National Institute for Health and Care Excellence

Draft for consultation

# Fertility problems: assessment and treatment

## [X] Treatments for varicocele

*NICE guideline NGXXX*

*Evidence reviews underpinning recommendation 1.4.12 and research recommendation in the NICE guideline*

*September 2025*

*Draft for consultation*

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## Contents

# Treatments for varicocele

## Review question

What is the clinical and cost effectiveness of surgical and radiological treatments for fertility problems associated with varicocele?

### Introduction

Varicocele, an abnormal dilation and distention of veins in the scrotum, is a common cause of male factor fertility problems. The mechanism by which varicocele impair male fertility remains unclear, but detrimental effects have been suggested to include sperm production, sperm quality, development of testicle, and testosterone production. Varicocele is a reversible condition, and various surgical or radiological interventions are available to treat fertility problems associated with varicocele. This review aims to investigate the clinical and cost effectiveness of different surgical and radiological treatments for fertility problems associated with varicocele.

### Summary of the protocol

See Table 1 for a summary of the Population, Intervention, Comparison and Outcome (PICO) characteristics of this review.

**Table 1: Summary of the protocol (PICO table)**

| | |
|---|---|
| **Population** | People with fertility problems associated with varicocele |
| **Intervention** | Radiological interventions:<br>• Varicocele embolization<br>• Sclerotherapy<br><br>Surgical interventions:<br>• Varicocelectomy (microscopic, laparoscopic, open) |
| **Comparison** | • Head-to-head comparisons of different surgical or radiological interventions<br>• No treatment or delayed treatment |
| **Outcome** | **Critical**<br>• Live birth (as defined by study, risk of bias assessments will reflect where this is not defined as a live birth to include a gestational age of ≥20 weeks)<br>• Clinical pregnancy (as defined by study, risk of bias assessments will reflect where this is not defined as an ultrasound scan that has shown at least one foetal heart rate)<br>**Important**<br>• Varicocele recurrence<br>• Adverse events<br>  ○ hydrocele formation<br>  ○ pain<br>  ○ haematoma<br>  ○ infection<br>  ○ testicular atrophy |

For further details see the review protocol in appendix A.

## Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A and the methods document (supplementary document 1).

During the development of this guideline, a Cochrane review was identified which matched the committee's intended PICO (Persad 2021). The committee agreed to include this review and to restrict the search to papers published from 2020 in order to capture and integrate any new evidence. Cochrane's methods are closely aligned to standard NICE methods, and minor deviations (reporting summary of findings tables instead of full GRADE tables, defining primary and secondary outcomes as opposed to critical and important, using random-effect model because of the variation in delivering surgical and radiological treatment (clinical heterogeneity), and assessing the risk of bias in primary studies using version 1 as opposed to version 2) were taken into account by the committee in discussions of the evidence.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

## Effectiveness evidence

### Included studies

One Cochrane review (Persad 2021) including 48 randomised controlled trials (RCTs: Abdel-Meguid 2011; Al Kandari 2007; Al Said 2008; Barbalias 1998; Barry 2012; Bo 1996; Breznik 1993; Bryniarski 2016; Cayan 2000; Chaudhary 2000; Chen 1996; De Rose 2003; Dohle 2010; Fang 2013; Fayez 2010; Gao 2015; Gao 2017; Ghanaie 2012; Gontero 2005; Grasso 2000; Hargreave 1996; Ketabchi 2018a; Ketabchi 2018b; Krause 2002; Madgar 1995; Meng 2017; Min 2011; Nieschlag 1993; Nieschlag 1995/1998; Nilsson 1979; Niu 2017; Pan 2013; Pocek 1999; Pu 2014; Punekar 1999; Qi 2009; Ren 2015; Sautter 2002; Song 2012; Su 2017; Sun 2012; Telkar 2012; Unal 2001; Yamamoto 1996; Yang 2017; Yavetz 1992; Zhang 2015; Zheng 2012), and 1 RCT (Salem 2020) identified by the update search, were included in this review.

Sixteen studies compared surgical or radiological treatment to delayed or no treatment (Abdel-Meguid 2011; Bo 1996; Breznik 1993; De Rose 2003; Dohle 2010; Ghanaie 2012; Grasso 2000; Hargreave 1996; Ketabchi 2018a; Ketabchi 2018b; Krause 2002; Madgar 1995; Nieschlag 1995/1998; Nilsson 1979; Unal 2001; Yamamoto 1996), and 7 studies compared surgical treatment (any) to radiological treatment (Barbalias 1998; Chen 1996; Fayez 2010; Nieschlag 1993; Nieschlag 1995/1998; Sautter 2002; Yavetz 1992). Twenty studies compared microscopic subinguinal surgical treatment to other surgical treatment (Al Kandari 2007; Al Said 2008; Bryniarski 2016; Fang 2013; Gao 2015; Gao 2017; Gontero 2005; Meng 2017; Min 2011; Pan 2013; Pu 2014; Punekar 1999; Qi 2009; Ren 2015; Salem 2020; Song 2012; Su 2017; Yang 2017; Zhang 2015; Zheng 2012), and 1 study compared microscopic inguinal surgical treatment to laparoscopic surgical treatment (Niu 2017). Nine studies compared open inguinal surgical treatment to retroperitoneal surgical treatment (Barbalias 1998; Barry 2012; Cayan 2000; Chaudhary 2000; Fang 2013; Pu 2014; Su 2017; Sun 2012; Telkar 2012), and 1 study compared 2 types of radiological treatment (sclerotherapy relative to varicocele embolisation) (Pocek 1999).

The Cochrane review is summarised in Table 2 and the results of the review are summarised in evidence statements in this report, however full details of the Cochrane review including methods are available here: https://doi.org/10.1002/14651858.CD000479.pub6.

See the literature search strategy and study selection flow chart in appendix B, appendix C and the Cochrane review https://doi.org/10.1002/14651858.CD000479.pub6.

## Excluded studies

Studies not included in this review are listed, and reasons for their exclusion are provided in appendix J. Please also see the Cochrane review for the list of excluded studies with reasons for their exclusions: https://doi.org/10.1002/14651858.CD000479.pub6.

## Summary of included studies

Summaries of the studies that were included in this review are presented in Table 2.

**Table 2: Summary of included studies.**

| Study | Population | Comparisons | Outcomes | Comments |
|---|---|---|---|---|
| Persad 2021<br><br>Systematic review | Number of participants: 5384<br><br>Number of studies: 48<br><br>Adult male aged 18 years or over with a varicocele of any grade with normal or abnormal semen parameters, who were from couples with otherwise unexplained subfertility (female partner with no fertility problems)<br><br>Duration of infertility:<br>15 RCT: >1 year<br>1 RCT: ≥2 years<br>32 RCTs: NR | Surgical or radiological treatment vs non-surgical, non-radiological, delayed, or no treatment<br>16 RCTs, N=1817<br>(Abdel-Meguid 2011; Bo 1996; Breznik 1993; De Rose 2003; Dohle 2010; Ghanaie 2012; Grasso 2000; Hargreave 1996; Ketabchi 2018a; Ketabchi 2018b; Krause 2002; Madgar 1995; Nieschlag 1995/1998; Nilsson 1979; Unal 2001; Yamamoto 1996)<br><br>Surgical treatment vs radiological treatment<br>7 RCTs, N=602<br>(Barbalias 1998; Chen 1996; Fayez 2010; Nieschlag 1993; Nieschlag 1995/1998; Sautter 2002; Yavetz 1992)<br><br>Microscopic subinguinal surgical treatment vs other surgical treatment<br>19 RCTs, N=2201<br>(Al Kandari 2007; Al Said 2008; Bryniarski 2016; Fang 2013; Gao 2015; Gao 2017; Gontero 2005; Meng 2017; Min 2011; Pan 2013; Pu | • Live birth<br>• Clinical pregnancy<br>• Varicocele recurrence<br>• Hydrocele formation<br>• Pain<br>• Haematoma<br>• Infection<br>• Testicular atrophy | Only 2 included studies (Ghanaie 2012; Krause 2002) used ultrasound to confirm clinical pregnancy |

| Study | Population | Comparisons | Outcomes | Comments |
|---|---|---|---|---|
| | | 2014; Punekar 1999; Qi 2009; Ren 2015; Song 2012; Su 2017; Yang 2017; Zhang 2015; Zheng 2012)<br><br>Microscopic inguinal surgical treatment vs laparoscopic surgical treatment<br>1 RCT, N=76 (Niu 2017)<br><br>Open inguinal surgical treatment vs retroperitoneal surgical treatment<br>9 RCTs, N=1093 (Barbalias 1998; Barry 2012; Cayan 2000; Chaudhary 2000; Fang 2013; Pu 2014; Su 2017; Sun 2012; Telkar 2012)<br><br>Radiological treatment (sclerotherapy) vs radiological treatment (varicocele embolisation)<br>1 RCT, N=30 (Pocek 1999) | | |
| Salem 2020<br><br>RCT<br><br>Egypt | N=50<br><br>People with primary infertility and varicocele<br><br>Male age in years; mean (SD):<br>Laparoscopic varicocelectomy: 36.28 (8.21)<br>Subinguinal (microsurgical) varicocelectomy: 49.72 (7.89)<br><br>Duration of infertility: NR | Laparoscopic varicocelectomy vs subinguinal (microsurgical) varicocelectomy | • Clinical pregnancy<br>• Varicocele recurrence<br>• Hydrocele formation<br>• Pain<br>• Haematoma<br>• Infection | Method used to confirm pregnancy not reported |

1 *NR: not reported; RCT: randomised controlled trial; SD: standard deviation*

See the full evidence tables in appendix D and the forest plots in appendix E. Please also see the Cochrane review (Persad 2021) for characteristics of studies tables and forest plots: https://doi.org/10.1002/14651858.CD000479.pub6.

## Summary of the evidence

The results of the Cochrane review are summarised below and interpreted according to the minimal important differences (MIDs) used for this guideline (see Methods supplement). For comparison 3 (microscopic subinguinal surgical treatment vs other surgical treatment), a recently published RCT (Salem 2020) was identified and meta-analyses in the Cochrane review (Persad 2021) were updated by including this study.

### *Comparison 1: Surgical or radiological treatment vs non-surgical, non-radiological, delayed, or no treatment*

#### Critical outcomes

Very low quality evidence from 2 RCTs showed no clinically important difference in live birth between surgical treatment and no treatment (RR=2.27, 95% confidence interval [CI] 0.19 to 26.93). However, heterogeneity was serious for this outcome with 1 RCT showing a benefit of treatment and the other RCT showing a very seriously imprecise effect estimate with a point estimate in favour of no treatment.

Low quality evidence from 13 RCTs showed a higher pregnancy rate in people receiving surgical or radiological treatment relative to delayed or no treatment (RR=1.55, 95% CI 1.06 to 2.26). Subgroup analyses showed that a clinically important benefit was only observed for the subgroup with abnormal semen analysis and clinical varicocele (RR=1.94, 95% CI 1.23 to 3.05), and not for the subgroup with normal semen analysis and subclinical varicocele or where unspecified (RR=1.09, 95% CI 0.55 to 2.18).

#### Important outcomes

There was no relevant evidence for varicocele recurrence and adverse events (hydrocele formation, pain, haematoma, infection and testicular atrophy) for this comparison.

### *Comparison 2: Surgical treatment vs radiological treatment*

#### Critical outcomes

Very low quality evidence from 1 RCT showed no clinically important difference in live birth (RR=1.49, 95% CI 0.66 to 3.37) between surgical treatment and radiological treatment. Low quality evidence from 5 RCTs also showed no clinically important difference in pregnancy rate (RR=1.13, 95% CI 0.75 to 1.70) for surgical treatment relative to radiological treatment.

#### Important outcomes

Low to very low quality evidence from 1-3 RCTs showed no clinically important differences between surgical and radiological treatment in adverse events including: varicocele recurrence (RR=1.31, 95% CI 0.82 to 2.08, 3 RCTs); hydrocele formation (RR=4.24, 95% CI 0.53 to 33.76, 3 RCTs); pain (RR=11.00, 95% CI 0.64 to 190.26, 1 RCT); haematoma (RR=0.14, 95% CI 0.01 to 2.65, 1 RCT); and infection (epididymitis) (RR=3, 95% CI 0.33 to 27.18, 1 RCT).

