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Safety and efficacy of acupuncture for varicocele-induced male infertility: a systematic review protocol

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ABSTRACT

Introduction Varicocele (VC) is a common clinical disease in andrology. Among a number of ways for VC treatment, surgery is the most common one, but the measurable benefit of surgical repair was slight. A growing exploration of complementary therapies has been conducted in clinical research on acupuncture for VC, but there is no relevant systematic review and meta-analysis to assess the efficacy and safety of acupuncture for VC.

Methods and analysis All relevant publications published from database inception through August 2022 will be searched in three English-language databases (Embase, CENTRAL, MEDLINE) and four Chinese-language databases (China National Knowledge Infrastructure, China Science and Technology Journal Database, Chinese Biomedical Literature Database and Wanfang Data). Randomised controlled trials in English and Chinese concerned with acupuncture for patients with VC will be included. The input clinical data will be processed by the Review Manager software (RevMan). The literature will be appraised with the Cochrane Collaboration risk of bias tool. The Grading of Recommendations Assessment, Development and Evaluation system (GRADE system) will be used to evaluate the quality of evidence.

Ethics and dissemination This study is a secondary study based on clinical studies so it does not relate to any individual patient information or infringe the rights of participants. Hence no ethical approval is required. The results will be reported in peer-reviewed journals or disseminated at relevant conferences.

PROSPERO registration number CRD42022316005.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The data extraction and management, assessment of risk of bias sections will be carried out by two or more researchers independently.
⇒ Multiple types of acupuncture therapies may increase the risk of heterogeneity, this will be further explored in the subgroup analysis.
⇒ The exclusion of studies published in languages other than English and Chinese may result in limitations related to publication bias.

INTRODUCTION

Varicocele (VC) is regarded as the abnormal dilation of the internal testicular vein and pampiniform venus plexus within the spermatic cord, which is one of the most common causes of male infertility. It accounts for 35% of patients with primary infertility and up to 81% with secondary infertility.[1 2]

In addition to affecting fertility, VC may also cause symptoms such as enlargement of the scrotum, swelling, dull aching pain and cramping in the lower abdomen, which can be exacerbated by prolonged standing, walking or heavy physical work. Several theories explain the role of VC in terms of pathophysiology, including altered testicular blood flow, increased temperature, oxidative stress, development of antisperm antibodies, reflux of adrenal and gonadal hormone metabolites and alterations in the hypothalamic–pituitary–gonadal axis.[3] The precise mechanism by which VC potentially affects spermatogenesis remains unclear,[4 5] but some recent documents allow for the conclusion that VC can injure fertility by affecting testicular histology, sperm function, semen quality and reproductive hormones.[5–7] Currently surgery remains the main treatment option for VC, which includes surgical treatment and interventional treatment. Surgical treatments for VC include the traditional inguinal or high retroperitoneal ligation, laparoscopic repair and microsurgical repair via an inguinal or subinguinal incision and embolisation.[8–10] However there is some possibility of recurrence and complications with different surgical techniques (table 1); besides, the measurable benefit of surgical repair was slight according to the Cochrane review.[11] The recurrence rate varies depending on the technique of VC repair, ranging from 0% to 35% and the incidence of postoperative hydrocele formation varies from 0% to 29%.[12 13] For patients with mild symptoms, conventional medications such as clomiphene citrate and levocarnitine

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Table 1 Postoperative spontaneous pregnancy rates, recurrence rates, hydrocele formation rates among the techniques

Technique	Spontaneous pregnancy rate (%)	Recurrence rate (%)	Hydrocele formation rate (%)	Advantages	Disadvantages
Palomo[28–31]	37.69	14.97	8.24	Good for pain relief, shorter surgery time.	Highest recurrence rate and hydrocele formation rate.
Laparoscopic varicocelectomy[28 30–32]	30.07	4.3	2.84	Suitable for bilateral varicocele and recurrent varicocele. Less invasive surgery, faster recovery and fewer complications.	May cause damage to intestines and blood vessels. Requires high level of surgical skills, anaesthesia and is more expensive.
Radiologic embolisation[28 31 33 34]	33.2	12.7	0–12	Less damage and faster recovery. No accidental injury to the internal spermatic artery.	Potential risks of radiation exposure, misplaced embolism and displacement of embolic agents.
Microscopic inguinal (Ivanissevich)[28 35–37]	36	2.63	7.3	More effective in improving sperm concentration.	Increased chance of arterial and lymphatic vessel damage, requiring more surgical skill.
Microsurgical varicocelectomy[10 28 32 38 39]	41.97	1.05–2.60	0.44	Relatively good efficacy and low recurrence and complication rates. Better control of post-operative pain.	Less than 40% of infertile couples achieve spontaneous pregnancy after microsurgical varicocelectomy, and most of them still require additional interventions such as ARTs.
Subinguinal microsurgical varicocelectomy[1 34 37]	42.8	0.8	0.6	The 'gold standard' for the treatment of varicocele.	Most patients still need the help of advanced ARTs, such as the costly ICSI.

