without the valsalva maneuver; Grade III: Distention of intrascrotal veins that is visible through the scrotal skin

“Grade 0” is sometimes used to classify subclinical varicoceles that are not palpable, but rather are detected using ancillary diagnostic measures (*e.g.,* ultrasonography, venography, thermography and scintigraphy). Ultrasonography is one of the most popular of these ancillary measures and there are described systems of classifying varicocele using it[18].Scintigraphy and thermography have been suggested as methods that are comparable or even superior to ultrasonography in detecting varicocele[19, 20].With the exception of venography, these techniques are considered simple and non-invasive.

 Advocates of using ultrasonography contend that it helps avoid the risk of subjectivity that is associated with physical examination. However, no clear cut-off measurements have been agreed upon to establish the diagnosis of varicocele on ultrasonography[21]. Therefore, while it continues to be used widely to diagnose and classify varicocele, and is certainly indicated in cases were physical examination is inconclusive, some authorities caution that such procedures that detect subclinical varicoceles should be avoided[22].

**Indications for repair**

Varicocele repair in adults has been described to address several conditions. These include: (1) Male infertility, including non-obstructive azoospermia (NOA); (2) Pain; and (3) Low serum testosterone.

**Varicocele and Male factor infertility**

In 1992, the World Health Organization (WHO) assessed the influence of varicocele in more than nine thousand men who presented as partners in couples consulting for infertility across 24 countries[23].A clinically palpable varicocele was detected in 11.7% of men with normal semen analyses, compared to 25.4% in those with abnormal analyses. Varicocele was associated with a reduced left testicular size and semen count. Interestingly, there was a wide range of varicocele detection among different centers (6%-47%), with the presence of a urologist or andrologist helping increase the detection rate. Also noteworthy is that the spontaneous pregnancy rate was not significantly different between men with and without varicocele.

The exact mechanism by which varicocele may negatively affect male fertility potential remains undetermined. However, several mechanisms that may contribute to this detrimental effect have been proposed. These include: (1) Reflux of toxic adrenal and renal metabolites through the renal vein[24]; (2) Elevated intrascrotal temperatures[25]; (3) Elevated spermatozoal oxygen species[26,27]; (4) Local hypoxia and ischemia[28,29]; (5) Sperm chromosome aneuploidy[30]; and (6) Sperm nuclear DNA damage[27,31].

Varicocele repair can be considered when a man has a clinically palpable varicocele, abnormal semen analysis results and his female partner has normal (or correctable) fertility potential[22].The role of varicocele repair in managing men with male factor infertility has been a matter of heavy debate. A meta-analysis of randomized controlled trials (RCTs) to assess the influence of varicocele repair on pregnancy rates concluded that the treatment of varicocele in managing men from couples with unexplained infertility cannot be recommended[32].This study was criticized for including men with subclinical varicocele as well as those with normal semen parameters. Several meta-analyses proposed a contrary perspective. A meta-analysis of the same RCTs in the above-mentioned study, after exclusion of those including men with subclinical varicocele and/or normal semen parameters showed that pregnancy rates in the treatment group were significantly higher in the treatment group on “as-treated” analysis[33].A meta-analysis that included RCTs and observational studies, that were scored for bias, concluded that surgical repair of varicocele significantly improved the odds of spontaneous pregnancy[34]. An update of the aforementioned Chocrane Collaboration meta-analysis found pregnancy outcomes that favored varicocele treatment over observation[35].These results were even more pronounced when men with subclinical varicocele or normal semen parameters were excluded from analysis. However, the authors emphasized, as in most of these meta-analyses, the heterogeneity of the studies involved. Finally, a meta-analysis of RCTs involving only surgical repair of varicocele compared to observation found an even higher odds ratio (OR) of 4.15 favoring surgical repair after excluding men with normal semen parameters and subclinical varicocele[36].

Although pregnancy is the obvious desired principal outcome when managing men with infertility, there is a disadvantage to using it when assessing the effect of therapeutic interventions involving the male partner. This outcome inherently involves potential female partner factors that might impact the observed effect of treatment. Therefore, the role of semen analysis as a predictor of male fertility potential is probably just as important as that of pregnancy rates when assessing the benefit of varicocele repair on male fertility. There is evidence to suggest an improvement in sperm concentration, motility and morphology following varicocele repair[37-39]. According to a meta-analysis involving 22 prospective studies that addressed sperm concentration before and after varicocele repair, the combined post-repair improvement in sperm concentration postoperatively was 12.32 × 106 sperm/mL[40].Furthermore, in the same study, the combined improvements in total and progressive sperm motility were 10.86% and 10.67%, respectively. All of these findings were statistically significant. Significant improvements in seminal oxidative stress and sperm DNA damage following varicocele repair were also found in this meta-analysis. Sperm ultramorphology has also been shown to improve following surgical varicocele repair in a non-randomized prospective controlled study[41].