There was no relevant evidence for testicular atrophy for this comparison.

### *Comparison 3: Microscopic subinguinal surgical treatment vs other surgical treatment*

#### Critical outcomes

There was no relevant evidence for live birth for this comparison.

Low quality evidence from 13 RCTs showed a small and statistically significant benefit of microscopic subinguinal surgical treatment relative to other surgical treatments on pregnancy rate (RR=1.16, 95% CI 1.01 to 1.34), but this did not meet the threshold for a clinically important difference.

**Important outcomes**

Very low quality evidence from 5 RCTs showed no clinically important difference in hydrocele formation (RR=0.38, 95% CI 0.08 to 1.87) for microscopic subinguinal surgical treatment relative to other surgical treatments. Moderate quality evidence from 15 RCTs showed a lower varicocele recurrence rate (RR=0.47, 95% CI 0.29 to 0.78) in people receiving microscopic subinguinal surgical treatment relative to other surgical treatments.

Very low quality evidence from 2-3 RCTs showed no clinically important differences between microscopic subinguinal surgical treatment and other surgical treatments in adverse events, including: pain (RR=1.12, 95% CI 0.11 to 11.12, 2 RCTs); haematoma (RR=1.10, 95% CI 0.22 to 5.65, 3 RCTs); infection (wound infection) (RR=1.95, 95% CI 0.37 to 10.24, 2 RCTs); and testicular atrophy (RR=0.18, 95% CI 0.02 to 1.89, 3 RCTs).

***Comparison 4: Open inguinal surgical treatment vs retroperitoneal surgical treatment***

**Critical outcomes**

There was no relevant evidence for live birth for this comparison.

Low quality evidence from 5 RCTs showed no clinically important difference in pregnancy rate between open inguinal surgical treatment and retroperitoneal surgical treatment (RR=1.02, 95% CI 0.82 to 1.27).

**Important outcomes**

Very low quality evidence from 8 RCTs showed no clinically important difference in varicocele recurrence (RR=1.03, (95% CI 0.43 to 2.46) between open inguinal surgical treatment and retroperitoneal surgical treatment.

Very low quality evidence from 1-6 RCTs showed no clinically important differences between open inguinal surgical treatment and retroperitoneal surgical treatment in adverse events including: hydrocele formation (RR=1.03, 95% CI 0.31 to 3.47, 6 RCTs); pain (RR=0.86, 95% CI 0.29 to 2.56, 2 RCTs); haematoma (RR=3.75, 95% CI 0.62 to 22.71, 3 RCTs); infection (wound infection) (RR=2.96, 95% CI 0.79 to 11.07, 4 RCTs); infection (epididymitis) (RR=0.61, 95% CI 0.11 to 3.52, 1 RCT); infection (epididymo-orchitis) (RR=2.00, 95% CI 0.19 to 21.18, 1 RCT); and testicular atrophy (RR=0.33, 95% CI 0.01 to 7.87, 3 RCTs).

***Comparison 5: Radiological treatment (sclerotherapy) vs radiological treatment (varicocele embolisation)***

**Critical outcomes**

There was no relevant evidence for live birth or pregnancy rate for this comparison.

**Important outcomes**

Very low quality evidence from 1 RCT showed no clinically important difference in varicocele recurrence between sclerotherapy and varicocele embolization (RR=1.00, 95% CI 0.16 to 6.20).

There was no relevant evidence for adverse events (hydrocele formation, pain, haematoma, infection, testicular atrophy) for this comparison.

See appendix F for full GRADE tables for comparison between microscopic subinguinal surgical treatment and other surgical treatment. For other comparisons, please see the

Cochrane review for summary of findings tables and full results: https://doi.org/10.1002/14651858.CD000479.pub6.

## Economic evidence

A total of 103 studies were identified in the health economic search for this review question. After duplicates were removed, 74 studies were screened on title and abstract. Of these 74 studies, 69 studies were excluded at this stage and 5 were included for full text screening. Three of the five studies were subsequently excluded when screening on full text and two studies were included for a final, and more in-depth, full text assessment. This assessment is conducted using a health economic checklist that critically assess the studies' applicability and methodological quality. These two studies were excluded at this stage as they did not meet the criteria for inclusion.

### Included studies

A systematic review of the economic literature was conducted but no economic studies were identified which were applicable to this review question.

Also see the literature search strategy in appendix B and the economic study selection flow chart in appendix G.

### Excluded studies

Economic studies not included in this review are listed, and reasons for their exclusion are provided in appendix J.

## Economic model

No economic modelling was undertaken for this review because the committee agreed that other topics were higher priorities for economic evaluation.

## Unit costs

**Table 3: Unit costs**

| Resource | Unit costs | Source |
|---|---|---|
| ***Radiological interventions*** | | |
| Varicocele embolisation | £1,398 | Varicocele Embolisation, National schedule of NHS costs 2023/24, Currency code: YR56Z, Day case |
| Sclerotherapy | £2,436 | Minor, Scrotum, Testis or Vas Deferens Procedures, 19 years and over, National schedule of NHS costs 2023/24, Currency code: LB54A, day case |
| ***Surgical interventions*** | | |
| Microscopic & Laparoscopic varicocelectomy[(a)] | £2,436 | Minor, Scrotum, Testis or Vas Deferens Procedures, 19 years and over, National schedule of NHS costs 2023/24, Currency code: LB54A, Day case |
| Open varicocelectomy | £3,088 - £3,100 | Intermediate Open, Scrotum, Testis or Vas Deferens Procedures, 19 years and over, with CC Score 0 or a CC score 1+, National schedule of NHS costs, Currency code LB53C +LB53D, Day case |

*(a) Laparoscopic varicocelectomy may be more expensive than microscopic varicocelectomy, but both procedures are categorised under the same currency cost code.*

## The committee's discussion and interpretation of the evidence

### The outcomes that matter most

Live birth and clinical pregnancy were prioritised as critical outcomes by the committee. They were selected as the best indicators of effectiveness of fertility treatment and were specified in the core outcome set for fertility research (Duffy 2020).

Varicocele recurrence and adverse events (hydrocele formation, pain, haematoma, infection, and testicular atrophy) were prioritised as important outcomes as they provide meaningful information about the success of interventions and can have a significant impact on psychological and physical health.

### The quality of the evidence

The quality of the evidence was assessed using GRADE methodology and ranged from very low to moderate quality. The main reasons for downgrading were risk of bias (arising from randomisation process, missing outcome data, and measurement of outcome), inconsistency (serious heterogeneity unexplained by subgroup analysis), and imprecision (95% confidence intervals crossing decision making thresholds).

### Benefits and harms

The committee considered the evidence showing a higher pregnancy rate following surgical or radiological treatment for varicocele and noted that an important benefit was only observed for the subgroup with clinical varicocele (varicocele detected upon clinical examination) and abnormal semen analysis. The committee agreed that treatment for varicocele should be considered for this population. The committee also discussed that it is important to take into account female factors when considering treatment for varicocele in the male partner because where there is no chance of spontaneous conception because of severe female factor fertility problems, treating varicocele in the male partner may be redundant.

The committee highlighted that very few of the included studies reported live birth and those that did reported mixed results. The committee considered the evidence that showed no important difference between surgical and radiological treatment and discussed that there may be reasons based on cost, resource or patient preference for choosing one treatment over the other, but this was not captured by the evidence. The committee also discussed the limited evidence on adverse events and noted no important differences in hydrocele formation, pain, epididymitis and haematoma between surgical and radiological treatment. The committee also emphasised that not all varicoceles can be embolised. The committee noted the small and statistically significant benefit of microscopic subinguinal surgical treatment relative to other surgical treatments but agreed that although this option would likely be the preferred approach in specialist clinics it is not universally available across all geographical areas. Based on the limited evidence for the primary outcome of live birth and the uncertainty in terms of the relative clinical and cost effectiveness and adverse events of different radiological and surgical treatments, the committee agreed that it would not be appropriate to make a stronger recommendation, or to be more specific about the intervention for varicocele that should be considered. However, a research recommendation was made (see Appendix K) in order to address these limitations in the evidence.

The committee highlighted that the Cochrane review, on which this evidence review was based, restricted the inclusion criteria to couples attempting spontaneous conception and where there were no female factor fertility problems, and the recommendation and research recommendation were made to align with this population.

The committee discussed, based on their clinical knowledge and experience, potential benefits of varicocele treatment prior to assisted reproductive technologies (ART) treatment. However, the committee were not aware of any RCT evidence for this group and agreed that it was not appropriate to make any recommendation for this population based on current evidence.

**Cost effectiveness and resource use**

No health economic evidence was identified for this review question; therefore, the committee made a qualitative assessment of cost-effectiveness.

The committee discussed the costs for both radiological and surgical interventions, in line with the clinical evidence, and subsequently made a recommendation to consider radiological or surgical treatment for people with varicocele detected on clinical examination.

The committee noted that varicocele embolisation was the cheapest intervention of those being assessed for this review question. The committee also discussed the limitations of the unit costs presented for sclerotherapy, microscopic varicocelectomy and laparoscopic varicocelectomy which were all grouped under the same currency code in the national schedule of NHS costs. As these costs were grouped under the same currency cost code it was not possible to determine the differences in costs for these interventions, however the committee acknowledged that the cost difference was likely to be minimal for these interventions. This assumption was based on their own personal experiences and aligns with the assumption of NHS reference costs, given that these interventions have the same currency cost grouping. It was also noted that open varicocelectomy is the most expensive intervention, costing approximately £660 more than sclerotherapy, microscopic varicocelectomy and laparoscopic varicocelectomy; and £1,700 more than varicocele embolisation.

The committee discussed that treatment should only be considered for those with clinically detected varicocele and that people with only small varicoceles, for example, detected on an ultrasound do not require treatment. The committee also discussed the cost-effectiveness of the interventions and as there was no clear difference in effectiveness between surgical and radiological treatments, the committee noted that varicocele embolisation might be a more cost-effective treatment option because of the relatively lower cost. The committee, however, acknowledged that there are also instances where surgical treatment or sclerotherapy may be more appropriate and therefore made a recommendation to reflect this.

The committee discussed that the recommendation made may increase the rate of varicocele treatment, however, they also concluded that it may decrease inappropriate treatment. The committee therefore acknowledged that it was difficult to ascertain the exact cost impact of this recommendation. This is because the cost implications require an exact understanding of current practice – which the committee noted varies – and in turn, an understanding of how the recommendation will affect future clinical practice. The committee therefore concluded that there may be a small increase in costs for the NHS as a result of the recommendation made for this review question, but noted the recommendation is highly unlikely to result in a significant resource impact for the NHS.

## Recommendations supported by this evidence review

This evidence review supports recommendation 1.4.12 and the research recommendation on the clinical and cost effectiveness of radiological, surgical and microsurgical treatment for male factor fertility problems associated with clinically detected varicocele and reduced semen parameters on improving live births from spontaneous conception.

# References – included studies

## Effectiveness

### Persad 2021

Persad E, O'Loughlin CAA, Kaur S et al. (2021) Surgical or radiological treatment for varicoceles in subfertile men. Cochrane Database of Systematic Reviews issue 4: CD000479.

### Salem 2020

Salem AA, Elhabbaa GI, Nawar AM, Eldibany AA (2020) Comparative study between laparoscopic varicocelectomy and subinguinal varicocelectomy in treatment of primary infertility. Benha Journal of Applied Sciences 5(5): 79-85

## Other

### Duffy 2020

Duffy, J.M., AlAhwany, H., Bhattacharya, S., Collura, B., Curtis, C., Evers, J.L., Farquharson R.G., Franik, S., Giudice, L.C., Khalaf, Y., Knijnenburg, J.M., Developing a core outcome set for future infertility research: an international consensus development study, Human Reproduction, 35(12), 2725-2734, 2020

# Appendices

## Appendix A Review protocols

### Review protocol for review question: What is the clinical and cost effectiveness of surgical and radiological treatments for fertility problems associated with varicocele?