ARTs, advanced assisted reproductive technologies; ICSI, intracytoplasmic sperm injection.

are often used. These drugs mainly work by promoting sperm maturation, improving semen quality and dilating blood vessels. However, it cannot fundamentally address the anatomical basis of the disease, so the overall outcome is often unsatisfactory.[14–17]

Therefore, there is an urgent need to develop complementary therapies. Known as a safe therapy with low side effects, acupuncture has already been widely used in the treatment of VC. The incidence of adverse reactions to acupuncture is significantly lower than other drugs or other conventional medical procedures under the same conditions, which is one of the significant advantages of acupuncture.[18] Specific acupuncture methods that have been used clinically include manual acupuncture, electroacupuncture, needle warming moxibustion and needle pricking and so on. Acupuncture treatment for VC may have a therapeutic effect on VC by lowering the scrotal skin temperature of patients,[19] and inhibiting patient's oxidative stress process,[20 21] and adjust patients' serum testosterone (T) and follicle stimulating hormone (FSH) by stimulating the sympathetic trunk and regulating endocrine and gonadal axis function.[22–25] Also, it can increase the blood flow and vasodilatory elasticity of spermatic veins in patients with VC infertility, improve the blood circulation and relieve VC by lowering the viscosity of blood flow[25] and mitigate muscle tissue spasm and ischaemia by regulating pathologically tight muscles. It may touch on the anatomical basis of the disease, more specific and deeper mechanisms of action need to be explored in further studies.

At present, there are a certain number of documents on acupuncture treatment of VC. These experimental and theoretical studies on the improvement of treating VC by acupuncture can provide preliminary evidence that acupuncture is effective in treating VC-induced male infertility, but there still lacks a systematic review. Therefore, this paper is to evaluate the safety and efficacy of acupuncture in the treatment of VC.

METHODS AND ANALYSIS

Study registration

The protocol was registered on PROSPERO (https://www.crd.york.ac.uk/PROSPERO/), and the registration number is: CRD42022316005.

Criteria for included studies in this review

Type of studies

Inclusion criteria are as follows: (1) randomised controlled trials; and (2) articles published in the English or Chinese will be included.

Exclusion criteria are as follows: (1) case reports, animal studies; (2) meta-analysis and systematic review, narrative review, overviews and conference abstract; and (3) studies in which the required data were unavailable.

Types of participants

Taking into account the fact that the childbearing age of men varies in different countries and regions, we have adjusted the age limit appropriately. In addition,

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unilateral VC is more common in clinical practice, but there are also a small number of patients with bilateral VC, both with similar pathogenesis. To fully demonstrate the efficacy and safety of acupuncture as a complementary alternative therapy in improving the condition of patients with VC, randomised controlled trials (RCTs) containing a small number of patients with bilateral VC will also be included. To ensure the practicability of the study, we allow for deviations within reasonable limits. If an included RCT partially deviates from the criteria below, we will decide whether to include the RCT after panel discussion.

Inclusion criteria are as follows: (1) male participants diagnosed with VC infertility, regardless of restriction on racial origin; (2) male participants aged 18–55 years old; and (3) the couple in question having at least 12 months of infertility.

Exclusion criteria are as follows: (1) patients who had received acupuncture treatment or had taken Chinese herbal medicine in the previous 3 months; (2) bleeding disorders, genetic abnormalities, chronic inflammatory diseases and severe chronic diseases including cancer; (3) female partner documented with infertility (including ovulatory, uterine, cervical dysfunction and pathological changes); and (4) the presence of other causes of infertility in male patients.