A review that compared the various methods of varicocele repair in more than 5000 patients concluded that the microsurgical approaches (subinguinal or inguinal) offer better outcomes in terms of pregnancy, recurrence and complication rates[42]. Retrograde radiographic-guided embolization or sclerotherapy carries with it several potential advantages. It minimizes the risk of post-procedure hydrocele formation and of testicular artery injury and subsequent testicular atrophy. There is also no risk of injury to the vas deferens and the recovery time is rapid. However, it also comes with its unique set of potential complications, including those related to intravenous contrast media administration, puncture site complications (*e.g.,* hematoma formation) and coil migration. A recent review of 158 patients who underwent varicocele embolization revealed an 18.9% failure rate when treating bilateral varicocele[43].This relatively high failure rate was mainly due to technical difficulties when treating the right side. This brought the authors to suggest a microsurgical approach when treating bilateral varicocele. However, embolization remains a suitable option when treating left-sided varicocele.

**VARICOCELE AND NON-OBSTRUCTIVE AZOOSPERMIA:**

Patients with non-obstructive azoospermia (NOA) represent possibly the most challenging patients with male factor infertility in terms of achieving pregnancy. They might require sperm retrieval procedures which, if successful, would be followed by assisted reproductive techniques (ARTs), such as in vitro fertilization (IVF)/intracytoplasmic sperm injection (ICSI). The aim when managing these patients would be to help achieve a return of sperm to the ejaculate with enough quality that would help achieve the goal of spontaneous pregnancy or improve semen quality in order to “upgrade” the couple to be considered for intra-uterine insemination (IUI), or help the male partner avoid sperm retrieval procedures by restoring sperm in the ejaculate for use in IVF/ICSI, or at least potentially improve spermatogenesis to a degree that might hopefully improve the success of future sperm retrieval attempts.

The return of sperm to the ejaculate following varicocele repair has been described in several series of men with a clinical varicocele and NOA, with success rates ranging between 20.8%-56.2%[44-48].A meta-analysis that involved 233 patients from 11 retrospective studies found that motile sperm returned to the ejaculate in 39.1% following varicocele repair[49].Fourteen patients (6%) achieved spontaneous pregnancy and 10 (4%) IVF/ICSI pregnancies. After an initial return of sperm to the ejaculate, 11 patients (4.6%) reverted back to azoospermia within 2-6 mo. When available, the histopathological picture can help predict the outcomes of varicocele repair, with hypospermatogenesis and maturation arrest associated with significantly higher success rates than Sertoli-cell-only. Several studies have found an increase in sperm retrieval procedure success rates following varicocele repair when compared to proceeding with retrieval attempts without repairing the varicocele[50-52]. However, a retrospective study that included men with subclinical varicocele showed similar sperm retrieval rates between the two groups[48].

**PROPHYLACTIC VARICOCELECTOMY**

Progressive, duration-dependant, deterioration in semen quality has been described in infertile men with a clinical varicocele who originally had normal semen parameters and were followed over time, albeit in a small-sized study[53].Furthermore, the incidence of varicocele in men with secondary infertility is significantly higher than those with primary infertility, suggesting that prior fertility does not offer protection from possible varicocele-induced impairment of testicular function[54].This potentially deleterious effect of varicocele on male fertility, coupled with the relative safety and low complication rates of modern microsurgical procedures, has led to consideration by some of varicocele repair in men with normal semen parameters and a clinically palpable varicocele, especially if there is ipsilateral testicular hypotrophy. However, there is not enough evidence to strongly support the use of this theory in the clinical setting. There are no RCTs or prospective studies that have been conducted to address the use of prophylactic varicocelectomy in this setting.

**VARICOCELE AND SCROTAL PAIN:**

Varicocele has been reported as a cause of scrotal pain[55].The character of pain has been described as dull and one that is aggravated by exercise and straining[56].It has been estimated to occur in 2%–14% of men with varicocele[57]. Conservative measures that have been traditionally used to manage varicocele-associated pain include utilizing scrotal support, non-steroidal anti-inflammatory analgesics and limiting physical activity which are impractical and of limited benefit[56,58].In a study of 140 patients who were treated conservatively for up to 8 wk, only 5 patients had an improvement in symptoms, and even those 5 patients eventually opted for surgical management for recurrent pain[58].A low success rate (0.04%) for conservative management was also seen in another study when it was attempted for a mean of 4 wk[59].There is some evidence, based on the experience with a small number of patients, to suggest a possible benefit from the venotonic drug micronized purified flavonoid fraction in reducing varicocele-associated pain in men with normal sperm concentration[60].