**Table 4: Review protocol**

| Field | Content |
|---|---|
| PROSPERO registration number | CRD42023460905 |
| Review title | Clinical and cost effectiveness of surgical and radiological treatments for fertility problems associated with varicocele |
| Review question | What is the clinical and cost effectiveness of surgical and radiological treatments for fertility problems associated with varicocele? |
| Objective | To determine the clinical and cost effectiveness of surgical and radiological treatments for fertility problems associated with varicocele. |
| Searches | The following databases will be searched (from April 2020 [date of search for Cochrane review; Persad 2021] to date search conducted):<br><br>Clinical searches<br>• Cochrane Central Register of Controlled Trials (CENTRAL)<br>• Cochrane Database of Systematic Reviews (CDSR)<br>• Embase<br>• MEDLINE<br>• Epistemonikos<br><br>Searches will be restricted by:<br>• English language<br>• Human studies |

| Field | Content |
|---|---|
| | The guideline committee will decide whether and when to re-run the searches before final submission of the review to retrieve further studies for inclusion.<br><br>The full search strategies for MEDLINE database will be published in the final review. |
| Condition or domain being studied | Surgical and radiological interventions for fertility problems associated with varicocele |
| Population | Inclusion:<br>• People with fertility problems associated with varicocele<br><br>Exclusion:<br>• People trying to conceive with someone with female factor fertility problems |
| Intervention | Surgical and radiological interventions for the treatment of fertility problems associated with varicocele:<br><br>• Radiological interventions<br>  ○ Varicocele embolization<br>  ○ Sclerotherapy<br><br>• Surgical interventions:<br>  ○ Varicocelectomy<br>  ○ microscopic<br>  ○ laparoscopic<br>  ○ open |
| Comparator | • Head-to-head comparisons of different surgical or radiological interventions<br>• No treatment or delayed treatment |
| Types of study to be included | Include published full-text papers:<br>• Systematic reviews of RCTs<br>• Parallel RCTs (individual or cluster)*<br>*Cross-over RCTs will be included but only where data can be extracted for the end of the first phase |

| Field | Content |
|---|---|
| | Quasi-RCTs, such as trials in which allocation is determined by alternation or date of birth, will be excluded |
| Other exclusion criteria | Other exclusion criteria:<br>• Language limitations: non-English-language papers will be excluded (unless data can be obtained, and risk of bias assessed, from an existing systematic review)<br>• Conference abstracts, dissertations and unpublished data will not be included unless the data can be extracted (and risk of bias assessed) from elsewhere (for instance, from an existing systematic review) |
| Context | This guidance will fully update and replace the following NICE guideline: Fertility problems: assessment and treatment (last updated 2017; CG156) |
| Primary outcomes (critical outcomes) | • Live birth (as defined by study, risk of bias assessments will reflect where this is not defined as a live birth to include a gestational age of ≥ 20 weeks)<br>• Clinical pregnancy (as defined by study, risk of bias assessments will reflect where this is not defined as an ultrasound scan that has shown at least one foetal heart rate) |
| Secondary outcomes (important outcomes) | • Varicocele recurrence<br>• Adverse events<br>  ○ hydrocele formation<br>  ○ pain<br>  ○ haematoma<br>  ○ infection<br>  ○ testicular atrophy |
| Data extraction (selection and coding) | All references identified by the searches and from other sources will be uploaded into EPPI and de-duplicated. Titles and abstracts of the retrieved citations will be screened to identify studies that potentially meet the inclusion criteria outlined in the review protocol.<br>Dual sifting will be performed on at least 10% of records; 90% agreement is required. Disagreements will be resolved via discussion between the reviewers, and consultation with senior staff if necessary.<br>Full versions of the selected studies will be obtained for assessment. Studies that fail to meet the inclusion criteria once the full version has been checked will be excluded at this stage. Each study excluded after checking the full version will be listed, along with the |

| Field | Content |
|---|---|
| | reason for its exclusion. A standardised form will be used to extract data from studies included after full-text review. The following data will be extracted: study details (reference, country where study was carried out, and dates), participant characteristics, inclusion and exclusion criteria, details of the interventions, follow-up, relevant outcome data and source of funding. One reviewer will extract relevant data into a standardised form, and this will be quality assessed by a senior reviewer. |
| Risk of bias (quality) assessment | Quality assessment of individual studies will be performed using the following checklists:<br>• ROBIS tool for systematic reviews<br>• Cochrane RoB tool v.2 for RCTs<br>The quality assessment will be performed by one reviewer, and this will be quality assessed by a senior reviewer. |
| Strategy for data synthesis | Depending on the availability of the evidence, the findings will be summarised narratively or quantitatively. Where there is available data, meta-analyses will be conducted using Cochrane Review Manager software, and data will be presented as risk ratios or odds ratios (all included outcomes are dichotomous outcomes). It is considered likely that a random-effects model will be used for meta-analyses (based on assumptions about methodological diversity of studies). Funnel plot asymmetry (relationship between the magnitude of the effect estimate and study size) will be considered (for meta-analyses that include at least 10 studies), and where asymmetry is indicated a fixed-effects model will be conducted (and both random-effects and fixed-effects analyses will be presented) or sensitivity analyses excluding small studies will be considered.<br>Heterogeneity in the effect estimates of the individual studies will be assessed using the I2 statistic. Alongside visual inspection of the point estimates and confidence intervals, I2 values of greater than 50% and 80% will be considered as significant and very significant heterogeneity, respectively. Heterogeneity will be explored as appropriate using sensitivity analyses and pre-specified subgroup analyses.<br>The confidence in the findings across all available evidence will be evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group: http://www.gradeworkinggroup.org/<br>Importance and imprecision of findings will be assessed against minimally important differences (MIDs). The following MIDs will be used: |

| Field | Content | |
|---|---|---|
| | • Live birth: statistical significance<br>• Dichotomous outcomes (other than live birth): 0.8 and 1.25 for all other relative dichotomous outcomes | |
| Analysis of sub-groups | Evidence will be sub-grouped by the following:<br>• Clinical and subclinical varicocele<br>  ○ Clinical varicocele (WHO I to WHO III)<br>  ○ Subclinical varicocele (WHO 0)<br>  ○ Level of varicocele undefined<br><br>• Quality of the semen in males:<br>  ○ Azoospermia (no sperm count)<br>  ○ Oligospermia (low sperm count)<br>  ○ Normal sperm count<br><br>Evidence will be sub-grouped by the following only if there is significant heterogeneity in outcomes:<br>• Male age (based on the mean age in the study):<br>  ○ <45 years<br>  ○ ≥45 years<br><br>• Female age (based on the mean age reported in the study):<br>  ○ ≤35 years<br>  ○ >35 years<br><br>Where evidence is sub-grouped the committee will consider on a case by case basis if separate recommendations should be made for distinct groups. Separate recommendations may be made where there is evidence of a differential effect of interventions in distinct groups. If there is a lack of evidence in one group, the committee will consider, based on their experience, whether it is reasonable to extrapolate and assume the interventions will have similar effects in that group compared with others. | |
| Type and method of review | ☒ | Intervention |

| Field | Content | | | |
|---|---|---|---|---|
| | ☐ | Diagnostic | | |
| | ☐ | Prognostic | | |
| | ☐ | Qualitative | | |
| | ☐ | Epidemiologic | | |
| | ☐ | Service Delivery | | |
| | ☐ | Other (please specify) Proportional (single-arm) meta-analysis | | |
| Language | English | | | |
| Country | England | | | |
| Anticipated or actual start date | August 2023 | | | |
| Anticipated completion date | November 2024 | | | |
| Stage of review at time of this submission | Review stage | | Started | Completed |
| | Preliminary searches | | ☑ | ☑ |
| | Piloting of the study selection process | | ☑ | ☑ |
| | Formal screening of search results against eligibility criteria | | ☑ | ☑ |
| | Data extraction | | ☑ | ☑ |
| | Risk of bias (quality) assessment | | ☑ | ☑ |
| | Data analysis | | ☑ | ☑ |
| Named contact | Named contact: Guideline Development Team A<br><br>Named contact e-mail: FertilityProblems@nice.org.uk<br><br>Organisational affiliation of the review: Guideline Development Team A, Centre for Guidelines, National Institute for Health and Care Excellence (NICE) | | | |
| Review team members | • Senior Technical Analyst | | | |

| Field | Content | |
|---|---|---|
| | • Technical Analyst | |
| Funding sources/sponsor | This systematic review is being completed by NICE. | |
| Conflicts of interest | All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline. | |
| Collaborators | Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10263 | |
| Other registration details | None | |
| URL for published protocol | https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42023460905 | |
| Dissemination plans | NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as:<br>• notifying registered stakeholders of publication<br>• publicising the guideline through NICE's newsletter and alerts<br>• issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE. | |
| Keywords | Male factor infertility, varicocele, subfertility, surgical treatment, embolization | |
| Details of existing review of same topic by same authors | None | |
| Current review status | ☐ | Ongoing |
| | ☒ | Completed but not published |

| Field | Content | |
|---|---|---|
| | ☐ | Completed and published |
| | ☐ | Completed, published and being updated |
| | ☐ | Discontinued |
| Additional information | None | |
| Details of final publication | www.nice.org.uk | |

*CDSR: Cochrane Database of Systematic Reviews; CENTRAL: Cochrane Central Register of Controlled Trials; GRADE: Grading of Recommendations Assessment, Development and Evaluation; MEDLINE: Medical Literature Analysis and Retrieval System Online; MID: minimally important difference; NICE: National Institute for Health and Care Excellence; RCT: randomised controlled trial; RoB: risk of bias; ROBIS: risk of bias in systematic reviews; WHO: World Health Organization*

# Appendix B Literature search strategies

## Literature search strategies for review question: What is the clinical and cost effectiveness of surgical and radiological treatments for fertility problems associated with varicocele?

### Clinical literature searches

**Database: Ovid MEDLINE(R) ALL <1946 to January 03, 2025>**

**Date of last search: 06/01/2025**

| # | Searches |
|---|---|
| 1 | Varicocele/ |
| 2 | (Varicocele? or Varicocoele?).tw,kf. |
| 3 | ((varicos* or dilat* or enlarg* or tortuos*) adj4 (pampiniform adj2 plexus)).tw,kf. |
| 4 | ((varicos* or dilat* or enlarg* or tortuos*) adj4 (sperm* or scrot* or testic* or test?s or gonad*) adj3 (vein* or cord* or vessel* or tract* or duct*)).tw,kf. |
| 5 | or/1-4 |
| 6 | Radiology, Interventional/ |
| 7 | radiolog*.tw,kf. |
| 8 | Embolization, Therapeutic/ |
| 9 | (embol* or coil* or balloon* or plug*).tw,kf. |
| 10 | Sclerotherapy/ or exp Sclerosing Solutions/ |
| 11 | (sclero* or anti-varicos* or antivari*).tw,kf. |
| 12 | Urologic Surgical Procedures, Male/ |
| 13 | microsurgery/ or minimally invasive surgical procedures/ |
| 14 | (surg* or microsurg* or microscop* or magnif*).tw,kf. |
| 15 | ligation/ |
| 16 | (ligat* or constrict*).tw,kf. |
| 17 | Laparoscopy/ |
| 18 | (laparoscop* or laparoendoscop*).tw,kf. |
| 19 | or/6-18 |
| 20 | 5 and 19 |
| 21 | Varicocele/su, th |
| 22 | (varicocelectom* or varicocoelectom*).tw,kf. |
| 23 | ((Varicocele? or varicocoele? or (pampiniform adj2 plexus) or ((sperm* or scrot* or testic* or test?s or gonad*) adj3 (vein* or cord* or vessel* or tract* or duct*))) adj5 (repair* or correct* or treat* or operat* or therap* or interven* or manage* or occlu* or seal* or clip* or tie* or tying)).tw,kf. |
| 24 | or/21-23 |
| 25 | 20 or 24 |
| 26 | letter/ |
| 27 | editorial/ |
| 28 | news/ |
| 29 | exp historical article/ |
| 30 | Anecdotes as topic/ |
| 31 | comment/ |
| 32 | case reports/ |
| 33 | (letter or comment*).ti. |
| 34 | or/26-33 |
| 35 | randomized controlled trial/ or random*.ti,ab. |
| 36 | 34 not 35 |
| 37 | animals/ not humans/ |
| 38 | exp Animals, Laboratory/ |

| # | Searches |
|---|---|
| 39 | exp Animal Experimentation/ |
| 40 | exp Models, Animal/ |
| 41 | exp Rodentia/ |
| 42 | (rat or rats or rodent* or mouse or mice).ti. |
| 43 | or/36-42 |
| 44 | 25 not 43 |
| 45 | limit 44 to english language |
| 46 | limit 45 to ed=20200401-20250131 |
| 47 | limit 45 to dt=20200401-20250131 |
| 48 | 46 or 47 |