Types of interventions

Acupuncture therapy includes body acupuncture (manual/electric acupuncture), warm acupuncture, auricular acupuncture, acupoint catgut embedding, needle picking and other acupuncture techniques, where needles are used to penetrate acupoints, pain points or trigger points and so on. However, non-penetrating forms of stimulation of acupuncture points, such as moxibustion, acupressure or transcutaneous electrical nerve stimulation, will be excluded. Acupuncture combined with other positive treatments will also be included. There is no restriction on the frequency of treatment.

The included comparators or control groups will be considered as follows:

1. Acupuncture versus sham acupuncture.
2. Acupuncture versus surgical control.
3. Acupuncture versus conventional medication/herbal medicine.
4. Acupuncture plus positive treatment versus positive treatment alone.

Studies aiming to compare different acupuncture points, different methods of acupoint stimulation and different frequencies and durations of treatment were excluded.

Types of outcome measures

Primary outcome

A routine semen analysis (semen volume, sperm density, sperm viability, sperm deformity rate, sperm DNA fragmentation index)

Secondary outcomes

1. The pregnancy rates.
2. The maximum internal diameter of spermatic vein (D_R) during calm breathing under colour Doppler ultrasound.
3. The reproductive endocrine hormone level (FSH, luteinizing hormone (LH), prolactin (PRL) and others).
4. Adverse events such as local haematomas, haematuria and syncope induced by acupuncture interventions.

Search strategy

All relevant publications published from database inception through August 2022 will be searched in three English-language databases: Embase, CENTRAL (The Cochrane Central Register of Controlled Trials), MEDLINE and four Chinese-language databases: China National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (VIP Database), Chinese Biomedical Literature Database (SinoMed) and Wanfang Data. We will search the above databases using a combination of MeSH (Medical Subject Headings) terms and free words, using the following terms: (1) Varicocele; (2) Acupuncture therapy, acupuncture, electro-acupuncture, manual acupuncture, auricular acupuncture, needle picking, warm acupuncture and acupoint; and (3) Randomized controlled trial, RCT, randomized controlled, clinical trial. Languages are limited to English and Chinese. The researchers will then screen these literatures with EndNote software. The same Chinese search strategy, properly tuned where needed, will also be used for searches in Chinese databases. For small registries or registries with limited search tools, searches in the registry will be based on disease terms only. The recommended full search strategy for MEDLINE is shown in table 2. Full search strategies for all databases, registers and websites are shown in online supplemental file 1.

Searching other resources

The unpublished or ongoing RCTs will be searched on the International Clinical Trials Registry Platform, ClinicalTrials.gov, PROSPERO and Chinese Clinical Registry (CHICTR). In addition, relevant references will also be searched.

Data collection and analysis

Literature screening and data extraction

First, in accordance with the search strategy, two independent researchers will import the acquired articles into Endnote and read through the titles and abstracts to identify articles that will meet the filtering criteria. Then the included literature will be read in full by two researchers for a further screening. In case of a discrepancy of opinion between the two researchers, a group discussion will be held and an experienced researcher and corresponding author will be invited to arbitrate the final decision. Articles that have been excluded will be marked with the reason of their exclusion. The flow chart and selection process are shown in figure 1.

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Table 2 Medline (via Ovid) search strategy

PI(CO)S	#	Search
Population	#1	exp Varicocele/
	#2	exp Infertility, Male/
	#3	((male* or men) adj7 (infertil* or subfertil*)).tw.
	#4	(Varicocele* or Varicocoele*).tw.
	#5	(varicocele or varicocoele or varicoceles or spermatic vein varicosity or varicose spermatic veins or pampinocele or spermophlebectasia or cirsocele or varicole or ramex).tw.
	#6	or/1–5
Intervention	#7	exp Acupuncture/
	#8	exp Acupuncture Therapy/ or exp Electroacupuncture/ or acupuncture needle.mp.
	#9	exp Acupressure/
	#10	acupoint.mp. or exp Acupuncture Points/
	#11	needle pricking.mp.
	#12	warming needle moxibustion.mp.
	#13	(acupunctur* or acupressur*).tw.
	#14	(electrostimulat* or electroacupunctur*).tw.
	#15	(acupoint* or acupotom*).tw.
	#16	(auriculotherap* or auriculoacupunct*).tw.
	#17	(needl* or needl* prick*).tw.
	#18	body needl*.tw.
	#19	dry needl*.tw.
	#20	warm* needle moxibustion.mp. or warm* acupuncture.tw.(mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms)
	#21	meridian*.tw.
	#22	qi.tw.
	#23	or/7–22
Study design	#24	randomized controlled trial.pt.
	#25	controlled clinical trial.pt.
	#26	randomized.ab.
	#27	placebo.ab.
	#28	drug therapy.fs.
	#29	clinical trials as topic.sh.
	#39	randomly.ab.
	#31	trial.ti.
	#32	24 or 25 or 26 or 27 or 28 or 29 or 30 or 31
	#33	exp animals/ not humans.sh.
	#34	32 not 33
	#35	6 and 23 and 34