Studies that assess the effect of varicocele repair on pain are relatively few and the vast majority are retrospective studies. Most of these series showed a relatively high rate of post-procedure complete or partial pain resolution, ranging between 76.7%-94.8%[56-59,61-67].However, one of the earliest studies to address this issue described failure to resolve pain in 52% of the patients who underwent high ligation[55].To date, there are no studies that assess the effect of subclinical varicocele repair on scrotal pain.

Other potential causes of scrotal pain should be ruled out prior to treating varicocele in order to help reduce treatment failures. The character of pain experienced by the patient can provide a clue to the cause of the patient’s symptoms. Atypical pain properties, such as sharp pain might be due to causes other than varicocele. Indeed, the presence of a dull aching or dragging pain has been reported as a predictor of treatment success, while sharp or throbbing pain was associated with a higher rate of recurrence, persistence or even worsening of symptoms[62].In another study, post-operative success was significantly and independently higher in patients who were operated on for dull rather than “dragging” or “aching” pain and for mild or moderate rather than severe pain (≥ 7 on the 11-point numeric rating scale) [68].Yaman *et al*[59]  suggested that the grade of a painful varicocele might also influence the outcome of repair, as did Kim *et al* [57].However, this association was not observed in other studies[56,62,66,68].Further support for the notion that a cause other than varicocele might be a reason behind treatment failure is noticed in the finding that failure rates were significantly higher in patients with a duration of symptoms of less than 3 mo[66].But this association with symptom duration was not supported by findings in other studies[56,68].In one of the few prospective studies that assessed varicocele repair for pain management, neither preoperative varicocele grade, pain character or duration of symptoms were predictive of post-operative outcomes[64].In this study, among the patients who were available for their 3-month post-operative assessment, 95% stated that they would recommend the procedure for their relatives.

Various techniques have been reported when treating varicocele for pain, including high ligation, subinguinal and inguinal microsurgery, conventional inguinal (Ivanissevich), scrotal and laparoscopic approaches, as well as percutaneous interventional radiological procedures such as sclerotherapy or embolization with reasonable results. Microsurgical approaches might have a higher post-operative pain resolution rate[69].No difference in outcome was detected in a study that compared non-microsurgical approaches (inguinal, subinguinal and high ligation)[62].

Failure of varicocele resolution and its recurrence after treatment have been reported with varying rates. This might be a cause of persistent or recurrent scrotal pain following treatment[57]. Chawla *et al*[70] reported a series of 11 patients who presented with recurrent varicocele and pain and were treated with microsurgical subinguinal varicocelectomy. Ten of the patients had complete or partial resolution of pain and nine of them stated that they would undergo the same procedure for their presenting complaint.

**VARICOCELE AND HYPOGONADISM:**

Although the potential effect of varicocele and varicocelectomy on serum testosterone levels is one that has been studied in the past, this topic is garnering increasing interest more recently[71].A possible dysfunction in testosterone production in infertile men has been described[72]. Tanrikut *et al*[73] described significantly lower serum testosterone levels in men with varicocele than a control group of men undergoing vasectomy reversal.The effect of varicocele repair on serum testosterone levels has been debated. Some studies showed no increase in serum testosterone levels following repair[74-76].However, the baseline serum testosterone level in these studies was normal or somewhat higher, making it difficult to document an improvement following repair.

 A meta-analysis involving 9 studies (one prospective and 8 retrospective observational studies) in which men with clinical varicocele underwent surgical repair showed a significant post-operative increase in serum testosterone from baseline by 97.48 ng/dL[77].In a retrospective review of men who underwent microsurgical subinguinal varicocelectomy, men who had a baseline serum testosterone level of 400 ng/dL or less had a significant increase in their levels after surgery in all age groups[78]. In an interesting non-randomized prospective study, a hundred infertile men with clinical varicocele and low serum testosterone (< 280 ng/dL) who underwent microsurgical subinguinal repair were compared to a control group of hypogonadal varicocele patients who opted for ART utilization[79]. While there was a slight decrease in serum testosterone level in the control group at follow-up, the varicocelectomy group showed a significant increase in serum testosterone. Indeed, 78% of the men in the treatment arm went on to reach normal serum testosterone levels at follow-up, compared to only 16% in the control group. Similarly, serum tesosterone and erectile function significantly improved from baseline after microsurgical subinguinal varicocelectomy in hypogonadal (serum testosterone < 300 ng/dL) infertile men with clinical varicocele when compared to a similar control group who refused surgery and opted for ARTs[80]. It is worth emphasizing that most of these studies involved men who also complained of infertility and may not represent the general population. Findings in this group of patients would be difficult to extrapolate to the general population.