1 **Database: Embase <1974 to 2025 January 03>**

2 **Date of last search: 06/01/2025**

| # | Searches |
|---|---|
| 1 | exp varicocele/ |
| 2 | (Varicocele? or Varicocoele?).tw,kf. |
| 3 | ((varicos* or dilat* or enlarg* or tortuos*) adj4 (pampiniform adj2 plexus)).tw,kf. |
| 4 | ((varicos* or dilat* or enlarg* or tortuos*) adj4 (sperm* or scrot* or testic* or test?s or gonad*) adj3 (vein* or cord* or vessel* or tract* or duct*)).tw,kf. |
| 5 | or/1-4 |
| 6 | interventional radiology/ or radiological procedures/ |
| 7 | radiolog*.tw,kf. |
| 8 | artificial embolization/ or balloon embolization/ or coil embolization/ |
| 9 | (embol* or coil* or balloon* or plug*).tw,kf. |
| 10 | exp sclerotherapy/ or exp sclerosing agent/ |
| 11 | (sclero* or anti-varicos* or antivari*).tw,kf. |
| 12 | male genital system surgery/ |
| 13 | microsurgery/ or robot assisted microsurgery/ |
| 14 | minimally invasive surgery/ or minimally invasive procedure/ |
| 15 | microscopy/ |
| 16 | (surg* or microsurg* or microscop* or magnif*).tw,kf. |
| 17 | ligation/ or vein ligation/ |
| 18 | (ligat* or constrict*).tw,kf. |
| 19 | exp laparoscopy/ |
| 20 | (laparoscop* or laparoendoscop*).tw,kf. |
| 21 | or/6-20 |
| 22 | 5 and 21 |
| 23 | exp varicocelectomy/ |
| 24 | exp varicocele/su, th |
| 25 | (varicocelectom* or varicocoelectom*).tw,kf. |
| 26 | ((Varicocele? or varicocoele? or (pampiniform adj2 plexus) or ((sperm* or scrot* or testic* or test?s or gonad*) adj3 (vein* or cord* or vessel* or tract* or duct*))) adj5 (repair* or correct* or treat* or operat* or therap* or interven* or manage* or occlu* or seal* or clip* or tie* or tying)).tw,kf. |
| 27 | or/23-26 |
| 28 | 22 or 27 |
| 29 | letter.pt. or letter/ |
| 30 | note.pt. |
| 31 | editorial.pt. |
| 32 | case report/ or case study/ |
| 33 | (letter or comment*).ti. |
| 34 | or/29-33 |
| 35 | randomized controlled trial/ or random*.ti,ab. |

| # | Searches |
|---|---|
| 36 | 34 not 35 |
| 37 | animal/ not human/ |
| 38 | nonhuman/ |
| 39 | exp Animal Experiment/ |
| 40 | exp Experimental Animal/ |
| 41 | animal model/ |
| 42 | exp Rodent/ |
| 43 | (rat or rats or rodent* or mouse or mice).ti. |
| 44 | or/36-43 |
| 45 | 28 not 44 |
| 46 | (conference abstract* or conference review or conference paper or conference proceeding).db,pt,su. |
| 47 | 45 not 46 |
| 48 | limit 47 to english language |
| 49 | limit 48 to dc=20200401-20250131 |

1 **Database: Cochrane Database of Systematic Reviews Issue 1 of 12, January 2025**

2 **Date of last search: 06/01/2025**

| # | Searches |
|---|---|
| 1 | MeSH descriptor: [Varicocele] this term only |
| 2 | (Varicocele or varicoceles or varicocoele or varicocoeles):ti,ab,kw |
| 3 | ((varicos* or dilat* or enlarg* or tortuos*) near/4 (pampiniform near/2 plexus)):ti,ab,kw |
| 4 | ((varicos* or dilat* or enlarg* or tortuos*) near/4 (sperm* or scrot* or testic* or testes or testis or gonad*) near/3 (vein* or cord* or vessel* or tract* or duct*)):ti,ab,kw |
| 5 | {or #1-#4} |
| 6 | MeSH descriptor: [Radiology, Interventional] this term only |
| 7 | (radiolog*):ti,ab,kw |
| 8 | MeSH descriptor: [Embolization, Therapeutic] this term only |
| 9 | ((embol* or coil* or balloon* or plug*)):ti,ab,kw |
| 10 | MeSH descriptor: [Sclerotherapy] this term only |
| 11 | MeSH descriptor: [Sclerosing Solutions] explode all trees |
| 12 | ((sclero* or (anti next varicos*) or antivari*)):ti,ab,kw |
| 13 | MeSH descriptor: [Urologic Surgical Procedures, Male] this term only |
| 14 | MeSH descriptor: [Microsurgery] this term only |
| 15 | MeSH descriptor: [Minimally Invasive Surgical Procedures] this term only |
| 16 | (surg* or microsurg* or microscop* or magnif*):ti,ab,kw |
| 17 | MeSH descriptor: [Ligation] this term only |
| 18 | (ligat* or constrict*):ti,ab,kw |
| 19 | MeSH descriptor: [Laparoscopy] this term only |
| 20 | (laparoscop* or laparoendoscop*):ti,ab,kw |
| 21 | {or #6-#20} |
| 22 | #5 and #21 |
| 23 | MeSH descriptor: [Varicocele] this term only and with qualifier(s): [surgery - SU, therapy - TH] |
| 24 | (varicocelectom* or varicocoelectom*):ti,ab,kw |
| 25 | ((Varicocele or varicoceles or varicocoele or varicocoeles or (pampiniform near/2 plexus) or ((sperm* or scrot* or testic* or testes or testis or gonad*) near/3 (vein* or cord* or vessel* or tract* or duct*))) near/5 (repair* or correct* or treat* or operat* or therap* or interven* or manage* or occlu* or seal* or clip* or tie* or tying)):ti,ab,kw |
| 26 | {or #23-#25} |
| 27 | #22 or #26 |
| 28 | ((clinicaltrials or trialsearch* or trial-registry or trials-registry or clinicalstudies or trialsregister* or trialregister* or trial-number* or studyregister* or study-register* or controlled-trials-com or current-controlled-trial or AMCTR or ANZCTR or ChiCTR* or CRiS or CTIS or CTRI* or DRKS* or EU-CTR* or EUCTR* or EUDRACT* or ICTRP or IRCT* or JAPIC* or JMCTR* or JRCT or ISRCTN* or LBCTR* or NTR* or ReBec* or REPEC* or RPCEC* or SLCTR or TCTR* or UMIN*):so or (ctgov or ictrp)):an |

| # | Searches |
|---|---|
| 29 | #27 not #28 |
| 30 | "conference":pt |
| 31 | #29 not #30 with Cochrane Library publication date Between Apr 2020 and Jan 2025, in Cochrane Reviews |

**Database: Cochrane Central Register of Controlled Trials Issue 12 of 12, December 2024**

**Date of last search: 06/01/2025**

| # | Searches |
|---|---|
| 1 | MeSH descriptor: [Varicocele] this term only |
| 2 | (Varicocele or varicoceles or varicocoele or varicocoeles):ti,ab,kw |
| 3 | ((varicos* or dilat* or enlarg* or tortuos*) near/4 (pampiniform near/2 plexus)):ti,ab,kw |
| 4 | ((varicos* or dilat* or enlarg* or tortuos*) near/4 (sperm* or scrot* or testic* or testes or testis or gonad*) near/3 (vein* or cord* or vessel* or tract* or duct*)):ti,ab,kw |
| 5 | {or #1-#4} |
| 6 | MeSH descriptor: [Radiology, Interventional] this term only |
| 7 | (radiolog*):ti,ab,kw |
| 8 | MeSH descriptor: [Embolization, Therapeutic] this term only |
| 9 | ((embol* or coil* or balloon* or plug*)):ti,ab,kw |
| 10 | MeSH descriptor: [Sclerotherapy] this term only |
| 11 | MeSH descriptor: [Sclerosing Solutions] explode all trees |
| 12 | ((sclero* or (anti next varicos*) or antivari*)):ti,ab,kw |
| 13 | MeSH descriptor: [Urologic Surgical Procedures, Male] this term only |
| 14 | MeSH descriptor: [Microsurgery] this term only |
| 15 | MeSH descriptor: [Minimally Invasive Surgical Procedures] this term only |
| 16 | (surg* or microsurg* or microscop* or magnif*):ti,ab,kw |
| 17 | MeSH descriptor: [Ligation] this term only |
| 18 | (ligat* or constrict*):ti,ab,kw |
| 19 | MeSH descriptor: [Laparoscopy] this term only |
| 20 | (laparoscop* or laparoendoscop*):ti,ab,kw |
| 21 | {or #6-#20} |
| 22 | #5 and #21 |
| 23 | MeSH descriptor: [Varicocele] this term only and with qualifier(s): [surgery - SU, therapy - TH] |
| 24 | (varicocelectom* or varicocoelectom*):ti,ab,kw |
| 25 | ((Varicocele or varicoceles or varicocoele or varicocoeles or (pampiniform near/2 plexus) or ((sperm* or scrot* or testic* or testes or testis or gonad*) near/3 (vein* or cord* or vessel* or tract* or duct*))) near/5 (repair* or correct* or treat* or operat* or therap* or interven* or manage* or occlu* or seal* or clip* or tie* or tying)):ti,ab,kw |
| 26 | {or #23-#25} |
| 27 | #22 or #26 |
| 28 | ((clinicaltrials or trialsearch* or trial-registry or trials-registry or clinicalstudies or trialsregister* or trialregister* or trial-number* or studyregister* or study-register* or controlled-trials-com or current-controlled-trial or AMCTR or ANZCTR or ChiCTR* or CRiS or CTIS or CTRI* or DRKS* or EU-CTR* or EUCTR* or EUDRACT* or ICTRP or IRCT* or JAPIC* or JMCTR* or JRCT or ISRCTN* or LBCTR* or NTR* or ReBec* or REPEC* or RPCEC* or SLCTR or TCTR* or UMIN*):so or (ctgov or ictrp)):an |
| 29 | #27 not #28 |
| 30 | "conference":pt |
| 31 | #29 not #30 with Publication Year from 2020 to 2025, in Trials |

1 **Database: Epistemonikos**

2 **Date of last search: 06/01/2025**

| # | Searches |
|---|---|
| 1 | (Varicocele OR varicoceles OR varicocoele OR varicocoeles OR ((varicos* OR dilat* OR enlarg* OR tortuos*) AND ((pampiniform AND plexus) OR ((sperm* OR scrot* OR testic* OR testes OR testis OR gonad*) AND (vein* OR cord* OR vessel* OR tract* OR duct*))))) |
| 2 | (radiolog* OR embol* OR coil* OR balloon* OR plug* OR sclero* OR (anti AND varicos*) OR antivari* OR surg* OR microsurg* OR microscop* OR magnif* OR ligat* OR constrict* OR laparoscop* OR laparoendoscop*) |
| 3 | 1 AND 2 |
| 4 | (varicocelectom* OR varicocoelectom* OR ((Varicocele OR varicoceles OR varicocoele OR varicocoeles OR (pampiniform AND plexus) OR ((sperm* OR scrot* OR testic* OR testes OR testis OR gonad*) AND (vein* OR cord* OR vessel* OR tract* OR duct*))) AND (repair* OR correct* OR treat* OR operat* OR therap* OR interven* OR manage* OR occlu* OR seal* OR clip* OR tie* OR tying))) |
| 5 | 3 OR 4 |
| 6 | Limit to Systematic Reviews, 2020-2025 |