The following data will be extracted separately by the two researchers, including: title, first author, year of publication, country, participants (number, age), random method, blinding, treatment group, control group, follow-up, outcome, results and adverse events and so on. If there is any missing detail or unclear aspect of the presentation, the researchers will contact the corresponding author to make the supplementation or clarification accordingly.

Assessment of risk of bias

Two researchers will independently assess the risk of bias for this study using the latest version of the Cochrane risk-of-bias tool 2 (ROB 2)[26] and will assess bias from five domains (randomisation process, deviations from intended interventions, missing outcome data, measurement of the outcome and selection of the reported results). The risk of bias will be judged (low/high/some concerns) and the overall risk of bias of the assessment results will be predicated. The differences between the two researchers will be eventually resolved by the corresponding author. If a RCT was judged to have 'some concerns' about the risk of bias in three or more domains, it will be excluded from the systematic review due to the high risk of bias.

Measures of treatment effect

Data will be entered into RevMan software (RevMan V.5.4) for synthesis and statistical analysis. 95% CI for relative risk will be used for analysis of dichotomous variables (eg, adverse events for acupuncture interventions). Continuous variables (eg, semen analysis results, reproductive endocrine hormone level) will be analysed using the 95% CI for weighted mean difference (WMD) or standard mean difference.

The issue concerning the unit of analysis

As for the issue concerning the unit of analysis,[27] if the included RCTs have more than two intervention groups that are relevant to the systematic review/ particular meta-analysis, then the multiple groups qualified for experimental or comparator interventions will be combined to form a single pairwise comparison to overcome the unit of analysis error. For dichotomous results, both the sample size and the number of people who had an adverse event can be summed across groups. For continuous results, means and SD can be combined using the method described.

Dealing with missing data

As noted above, if there is any essential data missing, our researcher will contact the corresponding author to fill in the blanks. If the missing data are not recoverable, then sensitivity analysis will be conducted to address the issue of missing data. This will be elaborated in the discussion section.

Heterogeneity assessment

Heterogeneity assessment of all studies will be performed by RevMan. Statistical heterogeneity between studies will be calculated using I^2 values. To explore potential sources of heterogeneity, sensitivity analysis or subgroup analysis will be used for assessment.

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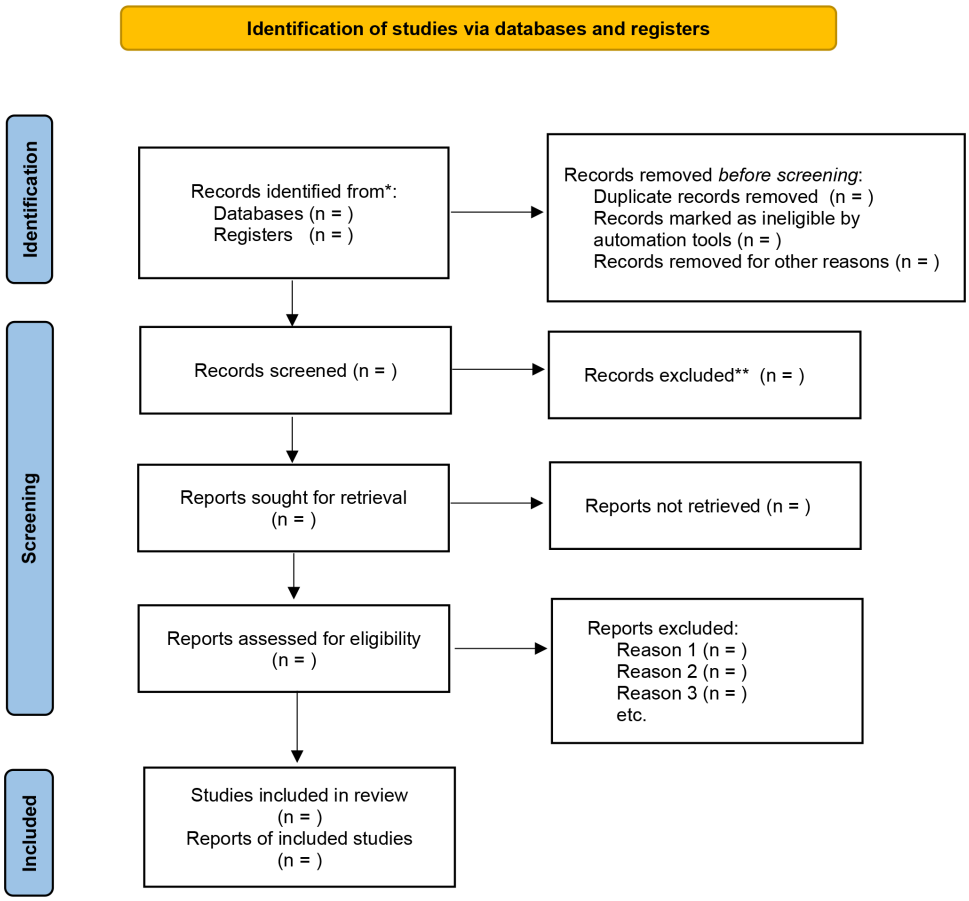