**REFERENCES**

1 **Clarke BG**. Incidence of varicocele in normal men and among men of different ages. *JAMA* 1966; **198**: 1121-1122 [PMID: 5953394 DOI: 10.1001/jama.1966.03110230137039]

2 **Soylemez H**, Atar M, Ali Sancaktutar A, Bozkurt Y, Penbegul N. Varicocele among healthy young men in Turkey; prevalence and relationship with body mass index. *Int Braz J Urol* 2012; **38**: 116-121 [PMID: 22397773 DOI: 10.1590/S1677-55382012000100016]

3 **Greenberg SH**, Lipshultz LI, Wein AJ. Experience with 425 subfertile male patients. *J Urol* 1978; **119**: 507-510 [PMID: 25971]

4 **Zargooshi J**. Sperm count and sperm motility in incidental high-grade varicocele. *Fertil Steril* 2007; **88**: 1470-1473 [PMID: 17451695 DOI: 10.1016/j.fertnstert.2007.01.016]

5 **Karazincir S**, Balci A, Görür S, Sumbas H, Kiper AN. Incidence of the retroaortic left renal vein in patients with varicocele. *J Ultrasound Med* 2007; **26**: 601-604 [PMID: 17460002]

6 **Wishahi MM**. Detailed anatomy of the internal spermatic vein and the ovarian vein. Human cadaver study and operative spermatic venography: clinical aspects. *J Urol* 1991; **145**: 780-784 [PMID: 2005700]

7 **Beinart C**, Sniderman KW, Tamura S, Vaughan ED, Sos TA. Left renal vein to inferior vena cava pressure relationship in humans. *J Urol* 1982; **127**: 1070-1071 [PMID: 7087011]

8 **Carl P**, Stark L, Ouzoun N, Reindl P. Venous pressure in idiopathic varicocele. *Eur Urol* 1993; **24**: 214-220 [PMID: 8375442]

9 **Kiliç S**, Aksoy Y, Sincer I, Oğuz F, Erdil N, Yetkin E. Cardiovascular evaluation of young patients with varicocele. *Fertil Steril* 2007; **88**: 369-373 [PMID: 17307174 DOI: 10.1016/j.fertnstert.2006.11.119]

10 **Yetkin E**, Kilic S, Acikgoz N, Ergin H, Aksoy Y, Sincer I, Aktürk E, Beytur A, Sivri N, Turhan H. Increased prevalence of varicocele in patients with coronary artery ectasia. *Coron Artery Dis* 2005; **16**: 261-264 [PMID: 16000882 DOI: 10.1097/00019501-200508000-00001]

11 **Levinger U**, Gornish M, Gat Y, Bachar GN. Is varicocele prevalence increasing with age? *Andrologia* 2007; **39**: 77-80 [PMID: 17683466 DOI: 10.1111/j.1439-0272.2007.00766.x]

12 **Canales BK**, Zapzalka DM, Ercole CJ, Carey P, Haus E, Aeppli D, Pryor JL. Prevalence and effect of varicoceles in an elderly population. *Urology* 2005; **66**: 627-631 [PMID: 16140091 DOI: 10.1016/j.urology.2005.03.062]

13 **Mokhtari G**, Pourreza F, Falahatkar S, Kamran AN, Jamali M. Comparison of prevalence of varicocele in first-degree relatives of patients with varicocele and male kidney donors. *Urology* 2008; **71**: 666-668 [PMID: 18279919 DOI: 10.1016/j.urology.2007.11.116]

14 **Raman JD**, Walmsley K, Goldstein M. Inheritance of varicoceles. *Urology* 2005; **65**: 1186-1189 [PMID: 15913726 DOI: 10.1016/j.urology.2004.12.057]

15 **Nielsen ME**, Zderic S, Freedland SJ, Jarow JP. Insight on pathogenesis of varicoceles: relationship of varicocele and body mass index. *Urology* 2006; **68**: 392-396 [PMID: 16904459 DOI: 10.1016/j.urology.2006.02.005]

16 **Kumanov P**, Deepinder F, Robeva R, Tomova A, Li J, Agarwal A. Relationship of adolescent gynecomastia with varicocele and somatometric parameters: a cross-sectional study in 6200 healthy boys. *J Adolesc Health* 2007; **41**: 126-131 [PMID: 17659215 DOI: 10.1016/j.jadohealth.2007.03.010]

17 **Dubin L**, Amelar RD. Varicocele size and results of varicocelectomy in selected subfertile men with varicocele. *Fertil Steril* 1970; **21**: 606-609 [PMID: 5433164]