3

4 **Health economic literature searches**

5 **Database: Ovid MEDLINE(R) ALL <1946 to January 06, 2025>**

6 **Date of last search: 08/01/2025**

| # | Searches |
|---|---|
| 1 | Varicocele/ |
| 2 | (Varicocele? or Varicocoele?).tw,kf. |
| 3 | ((varicos* or dilat* or enlarg* or tortuos*) adj4 (pampiniform adj2 plexus)).tw,kf. |
| 4 | ((varicos* or dilat* or enlarg* or tortuos*) adj4 (sperm* or scrot* or testic* or test?s or gonad*) adj3 (vein* or cord* or vessel* or tract* or duct*)).tw,kf. |
| 5 | or/1-4 |
| 6 | Radiology, Interventional/ |
| 7 | radiolog*.tw,kf. |
| 8 | Embolization, Therapeutic/ |
| 9 | (embol* or coil* or balloon* or plug*).tw,kf. |
| 10 | Sclerotherapy/ or exp Sclerosing Solutions/ |
| 11 | (sclero* or anti-varicos* or antivari*).tw,kf. |
| 12 | Urologic Surgical Procedures, Male/ |
| 13 | microsurgery/ or minimally invasive surgical procedures/ |
| 14 | (surg* or microsurg* or microscop* or magnif*).tw,kf. |
| 15 | ligation/ |
| 16 | (ligat* or constrict*).tw,kf. |
| 17 | Laparoscopy/ |
| 18 | (laparoscop* or laparoendoscop*).tw,kf. |
| 19 | or/6-18 |
| 20 | 5 and 19 |
| 21 | Varicocele/su, th |
| 22 | (varicocelectom* or varicocoelectom*).tw,kf. |
| 23 | ((Varicocele? or varicocoele? or (pampiniform adj2 plexus) or ((sperm* or scrot* or testic* or test?s or gonad*) adj3 (vein* or cord* or vessel* or tract* or duct*))) adj5 (repair* or correct* or treat* or operat* or therap* or interven* or manage* or occlu* or seal* or clip* or tie* or tying)).tw,kf. |
| 24 | or/21-23 |
| 25 | 20 or 24 |
| 26 | letter/ |
| 27 | editorial/ |

| # | Searches |
|---|---|
| 28 | news/ |
| 29 | exp historical article/ |
| 30 | Anecdotes as topic/ |
| 31 | comment/ |
| 32 | case reports/ |
| 33 | (letter or comment*).ti. |
| 34 | or/26-33 |
| 35 | randomized controlled trial/ or random*.ti,ab. |
| 36 | 34 not 35 |
| 37 | animals/ not humans/ |
| 38 | exp Animals, Laboratory/ |
| 39 | exp Animal Experimentation/ |
| 40 | exp Models, Animal/ |
| 41 | exp Rodentia/ |
| 42 | (rat or rats or rodent* or mouse or mice).ti. |
| 43 | or/36-42 |
| 44 | 25 not 43 |
| 45 | limit 44 to english language |
| 46 | limit 45 to ed=20200401-20250131 |
| 47 | limit 45 to dt=20200401-20250131 |
| 48 | 46 or 47 |
| 49 | Economics/ |
| 50 | Value of life/ |
| 51 | exp "Costs and Cost Analysis"/ |
| 52 | exp Economics, Hospital/ |
| 53 | exp Economics, Medical/ |
| 54 | exp Resource Allocation/ |
| 55 | Economics, Nursing/ |
| 56 | Economics, Pharmaceutical/ |
| 57 | exp "Fees and Charges"/ |
| 58 | exp Budgets/ |
| 59 | budget*.ti,ab. |
| 60 | cost*.ti,ab. |
| 61 | (economic* or pharmaco?economic*).ti,ab. |
| 62 | (price* or pricing*).ti,ab. |
| 63 | (financ* or fee or fees or expenditure* or saving*).ti,ab. |
| 64 | (value adj2 (money or monetary)).ti,ab. |
| 65 | resourc* allocat*.ti,ab. |
| 66 | (fund or funds or funding* or funded).ti,ab. |
| 67 | (ration or rations or rationing* or rationed).ti,ab. |
| 68 | ec.fs. |
| 69 | or/49-68 |
| 70 | quality-adjusted life years/ |
| 71 | sickness impact profile/ |
| 72 | (quality adj2 (wellbeing or well being)).ti,ab. |
| 73 | sickness impact profile.ti,ab. |
| 74 | disability adjusted life.ti,ab. |
| 75 | (qal* or qtime* or qwb* or daly*).ti,ab. |
| 76 | (euroqol* or eq5d* or eq 5*).ti,ab. |
| 77 | (qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab. |
| 78 | (health utility* or utility score* or disutilit* or utility value*).ti,ab. |
| 79 | (hui or hui1 or hui2 or hui3).ti,ab. |

| # | Searches |
|---|---|
| 80 | (health* year* equivalent* or hye or hyes).ti,ab. |
| 81 | discrete choice*.ti,ab. |
| 82 | rosser.ti,ab. |
| 83 | (willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab. |
| 84 | (sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab. |
| 85 | (sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab. |
| 86 | (sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab. |
| 87 | (sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab. |
| 88 | (sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab. |
| 89 | or/70-88 |
| 90 | 48 and (69 or 89) |

1 **Database: Embase <1974 to 2025 January 07>**

2 **Date of last search: 08/01/2025**

| # | Searches |
|---|---|
| 1 | exp varicocele/ |
| 2 | (Varicocele? or Varicocoele?).tw,kf. |
| 3 | ((varicos* or dilat* or enlarg* or tortuos*) adj4 (pampiniform adj2 plexus)).tw,kf. |
| 4 | ((varicos* or dilat* or enlarg* or tortuos*) adj4 (sperm* or scrot* or testic* or test?s or gonad*) adj3 (vein* or cord* or vessel* or tract* or duct*)).tw,kf. |
| 5 | or/1-4 |
| 6 | interventional radiology/ or radiological procedures/ |
| 7 | radiolog*.tw,kf. |
| 8 | artificial embolization/ or balloon embolization/ or coil embolization/ |
| 9 | (embol* or coil* or balloon* or plug*).tw,kf. |
| 10 | exp sclerotherapy/ or exp sclerosing agent/ |
| 11 | (sclero* or anti-varicos* or antivari*).tw,kf. |
| 12 | male genital system surgery/ |
| 13 | microsurgery/ or robot assisted microsurgery/ |
| 14 | minimally invasive surgery/ or minimally invasive procedure/ |
| 15 | microscopy/ |
| 16 | (surg* or microsurg* or microscop* or magnif*).tw,kf. |
| 17 | ligation/ or vein ligation/ |
| 18 | (ligat* or constrict*).tw,kf. |
| 19 | exp laparoscopy/ |
| 20 | (laparoscop* or laparoendoscop*).tw,kf. |
| 21 | or/6-20 |
| 22 | 5 and 21 |
| 23 | exp varicocelectomy/ |
| 24 | exp varicocele/su, th |
| 25 | (varicocelectom* or varicocoelectom*).tw,kf. |
| 26 | ((Varicocele? or varicocoele? or (pampiniform adj2 plexus) or ((sperm* or scrot* or testic* or test?s or gonad*) adj3 (vein* or cord* or vessel* or tract* or duct*))) adj5 (repair* or correct* or treat* or operat* or therap* or interven* or manage* or occlu* or seal* or clip* or tie* or tying)).tw,kf. |
| 27 | or/23-26 |
| 28 | 22 or 27 |
| 29 | letter.pt. or letter/ |
| 30 | note.pt. |
| 31 | editorial.pt. |
| 32 | case report/ or case study/ |
| 33 | (letter or comment*).ti. |
| 34 | or/29-33 |

| # | Searches |
|---|---|
| 35 | randomized controlled trial/ or random*.ti,ab. |
| 36 | 34 not 35 |
| 37 | animal/ not human/ |
| 38 | nonhuman/ |
| 39 | exp Animal Experiment/ |
| 40 | exp Experimental Animal/ |
| 41 | animal model/ |
| 42 | exp Rodent/ |
| 43 | (rat or rats or rodent* or mouse or mice).ti. |
| 44 | or/36-43 |
| 45 | 28 not 44 |
| 46 | (conference abstract* or conference review or conference paper or conference proceeding).db,pt,su. |
| 47 | 45 not 46 |
| 48 | limit 47 to english language |
| 49 | limit 48 to dc=20200401-20250131 |
| 50 | health economics/ |
| 51 | exp economic evaluation/ |
| 52 | exp health care cost/ |
| 53 | exp fee/ |
| 54 | budget/ |
| 55 | funding/ |
| 56 | resource allocation/ |
| 57 | budget*.ti,ab. |
| 58 | cost*.ti,ab. |
| 59 | (economic* or pharmaco?economic*).ti,ab. |
| 60 | (price* or pricing*).ti,ab. |
| 61 | (financ* or fee or fees or expenditure* or saving*).ti,ab. |
| 62 | (value adj2 (money or monetary)).ti,ab. |
| 63 | resourc* allocat*.ti,ab. |
| 64 | (fund or funds or funding* or funded).ti,ab. |
| 65 | (ration or rations or rationing* or rationed).ti,ab. |
| 66 | or/50-65 |
| 67 | quality adjusted life year/ |
| 68 | "quality of life index"/ |
| 69 | short form 12/ or short form 20/ or short form 36/ or short form 8/ |
| 70 | sickness impact profile/ |
| 71 | (quality adj2 (wellbeing or well being)).ti,ab. |
| 72 | sickness impact profile.ti,ab. |
| 73 | disability adjusted life.ti,ab. |
| 74 | (qal* or qtime* or qwb* or daly*).ti,ab. |
| 75 | (euroqol* or eq5d* or eq 5*).ti,ab. |
| 76 | (qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab. |
| 77 | (health utility* or utility score* or disutilit* or utility value*).ti,ab. |
| 78 | (hui or hui1 or hui2 or hui3).ti,ab. |
| 79 | (health* year* equivalent* or hye or hyes).ti,ab. |
| 80 | discrete choice*.ti,ab. |
| 81 | rosser.ti,ab. |
| 82 | (willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab. |
| 83 | (sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab. |
| 84 | (sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab. |
| 85 | (sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab. |
| 86 | (sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab. |

| # | Searches |
|---|---|
| 87 | (sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab. |
| 88 | or/67-87 |
| 89 | 49 and (66 or 88) |