Figure 1 Flow diagram of the trial selection process.

Data synthesis

Based on some preliminary research, we will use the random-effects model for this section. The input clinical data will be processed by the RevMan and the forest plot can be generated by this software to make the presentation of the study results more understandable. The results of the study will be presented in tabular form, including key information on the quality of the evidence, the effect sizes of the interventions and the sum of the available data for all important outcomes for a given comparison.

Subgroup analysis and investigation of heterogeneity

A random effects model will be used since individual RCTs were conducted in different locations and there will be certainly discrepancy across different experimental protocols, and among different groups of patients. Heterogeneity will always be present regardless of the sample size of the study, so we will switch our focus from examining the presence of heterogeneity to assessing the impact of heterogeneity on the meta-analysis. Our researchers will explore the sources of heterogeneity in four dimensions: population, intervention, outcome, study design and implementation, and will explain heterogeneity through subgroup analysis, meta-regression or sensitivity analysis. If sufficient studies are identified, subgroup analyses can be performed among different types of acupuncture methods, as well as different follow-up times, types of controls or intensity of treatment.

Sensitivity analysis

Sensitivity analysis will be applied to assess the robustness of the study results. The specific implementation method will be based on the 'change model analysis' and the 'exclusion of literature on a case-by-case basis'. When using the literature-by-exclusion method, any change in heterogeneity will be observed after the exclusion of each literature, and the change in the value of the combined effect, WMD, RR need to be recorded at the same time. If heterogeneity changes after the exclusion of a piece of literature, then that piece of literature may be the source of the heterogeneity.

Assessment of reporting biases

If the number of studies is more than 10, our researchers will use funnel plots to detect reporting bias; if not, the detection of the reporting bias is infeasible. Our study will try to avoid reporting bias as much as possible by conducting a comprehensive search for studies that meet the inclusion criteria by incorporating unpublished studies and searching the trial registries.

Summary of evidence

Our researchers will use the Grading of Recommendation Assessment, Development and Evaluation (GRADE

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system) to assess the quality of the evidence for the results reported in systematic reviews. The system requires an assessment of the quality of evidence for each individual outcome. The assessment includes limitations in the design and implementation of available studies, suggesting that there is high likelihood of bias, unexplained heterogeneity or inconsistency of results, indirectness of evidence, imprecision of results and high probability of publication biases.

Patient and public involvement

As mentioned, this study is a secondary study based on clinical studies so it does not involve any patient or the public.

DISCUSSION

VC is one of the most common causes of male infertility although it can occur without causing infertility. In mild cases, there may be no obvious clinical symptoms; however, in severe cases, there may be a sensation of swelling or dull pain in the scrotum, which worsens after prolonged standing and exertion and mitigates or disappears after lying down or resting. Considering that some patients with VC may not seek medical help because they have no need for fertility or their discomfort has little impact on their daily lives, our study was limited to recruiting patients with VC-induced infertility. The exact mechanism by which VC may affect spermatogenesis remains obscure,[4] but some recent literature can conclude that VC can affect fertility by influencing testicular histology, sperm function, semen quality and reproductive hormones.[6 7] As all surgical methods have some potential risks of recurrence and complications, non-surgical treatments have attracted the interest of clinicians and acupuncture is increasingly being used to relieve VC. This systematic evaluation will assess evidence from RCTs to demonstrate the effectiveness and safety of acupuncture in the treatment of VC. The aim is to provide more effective and safe treatment options for clinical practice. The potential limitations of this study may have some impact on the results. The exclusion of studies published in languages other than English and Chinese may result in publication bias, and the adoption of multiple types of acupuncture therapies may have the potential to increase the risk of heterogeneity.