18 **Hirsh AV**, Cameron KM, Tyler JP, Simpson J, Pryor JP. The Doppler assessment of varicoceles and internal spermatic vein reflux in infertile men. *Br J Urol* 1980; **52**: 50-56 [PMID: 7426951 DOI: 10.1111/j.1464-410X.1980.tb02919.x]

19 **Gat Y**, Bachar GN, Zukerman Z, Belenky A, Gorenish M. Physical examination may miss the diagnosis of bilateral varicocele: a comparative study of 4 diagnostic modalities. *J Urol* 2004; **172**: 1414-1417 [PMID: 15371858 DOI: 10.1097/01.ju.0000138540.57137.5f]

20 **Ortapamuk H**, Tekdogan UY, Naldoken S, Bulut S, Atan A. Hemodynamic evaluation of varicocele: the role of scrotal scintigraphy and Doppler ultrasonography in the prediction of postoperative seminal improvement. *Ann Nucl Med* 2005; **19**: 529-534 [PMID: 16363616 DOI: 10.1007/BF02985044]

21 **Lee J**, Binsaleh S, Lo K, Jarvi K. Varicoceles: the diagnostic dilemma. *J Androl* ; **29**: 143-146 [PMID: 18077824 DOI: 10.2164/jandrol.107.003467]

22 Report on varicocele and infertility. *Fertil Steril* 2008; **90**: S247-S249 [PMID: 19007639 DOI: 10.1016/j.fertnstert.2008.08.050]

23 The influence of varicocele on parameters of fertility in a large group of men presenting to infertility clinics. World Health Organization. *Fertil Steril* 1992; **57**: 1289-1293 [PMID: 1601152]

24 **Comhaire F**, Vermeulen A. Varicocele sterility: cortisol and catecholamines. *Fertil Steril* 1974; **25**: 88-95 [PMID: 4810205]

25 **Zorgniotti AW**, Macleod J. Studies in temperature, human semen quality, and varicocele. *Fertil Steril* 1973; **24**: 854-863 [PMID: 4742006]

26 **Hendin BN**, Kolettis PN, Sharma RK, Thomas AJ, Agarwal A. Varicocele is associated with elevated spermatozoal reactive oxygen species production and diminished seminal plasma antioxidant capacity. *J Urol* 1999; **161**: 1831-1834 [PMID: 10332447 DOI: 10.1016/S0022-5347(05)68818-0]

27 **Smith R**, Kaune H, Parodi D, Madariaga M, Rios R, Morales I, Castro A. Increased sperm DNA damage in patients with varicocele: relationship with seminal oxidative stress. *Hum Reprod* 2006; **21**: 986-993 [PMID: 16361286 DOI: 10.1093/humrep/dei429]

28 **Donohue RE**, Brown JS. Blood gases and pH determinations in the internal spermatic veins of subfertile men with varicocele. *Fertil Steril* 1969; **20**: 365-369 [PMID: 5767279]

29 **Chakraborty J**, Hikim AP, Jhunjhunwala JS. Stagnation of blood in the microcirculatory vessels in the testes of men with varicocele. *J Androl* 1985; **6**: 117-126 [PMID: 3988623]

30 **Baccetti BM**, Bruni E, Capitani S, Collodel G, Mancini S, Piomboni P, Moretti E. Studies on varicocele III: ultrastructural sperm evaluation and 18, X and Y aneuploidies. *J Androl* 2006; **27**: 94-101 [PMID: 16400084 DOI: 10.2164/jandrol.05081]

31 **Saleh RA**, Agarwal A, Sharma RK, Said TM, Sikka SC, Thomas AJ. Evaluation of nuclear DNA damage in spermatozoa from infertile men with varicocele. *Fertil Steril* 2003; **80**: 1431-1436 [PMID: 14667879 DOI: 10.1016/S0015-0282(03)02211-8]

32 **Evers JH**, Collins J, Clarke J. Surgery or embolisation for varicoceles in subfertile men. *Cochrane Database Syst Rev* 2009; : CD000479 [PMID: 19160180]

33 **Ficarra V**, Cerruto MA, Liguori G, Mazzoni G, Minucci S, Tracia A, Gentile V. Treatment of varicocele in subfertile men: The Cochrane Review--a contrary opinion. *Eur Urol* 2006; **49**: 258-263 [PMID: 16426727 DOI: 10.1016/j.eururo.2005.11.023]