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2 **Database: INAHTA**

3 **Date of last search: 08/01/2025**

| # | Searches |
|---|---|
| 1 | "Varicocele"[mh] |
| 2 | varicocele or varicoceles or varicocoele or varicocoele |
| 3 | ((varicos* or dilat* or enlarg* or tortuos*) AND (pampiniform AND plexus)) |
| 4 | ((varicos* or dilat* or enlarg* or tortuos*) AND (sperm* or scrot* or testic* or testis or testes or gonad*) AND (vein* or cord* or vessel* or tract* or duct*)) |
| 5 | #4 OR #3 OR #2 OR #1 |
| 6 | "Radiography, Interventional"[mh] |
| 7 | radiolog* |
| 8 | "Embolization, Therapeutic"[mh] |
| 9 | (embol* or coil* or balloon* or plug*) |
| 10 | "Sclerotherapy"[mh] |
| 11 | "Sclerosing Solutions"[mhe] |
| 12 | (sclero* or anti-varicos or (anti AND varicos*) or antivari*) |
| 13 | "Urologic Surgical Procedures, Male"[mh] |
| 14 | "Microsurgery"[mh] |
| 15 | "Minimally Invasive Surgical Procedures"[mh] |
| 16 | (surg* or microsurg* or microscop* or magnif*) |
| 17 | "Ligation"[mh] |
| 18 | (ligat* or constrict*) |
| 19 | "Laparoscopy"[mh] |
| 20 | (laparoscop* or laparoendoscop*) |
| 21 | #20 OR #19 OR #18 OR #17 OR #16 OR #15 OR #14 OR #13 OR #12 OR #11 OR #10 OR #9 OR #8 OR #7 OR #6 |
| 22 | #21 AND #5 |
| 23 | (varicocelectom* or varicocoelectom*) |
| 24 | ((Varicocele or varicoceles or varicocoele or varicoceles or (pampiniform AND plexus) or ((sperm* or scrot* or testic* or testis or testes or gonad*) AND (vein* or cord* or vessel* or tract* or duct*))) AND (repair* or correct* or treat* or operat* or therap* or interven* or manage* or occlu* or seal* or clip* or tie* or tying)) |
| 25 | #24 OR #23 OR #22 |

4 **Database: HTA via CRD**

5 **Date of last search: 08/01/2025**

| # | Searches |
|---|---|
| 1 | MESH DESCRIPTOR Varicocele |
| 2 | (Varicocele or varicoceles or varicocoele or varicocoeles) |
| 3 | ((varicos* or dilat* or enlarg* or tortuos*) near4 (pampiniform near2 plexus)) |
| 4 | ((varicos* or dilat* or enlarg* or tortuos*) near4 (sperm* or scrot* or testic* or testes or testis or gonad*) near3 (vein* or cord* or vessel* or tract* or duct*)) |
| 5 | #1 or #2 or #3 or #4 |
| 6 | MESH DESCRIPTOR Radiology, Interventional |
| 7 | (radiolog*) |
| 8 | MESH DESCRIPTOR Embolization, Therapeutic |
| 9 | ((embol* or coil* or balloon* or plug*)) |

| # | Searches |
|---|---|
| 10 | MESH DESCRIPTOR Sclerotherapy |
| 11 | MESH DESCRIPTOR Sclerosing Solutions EXPLODE ALL TREES |
| 12 | ((sclero* or (anti next varicos*) or antivari*)) |
| 13 | MESH DESCRIPTOR Urologic Surgical Procedures, Male |
| 14 | MESH DESCRIPTOR Microsurgery |
| 15 | MESH DESCRIPTOR Minimally Invasive Surgical Procedures |
| 16 | (surg* or microsurg* or microscop* or magnif*) |
| 17 | MESH DESCRIPTOR Ligation |
| 18 | (ligat* or constrict*) |
| 19 | MESH DESCRIPTOR Laparoscopy |
| 20 | (laparoscop* or laparoendoscop*) |
| 21 | #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 |
| 22 | #5 and #21 |
| 23 | MESH DESCRIPTOR Varicocele and with qualifier(s) |
| 24 | (varicocelectom* or varicocoelectom*) |
| 25 | ((Varicocele or varicoceles or varicocoele or varicocoeles or (pampiniform near2 plexus) or ((sperm* or scrot* or testic* or testes or testis or gonad*) near3 (vein* or cord* or vessel* or tract* or duct*))) near5 (repair* or correct* or treat* or operat* or therap* or interven* or manage* or occlu* or seal* or clip* or tie* or tying)) |
| 26 | #23 or #24 or #25 |
| 27 | #22 or #26 |
| 28 | (#22 or #26) IN HTA FROM 2020 TO 2025 |

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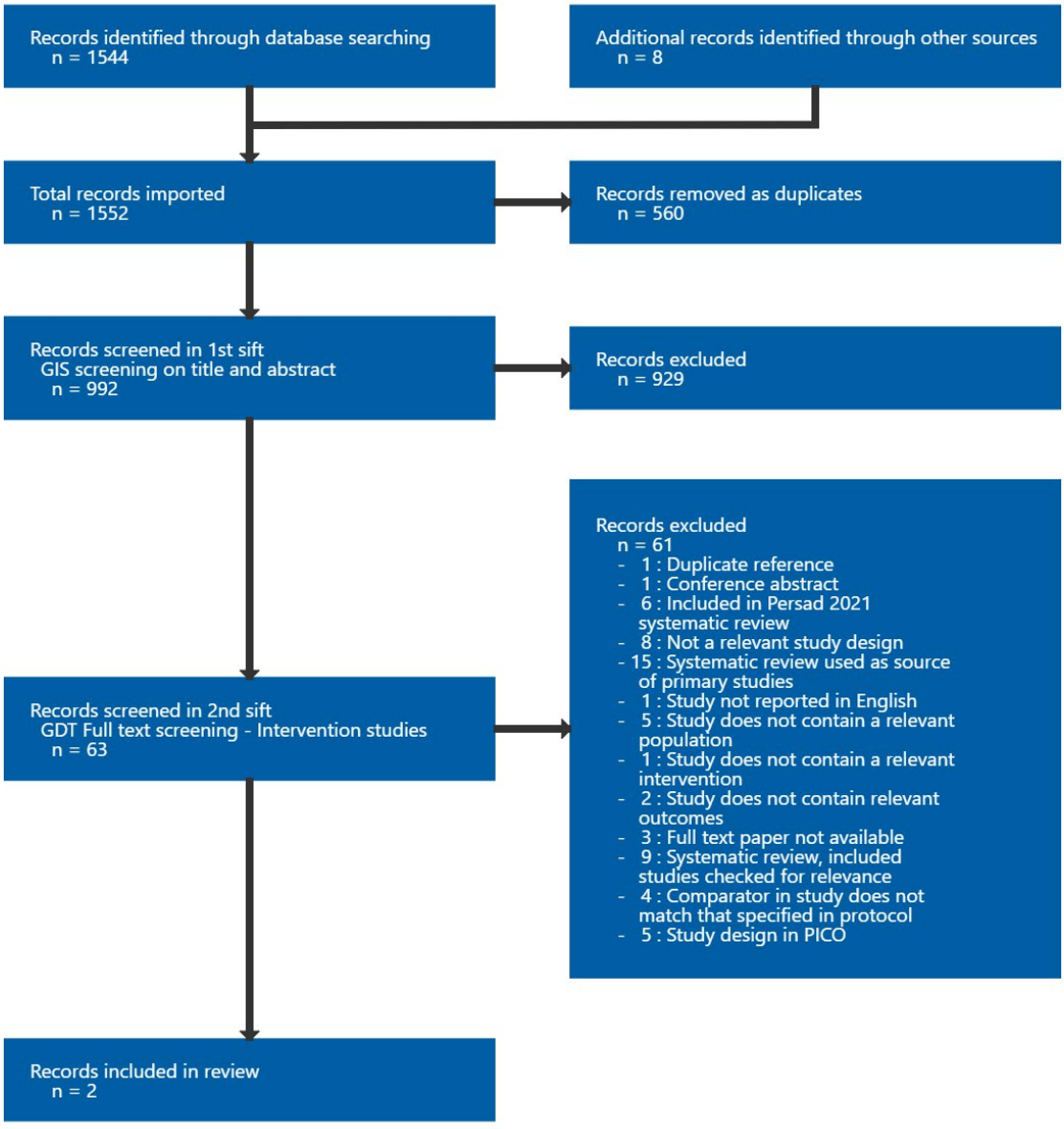
# Appendix C Effectiveness evidence study selection

## Study selection for review question: What is the clinical and cost effectiveness of surgical and radiological treatments for fertility problems associated with varicocele?

### Clinical search

**Figure 1: Study selection flow chart**



# Appendix D Characteristics of studies tables

## Characteristics of studies tables for review question: What is the clinical and cost effectiveness of surgical and radiological treatments for fertility problems associated with varicocele?

### Persad, 2021

See the Characteristics of included studies tables from the Cochrane review (Persad 2021): https://doi.org/10.1002/14651858.CD000479.pub6

### Salem, 2020

| | |
|---|---|
| **Bibliographic Reference** | Salem AA, Elhabbaa GI, Nawar AM, Eldibany AA (2020) Comparative study between laparoscopic varicocelectomy and subinguinal varicocelectomy in treatment of primary infertility. Benha Journal of Applied Sciences 5(5): 79-85 |

**Study details**

| | |
|---|---|
| **Country/ies where study was carried out** | Egypt |
| **Study type** | Randomised controlled trial (RCT) |
| **Study dates** | April 2018 - June 2020 |
| **Inclusion criteria** | People with primary infertility (with a main complaint with abnormal semen parameters) and varicocele |
| **Exclusion criteria** | NR |
| **Patient characteristics** | Male age in years, mean (SD):<br>Laparoscopic varicocelectomy: 36.28 (8.21)<br>Subinguinal (microsurgical) varicocelectomy: 49.72 (7.89)<br><br>Female age in years, mean (SD): NR<br><br>BMI in kg/m$^2$: NR |

| | |
|---|---|
| | Duration of infertility: NR<br><br>Clinical varicocele; N:<br>Laparoscopic varicocelectomy: 25<br>Subinguinal (microsurgical) varicocelectomy: 25<br><br>Quality of the semen in males: NR*<br><br>*Unclear whether participants (how many participants) had azoospermia, oligospermia or normal sperm count |
| **Intervention(s)/control** | Laparoscopic varicocelectomy<br><br>Subinguinal (microsurgical) varicocelectomy |
| **Duration of follow-up** | Over 1 year |
| **Sources of funding** | NR |
| **Sample size** | N=50<br><br>N randomised:<br>Laparoscopic varicocelectomy: 25<br>Subinguinal (microsurgical) varicocelectomy: 25<br><br>N included in final analysis:<br>Laparoscopic varicocelectomy: 25<br>Subinguinal (microsurgical) varicocelectomy: 25 |
| **Other information** | Clinical pregnancy: unclear whether ultrasound was used to confirm pregnancy |

*BMI: body mass index; NR: not reported; RCT: randomised controlled trial; SD: standard deviation*

**Outcomes**

**Laparoscopic varicocelectomy versus Subinguinal (microsurgical) varicocelectomy**

| Outcome | Laparoscopic varicocelectomy, N = 25 | Subinguinal (microsurgical) varicocelectomy, N = 25 |
|---|---|---|
| **Clinical pregnancy**<br>No of events | n = 10 | n = 8 |
| **Varicocele recurrence**<br>No of events | n = 1 | n = 0 |
| **Adverse event (hydrocele formation)**<br>No of events | n = 0 | n = 1 |
| **Adverse event (pain)***<br>No of events | n = 6 | n = 19 |
| **Adverse event (haematoma)**<br>No of events | n = 0 | n = 1 |
| **Adverse event (wound infection)**<br>No of events | n = 0 | n = 1 |

**Number of participants with moderate and severe pain was extracted*

**Critical appraisal**

| Section | Question | Answer |
|---|---|---|
| Domain 1: Bias arising from the randomisation process | Risk of bias judgement for the randomisation process | High<br>*(No information of randomisation process and allocation sequence concealment)* |

| Section | Question | Answer |
|---|---|---|
| Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) | Risk of bias for deviations from the intended interventions (effect of assignment to intervention) | Low<br>*(There were no deviations from the intended interventions and appropriate analysis was used.)* |
| Domain 3. Bias due to missing outcome data | Risk-of-bias judgement for missing outcome data | Low<br>*(Data were available for all participants.)* |
| Domain 4. Bias in measurement of the outcome | Risk-of-bias judgement for measurement of the outcome | High<br>*(Observation method (subjective method) was used to assess postoperative pain and other complications (haematoma and infection). Method of measuring the outcome was not reported for recurrence, hydrocele formation, and pregnancy rate.)* |
| Domain 5. Bias in selection of the reported result | Risk-of-bias judgement for selection of the reported result | Some concerns<br>*(Unclear whether trial was analysed in accordance with a pre-specified plan)* |
| Overall bias and Directness | Risk of bias judgement | High<br>*(The study is judged to be at high risk of bias in at least one domain)* |
| Overall bias and Directness | Overall Directness | Directly applicable |
| Overall bias and Directness | Risk of bias variation across outcomes | None |

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# Appendix E Forest plots and data and analyses tables

## Forest plots for review question: What is the clinical and cost effectiveness of surgical and radiological treatments for fertility problems associated with varicocele?