Amendments to protocol

To ensure transparency, any change from this protocol will be amended on the PROSPERO database.

Ethics and dissemination

This study is a secondary study based on clinical studies, and thus it is unnecessary to obtain ethical approval. The results will be reported in peer-reviewed journals or disseminated at relevant conferences.

Contributors SW, ZT and GZ participated in the research design. RL, JR and JC developed the search strategies. RL, CW and QL implemented the search strategies and screened data extraction. RL, MS and JD did some statistical analysis. SW conceived the review protocol and drafted the manuscript. Several studies from different opinions were determined by ZT. SW, RL and HS participated in the correction of the manuscript. All authors reviewed the manuscript. All authors read and approved the final version of the manuscript.

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Competing interests None declared.

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REFERENCES

1 Liao B, Liu J, Chen S, *et al*. Efficacy and safety of microsurgical subinguinal varicocelectomy with and without testicular delivery for varicocele patients: a systematic review and meta-analysis. *Urol J* 2019;16:417–26.
2 Gorelick JI, Goldstein M, Jeffrey I. Loss of fertility in men with varicocele. *Fertil Steril* 1993;59:613–6.
3 Elbardisi H, El Ansari W, Majzoub A, *et al*. Does varicocelectomy improve semen in men with azoospermia and clinically palpable varicocele? *Andrologia* 2020;52:e13486.
4 Clavijo RI, Carrasquillo R, Ramasamy R. Varicoceles: prevalence and pathogenesis in adult men. *Fertil Steril* 2017;108:364–9.
5 Fretz PC, Sandlow JI. Varicocele: current concepts in pathophysiology, diagnosis, and treatment. *Urol Clin North Am* 2002;29:921–37.
6 Jensen CFS, Østergren P, Dupree JM, *et al*. Varicocele and male infertility. *Nat Rev Urol* 2017;14:523–33.
7 Damsgaard J, Joensen UN, Carlsen E, *et al*. Varicocele is associated with impaired semen quality and reproductive hormone levels: a study of 7035 healthy young men from six European countries. *Eur Urol* 2016;70:1019–29.
8 Mehta A, Goldstein M. Microsurgical varicocelectomy: a review. *Asian J Androl* 2013;15:56–60.
9 Zhou T, Zhang W, Chen Q, *et al*. Effect of varicocelectomy on testis volume and semen parameters in adolescents: a meta-analysis. *Asian J Androl* 2015;17:1012–6.
10 Wan X, Wang H, Ji Z. Microsurgical varicocelectomy for clinical varicocele: a review for potential new indications. *Andrologia* 2017;49. doi:10.1111/and.12827. [Epub ahead of print: 03 07 2017].
11 Chiba K, Ramasamy R, Lamb DJ, *et al*. The varicocele: diagnostic dilemmas, therapeutic challenges and future perspectives. *Asian J Androl* 2016;18:276–81.
12 Lurvey R, Durbin-Johnson B, Kurzrock EA. Adolescent varicocele: a large multicenter analysis of complications and recurrence in academic programs. *J Pediatr Urol* 2015;11:186.e1–186.e6.
13 Rotker K, Sigman M. Data from: recurrent varicocele. *Asian J Androl* 2016;18:229–33.