34 **Marmar JL**, Agarwal A, Prabakaran S, Agarwal R, Short RA, Benoff S, Thomas AJ. Reassessing the value of varicocelectomy as a treatment for male subfertility with a new meta-analysis. *Fertil Steril* 2007; **88**: 639-648 [PMID: 17434508 DOI: 10.1016/j.fertnstert.2006.12.008]

35 **Kroese AC**, de Lange NM, Collins J, Evers JL. Surgery or embolization for varicoceles in subfertile men. *Cochrane Database Syst Rev* 2012; **10**: CD000479 [PMID: 23076888]

36 **Kim KH**, Lee JY, Kang DH, Lee H, Seo JT, Cho KS. Impact of surgical varicocele repair on pregnancy rate in subfertile men with clinical varicocele and impaired semen quality: a meta-analysis of randomized clinical trials. *Korean J Urol* 2013; **54**: 703-709 [PMID: 24175046 DOI: 10.4111/kju.2013.54.10.703]

37 **Kibar Y**, Seckin B, Erduran D. The effects of subinguinal varicocelectomy on Kruger morphology and semen parameters. *J Urol* 2002; **168**: 1071-1074 [PMID: 12187225 DOI: 10.1016/S0022-5347(05)64577-6]

38 **Madgar I**, Weissenberg R, Lunenfeld B, Karasik A, Goldwasser B. Controlled trial of high spermatic vein ligation for varicocele in infertile men. *Fertil Steril* 1995; **63**: 120-124 [PMID: 7805900]

39 **Boman JM**, Libman J, Zini A. Microsurgical varicocelectomy for isolated asthenospermia. *J Urol* 2008; **180**: 2129-2132 [PMID: 18804226 DOI: 10.1016/j.juro.2008.07.046]

40 **Baazeem A**, Belzile E, Ciampi A, Dohle G, Jarvi K, Salonia A, Weidner W, Zini A. Varicocele and male factor infertility treatment: a new meta-analysis and review of the role of varicocele repair. *Eur Urol* 2011; **60**: 796-808 [PMID: 21733620 DOI: 10.1016/j.eururo.2011.06.018]

41 **Reichart M**, Eltes F, Soffer Y, Zigenreich E, Yogev L, Bartoov B. Sperm ultramorphology as a pathophysiological indicator of spermatogenesis in males suffering from varicocele. *Andrologia* 2000; **32**: 139-145 [PMID: 10863968 DOI: 10.1046/j.1439-0272.2000.00355.x]

42 **Diegidio P**, Jhaveri JK, Ghannam S, Pinkhasov R, Shabsigh R, Fisch H. Review of current varicocelectomy techniques and their outcomes. *BJU Int* 2011; **108**: 1157-1172 [PMID: 21435155 DOI: 10.1111/j.1464-410X.2010.09959.x]

43 **Cassidy D**, Jarvi K, Grober E, Lo K. Varicocele surgery or embolization: Which is better? *Can Urol Assoc J* 2012; **6**: 266-268 [PMID: 23093537]

44 **Kadioglu A**, Tefekli A, Cayan S, Kandirali E, Erdemir F, Tellaloglu S. Microsurgical inguinal varicocele repair in azoospermic men. *Urology* 2001; **57**: 328-333 [PMID: 11182347 DOI: 10.1016/S0090-4295(00)00908-0]

45 **Gat Y**, Bachar GN, Everaert K, Levinger U, Gornish M. Induction of spermatogenesis in azoospermic men after internal spermatic vein embolization for the treatment of varicocele. *Hum Reprod* 2005; **20**: 1013-1017 [PMID: 15618245 DOI: 10.1093/humrep/deh706]

46 **Matthews GJ**, Matthews ED, Goldstein M. Induction of spermatogenesis and achievement of pregnancy after microsurgical varicocelectomy in men with azoospermia and severe oligoasthenospermia. *Fertil Steril* 1998; **70**: 71-75 [PMID: 9660424 DOI: 10.1016/S0015-0282(98)00108-3]

47 **Pasqualotto FF**, Sobreiro BP, Hallak J, Pasqualotto EB, Lucon AM. Induction of spermatogenesis in azoospermic men after varicocelectomy repair: an update. *Fertil Steril* 2006; **85**: 635-639 [PMID: 16500331 DOI: 10.1016/j.fertnstert.2005.08.043]

48 **Schlegel PN**, Kaufmann J. Role of varicocelectomy in men with nonobstructive azoospermia. *Fertil Steril* 2004; **81**: 1585-1588 [PMID: 15193481 DOI: 10.1016/j.fertnstert.2003.10.036]

49 **Weedin JW**, Khera M, Lipshultz LI. Varicocele repair in patients with nonobstructive azoospermia: a meta-analysis. *J Urol* 2010; **183**: 2309-2315 [PMID: 20400156 DOI: 10.1016/j.juro.2010.02.012]