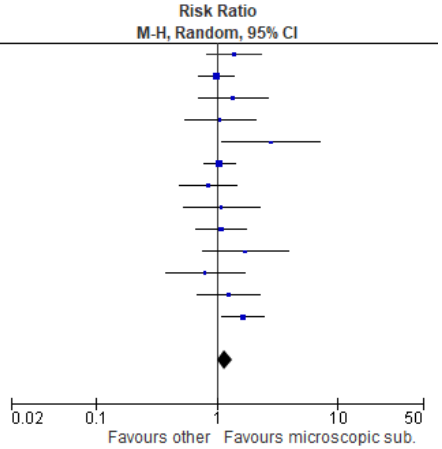
This section includes forest plots only for outcomes that are meta-analysed for comparison between microscopic subinguinal surgical treatment and other surgical treatment. For other comparisons, please see the Data and analyses tables from the Cochrane review (Persad 2021): https://doi.org/10.1002/14651858.CD000479.pub6

### Microscopic subinguinal surgical treatment versus other surgical treatment

**Figure 2: Clinical pregnancy**

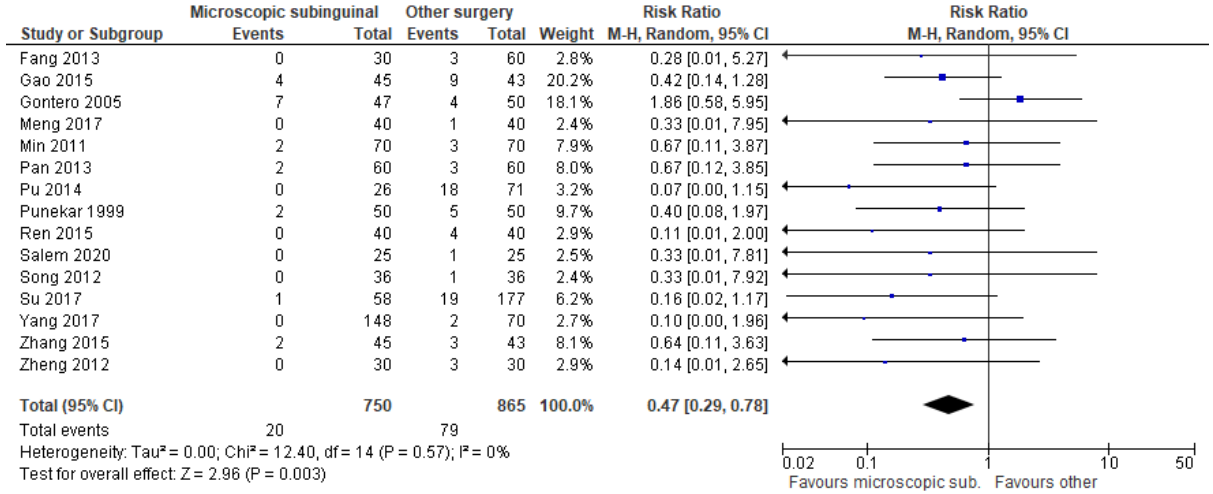
| Study or Subgroup | Microscopic subinguinal Events | Total | Other surgery Events | Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Al Kandari 2007 | 16 | 40 | 23 | 80 | 7.3% | 1.39 [0.83, 2.32] |
| Al Said 2008 | 38 | 112 | 64 | 186 | 18.2% | 0.99 [0.71, 1.37] |
| Bryniarski 2016 | 15 | 42 | 11 | 42 | 4.6% | 1.36 [0.71, 2.61] |
| Fang 2013 | 9 | 30 | 17 | 60 | 4.2% | 1.06 [0.54, 2.09] |
| Gao 2017 | 14 | 47 | 5 | 47 | 2.2% | 2.80 [1.10, 7.15] |
| Min 2011 | 39 | 70 | 37 | 70 | 20.9% | 1.05 [0.78, 1.43] |
| Pan 2013 | 17 | 60 | 20 | 60 | 6.7% | 0.85 [0.50, 1.46] |
| Punekar 1999 | 12 | 50 | 11 | 50 | 3.7% | 1.09 [0.53, 2.24] |
| Qi 2009 | 13 | 20 | 12 | 20 | 8.3% | 1.08 [0.67, 1.75] |
| Ren 2015 | 12 | 40 | 7 | 40 | 2.9% | 1.71 [0.75, 3.90] |
| Salem 2020 | 8 | 25 | 10 | 25 | 3.5% | 0.80 [0.38, 1.69] |
| Song 2012 | 15 | 36 | 12 | 36 | 5.3% | 1.25 [0.68, 2.28] |
| Su 2017 | 24 | 58 | 45 | 177 | 12.3% | 1.63 [1.09, 2.42] |
| **Total (95% CI)** | | **630** | | **893** | **100.0%** | **1.16 [1.01, 1.34]** |
| Total events | 232 | | 274 | | | |

Heterogeneity: Tau² = 0.00; Chi² = 11.63, df = 12 (P = 0.48); I² = 0%
Test for overall effect: Z = 2.12 (P = 0.03)



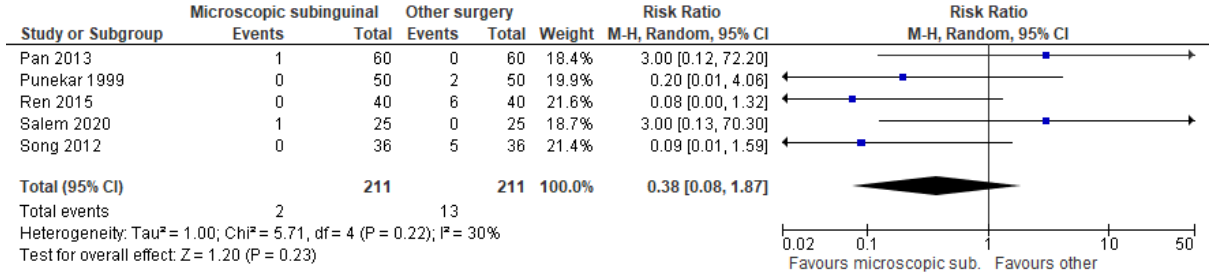
*CI: confidence interval; M-H: Mantel-Haenszel*

**Figure 3: Varicocele recurrence**



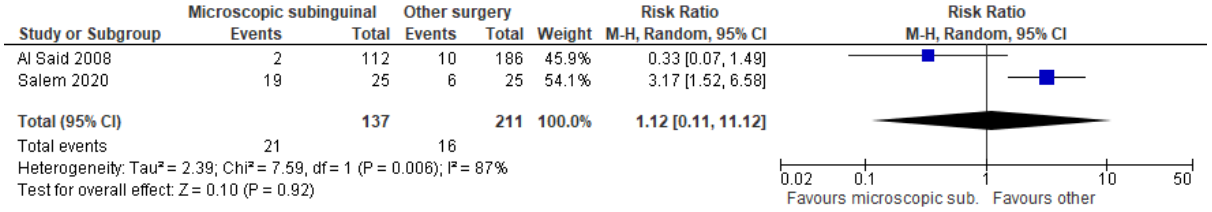

*CI: confidence interval; M-H: Mantel-Haenszel*

**Figure 4: Adverse event (hydrocele formation)**



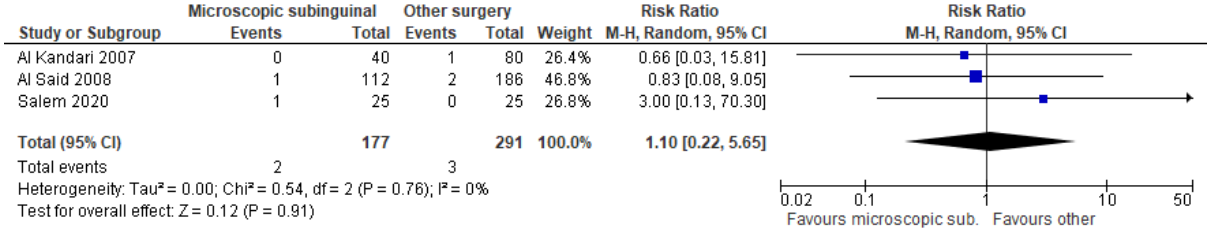
*CI: confidence interval; M-H: Mantel-Haenszel*

**Figure 5: Adverse event (pain)**



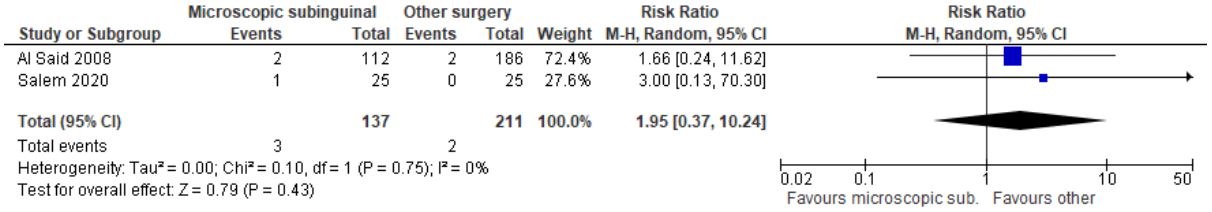

*CI: confidence interval; M-H: Mantel-Haenszel*

**Figure 6: Adverse event (haematoma)**




*CI: confidence interval; M-H: Mantel-Haenszel*

**Figure 7: Adverse event (wound infection)**




*CI: confidence interval; M-H: Mantel-Haenszel*

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# Appendix F GRADE tables and summary of findings tables

## GRADE tables and summary of findings tables for review question: What is the clinical and cost effectiveness of surgical and radiological treatments for fertility problems associated with varicocele?

This section includes GRADE tables only for comparison between microscopic subinguinal surgical treatment and other surgical treatment. For other comparisons, please see the Summary of findings tables from the Cochrane review (Persad 2021): https://doi.org/10.1002/14651858.CD000479.pub6

**Table 5: Evidence profile for comparison between microscopic subinguinal surgical (microsurgical) treatment versus other surgical treatment**

| Quality assessment | | | | | | | No of patients | | Effect | | Quality | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Microscopic subinguinal surgical (microsurgical) treatment | Other surgical treatment | Relative (95% CI) | Absolute | | |
| **Clinical pregnancy** | | | | | | | | | | | | |
| 13[1] | randomised trials | serious[2] | no serious inconsistency | no serious indirectness | serious[3] | none | 232/630 (36.8%) | 274/893 (30.7%) | RR 1.16 (1.01 to 1.34) | 49 more per 1000 (from 3 more to 104 more) | LOW | CRITICAL |
| **Varicocele recurrence** | | | | | | | | | | | | |
| 15[4] | randomised trials | serious[2] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 20/750 (2.7%) | 79/865 (9.1%) | RR 0.47 (0.29 to 0.78) | 48 fewer per 1000 (from 20 fewer to 65 fewer) | MODERATE | IMPORTANT |
| **Adverse event (hydrocele formation)** | | | | | | | | | | | | |
| 5[5] | randomised trials | serious[2] | no serious inconsistency | no serious indirectness | very serious[6] | none | 2/211 (0.95%) | 13/211 (6.2%) | RR 0.38 (0.08 to 1.87) | 38 fewer per 1000 (from 57 fewer to 54 more) | VERY LOW | IMPORTANT |
| **Adverse event (pain)** | | | | | | | | | | | | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 2[7] | randomised trials | very serious[8] | very serious[9] | no serious indirectness | very serious[6] | none | 21/137 (15.3%) | 16/211 (7.6%) | RR 1.12 (0.11 to 11.12) | 9 more per 1000 (from 67 fewer to 767 more) | VERY LOW | IMPORTANT |
| **Adverse event (haematoma)** | | | | | | | | | | | | |
| 3[10] | randomised trials | serious[2] | no serious inconsistency | no serious indirectness | very serious[6] | none | 2/177 (1.1%) | 3/291 (1%) | RR 1.10 (0.22 to 5.65) | 1 more per 1000 (from 8 fewer to 48 more) | VERY LOW | IMPORTANT |
| **Adverse event (wound infection)** | | | | | | | | | | | | |
| 2[11] | randomised trials | serious[2] | no serious inconsistency | no serious indirectness | very serious[6] | none | 3/137 (2.2%) | 2/211 (0.95%) | RR 1.95 (0.37 to 10.24) | 9 more per 1000 (from 6 fewer to 88 more) | VERY LOW | IMPORTANT |