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14 Yizhao L, Min L, Ningning C. Current situation and analysis of clinical treatment of varicocele in China. *Chinese Journal of Human Sexuality* 2021;30:23–5.
15 Park HJ, Lee SS, Park NC. Predictors of pain resolution after varicocelectomy for painful varicocele. *Asian J Androl* 2011;13:754–8.
16 Jiwei Y, Yuanjing S. Clinical study on Aescuven forte combined with routine drugs in the treatment of varicocele. *China Pharmacy* 2017;28:3663–6.
17 Kim HJ, Seo JT, Kim KJ, *et al*. Clinical significance of subclinical varicocelectomy in male infertility: systematic review and meta-analysis. *Andrologia* 2016;48:654–61.
18 Franconi G, Manni L, Aloe L, *et al*. Acupuncture in clinical and experimental reproductive medicine: a review. *J Endocrinol Invest* 2011;34:307–11.
19 Siterman S, Eltes F, Schechter L, *et al*. Success of acupuncture treatment in patients with initially low sperm output is associated with a decrease in scrotal skin temperature. *Asian J Androl* 2009;11:200–8.
20 Karna KK, Choi BR, Kim M-J, *et al*. The effect of schisandra chinensis baillon on cross-talk between oxidative stress, endoplasmic reticulum stress, and mitochondrial signaling pathway in testes of varicocele-induced SD rat. *Int J Mol Sci* 2019;20. doi:10.3390/ijms20225785. [Epub ahead of print: 17 Nov 2019].
21 Yu Y-P, Ju W-P, Li Z-G, *et al*. Acupuncture inhibits oxidative stress and rotational behavior in 6-hydroxydopamine lesioned rat. *Brain Res* 2010;1336:58–65.
22 Chang R, Chung PH, Rosenwaks Z. Role of acupuncture in the treatment of female infertility. *Fertil Steril* 2002;78:1149–53.
23 Cho C-L, Esteves SC, Agarwal A. Indications and outcomes of varicocele repair. *Panminerva Med* 2019;61:152–63.
24 Li J, Wu X-K, Zhang J-X. [Acupuncture treatment of oligoasthenozoospermia]. *Zhonghua Nan Ke Xue* 2018;24:86–90.
25 Chen D, He X, Chen Z-M, *et al*. [Effect of needle pricking therapy on rheological indices and efficacy for infertile patients with varicocele]. *Zhongguo Zhong Xi Yi Jie He Za Zhi* 2017;37:326–30.
26 Sterne JAC, Savović J, Page MJ, *et al*. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019;366:l4898.
27 Higgins JP, Eldridge S, Li T. Chapter 23: Including variants on randomized trials. In: Higgins JPT, Thomas J, Chandler J, *et al*, eds. *Cochrane Handbook for systematic reviews of interventions version 63 (updated February 2022)*, 2022.
28 Cayan S, Shavakhabov S, Kadioğlu A. Treatment of palpable varicocele in infertile men: a meta-analysis to define the best technique. *J Androl* 2009;30:33–40.
29 Akkoç A, Aydın C, Topaktaş R, *et al*. Retroperitoneal high ligation versus subinguinal varicocelectomy: effectiveness of two different varicocelectomy techniques on the treatment of painful varicocele. *Andrologia* 2019;51:e13293.
30 Caradonti M. Effect of varicocelectomy on fertility. Indications, techniques and results. *Actas Urol Esp* 2020;44:276–80.
31 Shundong H, Yuming P. Analysis of the clinical efficacy of different surgical procedures for the treatment of varicocele. *The Journal of Practical Medicine* 2009;25:1615–7.
32 Huang Y-feng, Yu-feng H. [Varicocele and male infertility]. *Zhonghua Nan Ke Xue* 2010;16:195–200.
33 Halpern J, Mittal S, Pereira K, *et al*. Percutaneous embolization of varicocele: technique, indications, relative contraindications, and complications. *Asian J Androl* 2016;18:234–8.
34 Yao Y, Hua X. Advances in the study of adolescent varicocele. *Chinese Journal of Pediatric Surgery* 2014;35:619–22.
35 Hopps CV, Lemer ML, Schlegel PN, *et al*. Intraoperative varicocele anatomy: a microscopic study of the inguinal versus subinguinal approach. *J Urol* 2003;170:2366–70.
36 Raman JD, Goldstein M. Intraoperative characterization of arterial vasculature in spermatic cord. *Urology* 2004;64:561–4.
37 Neng-wang Y, Yizhen S, Hua S. Data from: meta analysis to define the best technique for varicocele treatment. *Chinese Journal of Urology* 2013;34:45–9.
38 Ding H, Tian J, Du W, *et al*. Open non-microsurgical, laparoscopic or open microsurgical varicocelectomy for male infertility: a meta-analysis of randomized controlled trials. *BJU Int* 2012;110:1536–42.
39 Baazeem A, Belzile E, Ciampi A, *et al*. Varicocele and male factor infertility treatment: a new meta-analysis and review of the role of varicocele repair. *Eur Urol* 2011;60:796–808.

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