50 **Zampieri N**, Bosaro L, Costantini C, Zaffagnini S, Zampieri G. Relationship between testicular sperm extraction and varicocelectomy in patients with varicocele and nonobstructive azoospermia. *Urology* 2013; **82**: 74-77 [PMID: 23680120 DOI: 10.1016/j.urology.2013.03.037]

51 **Inci K**, Hascicek M, Kara O, Dikmen AV, Gürgan T, Ergen A. Sperm retrieval and intracytoplasmic sperm injection in men with nonobstructive azoospermia, and treated and untreated varicocele. *J Urol* 2009; **182**: 1500-1505 [PMID: 19683732 DOI: 10.1016/j.juro.2009.06.028]

52 **Haydardedeoglu B**, Turunc T, Kilicdag EB, Gul U, Bagis T. The effect of prior varicocelectomy in patients with nonobstructive azoospermia on intracytoplasmic sperm injection outcomes: a retrospective pilot study. *Urology* 2010; **75**: 83-86 [PMID: 19913887 DOI: 10.1016/j.urology.2009.09.023]

53 **Chehval MJ**, Purcell MH. Deterioration of semen parameters over time in men with untreated varicocele: evidence of progressive testicular damage. *Fertil Steril* 1992; **57**: 174-177 [PMID: 1730313]

54 **Gorelick JI**, Goldstein M. Loss of fertility in men with varicocele. *Fertil Steril* 1993; **59**: 613-616 [PMID: 8458466]

55 **Biggers RD**, Soderdahl DW. The painful varicocele. *Mil Med* 1981; **146**: 440-441 [PMID: 6787479]

56 **Peterson AC**, Lance RS, Ruiz HE. Outcomes of varicocele ligation done for pain. *J Urol* 1998; **159**: 1565-1567 [PMID: 9554356 DOI: 10.1097/00005392-199805000-00043]

57 **Kim SO**, Jung H, Park K. Outcomes of microsurgical subinguinal varicocelectomy for painful varicoceles. *J Androl* 2012; **33**: 872-875 [PMID: 22174387 DOI: 10.2164/jandrol.111.014993]

58 **Yeniyol CO**, Tuna A, Yener H, Zeyrek N, Tilki A. High ligation to treat pain in varicocele. *Int Urol Nephrol* 2003; **35**: 65-68 [PMID: 14620287 DOI: 10.1023/A: 1025972601213]

59 **Yaman O**, Ozdiler E, Anafarta K, Göğüş O. Effect of microsurgical subinguinal varicocele ligation to treat pain. *Urology* 2000; **55**: 107-108 [PMID: 10654904 DOI: 10.1016/S0090-4295(99)00374-X]

60 **Söylemez H**, Kiliç S, Atar M, Penbegül N, Sancaktutar AA, Bozkurt Y. Effects of micronised purified flavonoid fraction on pain, semen analysis and scrotal color Doppler parameters in patients with painful varicocele; results of a randomized placebo-controlled study. *Int Urol Nephrol* 2012; **44**: 401-408 [PMID: 21805085 DOI: 10.1007/s11255-011-0038-3]

61 **Lee HJ**, Cheon SH, Ji YH, Moon KH, Kim KS, Park S, Park S. Clinical characteristics and surgical outcomes in adolescents and adults with varicocele. *Korean J Urol* 2011; **52**: 489-493 [PMID: 21860771 DOI: 10.4111/kju.2011.52.7.489]

62 **Al-Buheissi SZ**, Patel HR, Wazait HD, Miller RA, Nathan S. Predictors of success in surgical ligation of painful varicocele. *Urol Int* 2007; **79**: 33-36 [PMID: 17627165 DOI: 10.1159/000102910]

63 **Park HJ**, Lee SS, Park NC. Predictors of pain resolution after varicocelectomy for painful varicocele. *Asian J Androl* 2011; **13**: 754-758 [PMID: 21102471 DOI: 10.1038/aja.2010.87]

64 **Karademir K**, Senkul T, Baykal K, Ateş F, Işeri C, Erden D. Evaluation of the role of varicocelectomy including external spermatic vein ligation in patients with scrotal pain. *Int J Urol* 2005; **12**: 484-488 [PMID: 15948749 DOI: 10.1111/j.1442-2042.2005.01063.x]

65 **Ribé N**, Manasia P, Sàrquella J, Grimaldi S, Pomerol JM. Clinical follow-up after subinguinal varicocele ligation to treat pain. *Arch Ital Urol Androl* 2002; **74**: 51-53 [PMID: 12161934]

66 **Altunoluk B**, Soylemez H, Efe E, Malkoc O. Duration of preoperative scrotal pain may predict the success of microsurgical varicocelectomy. *Int Braz J Urol* 2010; **36**: 55-59 [PMID: 20202236 DOI: 10.1590/S1677-55382010000100009]

67 **Maghraby HA**. Laparoscopic varicocelectomy for painful varicoceles: merits and outcomes. *J Endourol* 2002; **16**: 107-110 [PMID: 11962551 DOI: 10.1089/089277902753619627]

68 **Kim HT**, Song PH, Moon KH. Microsurgical ligation for painful varicocele: effectiveness and predictors of pain resolution. *Yonsei Med J* 2012; **53**: 145-150 [PMID: 22187245 DOI: 10.3349/ymj.2012.53.1.145]

69 **Shridharani A**, Lockwood G, Sandlow J. Varicocelectomy in the treatment of testicular pain: a review. *Curr Opin Urol* 2012; **22**: 499-506 [PMID: 22965318 DOI: 10.1097/MOU.0b013e328358f69f]

70 **Chawla A**, Kulkarni G, Kamal K, Zini A. Microsurgical varicocelectomy for recurrent or persistent varicoceles associated with orchalgia. *Urology* 2005; **66**: 1072-1074 [PMID: 16286126 DOI: 10.1016/j.urology.2005.05.052]

71 **Su LM**, Goldstein M, Schlegel PN. The effect of varicocelectomy on serum testosterone levels in infertile men with varicoceles. *J Urol* 1995; **154**: 1752-1755 [PMID: 7563339 DOI: 10.1016/S0022-5347(01)66776-4]

72 **Weiss DB**, Rodriguez-Rigau LJ, Smith KD, Steinberger E. Leydig cell function in oligospermic men with varicocele. *J Urol* 1978; **120**: 427-430 [PMID: 702664]

73 **Tanrikut C**, Goldstein M, Rosoff JS, Lee RK, Nelson CJ, Mulhall JP. Varicocele as a risk factor for androgen deficiency and effect of repair. *BJU Int* 2011; **108**: 1480-1484 [PMID: 21435152 DOI: 10.1111/j.1464-410X.2010.10030.x]

74 **Di Bisceglie C**, Bertagna A, Baldi M, Lanfranco F, Tagliabue M, Gazzera C, Gandini G, Manieri C. Varicocele sclerotherapy improves serum inhibin B levels and seminal parameters. *Int J Androl* 2007; **30**: 531-536 [PMID: 17376219 DOI: 10.1111/j.1365-2605.2007.00747.x]

75 **Rodriguez Peña M**, Alescio L, Russell A, Lourenco da Cunha J, Alzu G, Bardoneschi E. Predictors of improved seminal parameters and fertility after varicocele repair in young adults. *Andrologia* 2009; **41**: 277-281 [PMID: 19737275 DOI: 10.1111/j.1439-0272.2009.00919.x]

76 **Zheng YQ**, Gao X, Li ZJ, Yu YL, Zhang ZG, Li W. Efficacy of bilateral and left varicocelectomy in infertile men with left clinical and right subclinical varicoceles: a comparative study. *Urology* 2009; **73**: 1236-1240 [PMID: 19371942 DOI: 10.1016/j.urology.2008.11.050]

77 **Li F**, Yue H, Yamaguchi K, Okada K, Matsushita K, Ando M, Chiba K, Fujisawa M. Effect of surgical repair on testosterone production in infertile men with varicocele: a meta-analysis. *Int J Urol* 2012; **19**: 149-154 [PMID: 22059526 DOI: 10.1111/j.1442-2042.2011.02890.x]

78 **Hsiao W**, Rosoff JS, Pale JR, Greenwood EA, Goldstein M. Older age is associated with similar improvements in semen parameters and testosterone after subinguinal microsurgical varicocelectomy. *J Urol* 2011; **185**: 620-625 [PMID: 21168880 DOI: 10.1016/j.juro.2010.09.114]

79 **Sathya Srini V**, Belur Veerachari S. Does varicocelectomy improve gonadal function in men with hypogonadism and infertility? Analysis of a prospective study. *Int J Endocrinol* 2011; **2011**: 916380 [PMID: 22190930]

80 **Zohdy W**, Ghazi S, Arafa M. Impact of varicocelectomy on gonadal and erectile functions in men with hypogonadism and infertility. *J Sex Med* 2011; **8**: 885-893 [PMID: 20722780 DOI: 10.1111/j.1743-6109.2010.01974.x]

**P-Reviewers:** FaintuchS, Kulis T **S-Editor:** Wen LL  **L-Editor:**  **E-Editor:**