*CI: confidence interval; MID: minimally important difference; RR: risk ratio; SR: systematic review*

*[1] Studies included in analysis of clinical pregnancy: 12 studies (Al Kandari 2007; Al Said 2008; Bryniarski 2016; Fang 2013; Gao 2017; Min 2011; Pan 2013; Punekar 1999; Qi 2009; Ren 2015; Song 2012; Su 2017) extracted from the Cochrane review (Persad 2021) and Salem 2020*

*[2] Serious risk of bias in the evidence contributing to the outcomes as per Cochrane RoB in SR (Persad 2021) and RoB 2*

*[3] 95% CI crosses 1 MID*

*[4] Studies included in analysis of varicocele recurrence: 14 studies (Fang 2013; Gao 2017; Gontero 2005; Meng 2017; Min 2011; Pan 2013; Pu 2014; Punekar 1999; Ren 2015; Song 2012; Su 2017; Yang 2017; Zhang 2015; Zheng 2012) extracted from the Cochrane review (Persad 2021) and Salem 2020*

*[5] Studies included in analysis of hydrocele formation: 4 studies (Pan 2013; Punekar 1999; Ren 2015; Song 2012) extracted from the Cochrane review (Persad 2021) and Salem 2020*

*[6] 95% CI crosses 2 MIDs*

*[7] Studies included in analysis of pain: 1 study (Al Said 2008) extracted from the Cochrane review (Persad 2021) and Salem 2020*

*[8] Very serious risk of bias in the evidence contributing to the outcomes as per Cochrane RoB in SR (Persad 2021) and RoB 2*

*[9] Very serious heterogeneity unexplained by subgroup analysis*

*[10] Studies included in analysis of haematoma: 2 studies (Al Kandari 2007; Al Said 2008) extracted from the Cochrane review (Persad 2021) and Salem 2020*

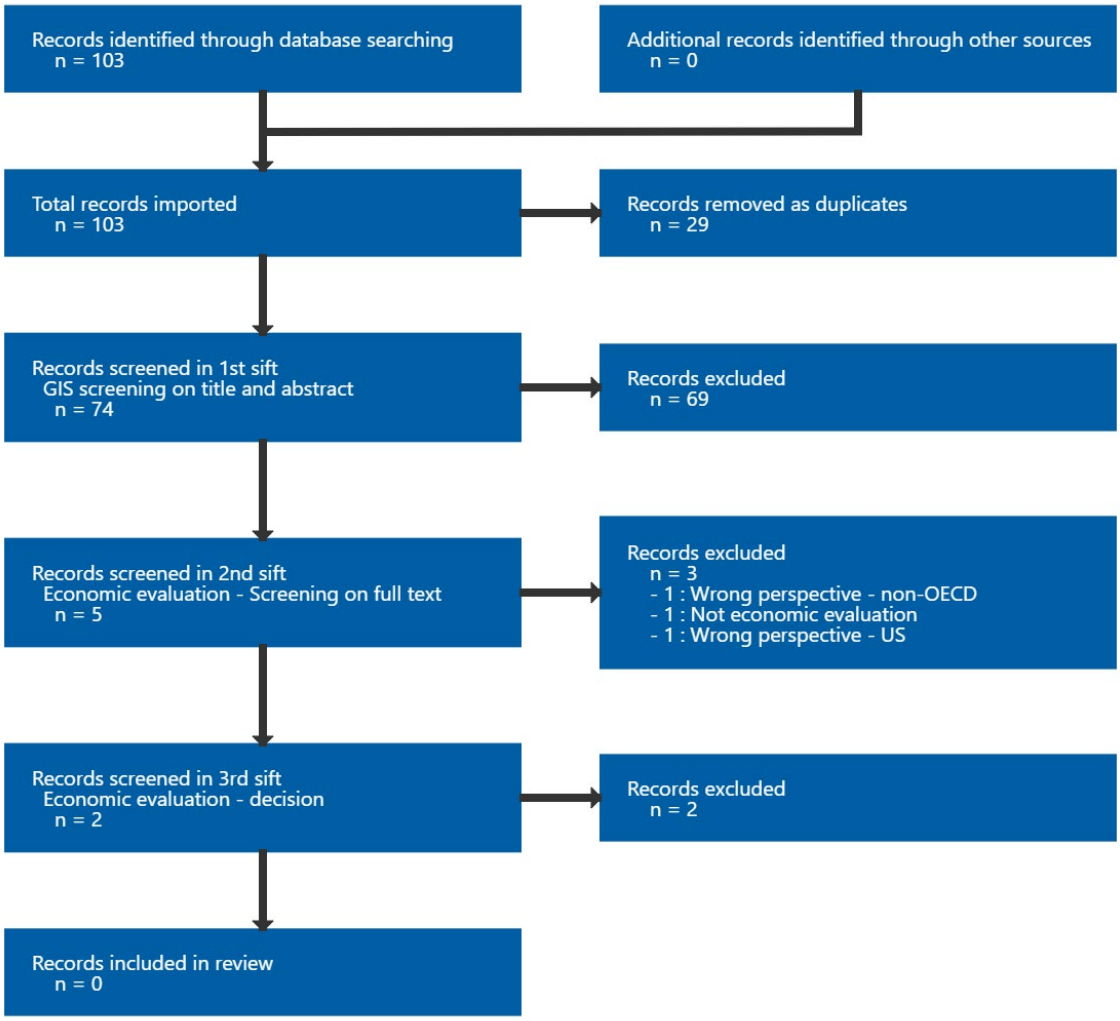
*[11] Studies included in analysis of wound infection: 1 study (Al Said 2008) extracted from the Cochrane review (Persad 2021) and Salem 2020*

# Appendix G Economic evidence study selection

## Study selection for review question: What is the clinical and cost effectiveness of surgical and radiological treatments for fertility problems associated with varicocele?

No health economic studies were included for this review question. Reasons for study exclusions can be found in Appendix J.

**Figure 8: Study selection flow chart**



# Appendix H Economic evidence tables

## Economic evidence tables for review question: What is the clinical and cost effectiveness of surgical and radiological treatments for fertility problems associated with varicocele?

No evidence was identified which was applicable to this review question.

# Appendix I Economic model

## Economic model for review question: What is the clinical and cost effectiveness of surgical and radiological treatments for fertility problems associated with varicocele?

No economic analysis was conducted for this review question.

# Appendix J Excluded studies

## Excluded studies for review question: What is the clinical and cost effectiveness of surgical and radiological treatments for fertility problems associated with varicocele?

### Excluded effectiveness studies

**Table 6: Excluded studies and reasons for their exclusion**

| Study | Code [Reason] |
|---|---|
| Adams, Yussif; Amidu, Nafiu; Afoko, Akisibadek Alekz (2023) Changes in testicular arterial hemodynamic, gonadotropin levels, and semen parameters among varicocele patients randomized to varicocelectomy or observed in Tamale, Ghana. Urologia 90(2): 286-294 | - Study does not contain relevant outcomes<br>*Reports sperm parameters outcomes* |
| Agarwal, Ashok, Cannarella, Rossella, Saleh, Ramadan et al. (2023) Impact of Varicocele Repair on Semen Parameters in Infertile Men: A Systematic Review and Meta-Analysis. The world journal of men's health 41(2): 289-310 | - Systematic review used as source of primary studies |
| Almekaty, K, Zahran, M H, Zoeir, A et al. (2019) The role of artery-preserving varicocelectomy in subfertile men with severe oligozoospermia: a randomized controlled study. Andrology 7(2): 193-198 | - Comparator in study does not match that specified in protocol<br>*Compares internal spermatic artery preservation vs. artery ligation* |
| Asafu-Adjei, D., Judge, C., Deibert, C.M. et al. (2020) Systematic Review of the Impact of Varicocele Grade on Response to Surgical Management. Journal of Urology 203(1): 48-56 | - Systematic review used as source of primary studies |
| Bhowmick, S. and Debbarma, M.K. (2024) PROSPECTIVE COMPARATIVE STUDY OF OPEN AND MICROSCOPIC (LOUPE-4X MAGNIFICATION) VARICOCELECTOMY USING SEMINAL AND HORMONAL PARAMETERS IN GRADES II AND III VARICOCELES. Journal of Population Therapeutics and Clinical Pharmacology 31(7): 806 | - Study does not contain a relevant population<br>*Only 66.67% of participants had infertility and data not reported for this group separately* |
| Birowo, Ponco, Tendi, William, Widyahening, Indah Suci et al. (2020) The benefits of varicocele repair for achieving pregnancy in male infertility: A systematic review and meta-analysis. Heliyon 6(11): e05439 | - Systematic review used as source of primary studies |
| Cannarella, Rossella, Shah, Rupin, Hamoda, Taha Abo-Almagd Abdel-Meguid et al. (2023) Does Varicocele Repair Improve Conventional Semen Parameters? A Meta-Analytic Study of Before-After Data. The world journal of men's health | - Systematic review used as source of primary studies |

| Study | Code [Reason] |
|---|---|
| Cannarella, Rossella, Shah, Rupin, Ko, Edmund et al. (2024) Effects of Varicocele Repair on Testicular Endocrine Function: A Systematic Review and Meta-Analysis. The world journal of men's health | - Systematic review, included studies checked for relevance |
| Cannarella, Rossella, Shah, Rupin, Saleh, Ramadan et al. (2024) Effects of Varicocele Repair on Sperm DNA Fragmentation and Seminal Malondialdehyde Levels in Infertile Men with Clinical Varicocele: A Systematic Review and Meta-Analysis. The world journal of men's health 42(2): 321-337 | - Systematic review, included studies checked for relevance |
| Cayan, Selahittin, Orhan, Irfan, Akbay, Erdem et al. (2019) Systematic review of treatment methods for recurrent varicoceles to compare post-treatment sperm parameters, pregnancy and complication rates. Andrologia 51(11): e13419 | - Systematic review used as source of primary studies |
| Chung, Kenneth L Y, Hung, Judy W S, Yam, Felix S D et al. (2023) Prospective Randomized Controlled Trial Comparing Laparoscopic Palomo Surgery vs Scrotal Antegrade Sclerotherapy in Adolescent Varicocele. The Journal of urology 209(3): 600-610 | - Study does not contain a relevant population *Participants are adolescents (mean age 14y.) with varicocele* |
| Chung, KLY, Hung, JWS, Yam, FSD et al. (2022) Prospective Randomized Controlled Trial Comparing Laparoscopic Palomo Surgery versus Scrotal Antegrade Sclerotherapy in Adolescent Varicocele. Journal of urology: 101097ju0000000000003087 | - Duplicate reference |
| Dursun, Murat, Besiroglu, Huseyin, Aydin, Resat et al. (2024) Is varicocoelectomy indicated in infertile men with isolated teratozoospermia? a systematic review and meta-analysis. Andrology 12(8): 1642-1650 | - Systematic review, included studies checked for relevance |
| Fabiani, Andrea, Pavia, Maria Pia, Stramucci, Silvia et al. (2022) Do sclero-embolization procedures have advantages over surgical ligature in treating varicocele in children, adolescents and adults? Results from a systematic review and meta-analysis. Andrologia 54(8): e14510 | - Systematic review used as source of primary studies |
| Fallara, Giuseppe, Capogrosso, Paolo, Pozzi, Edoardo et al. (2023) The Effect of Varicocele Treatment on Fertility in Adults: A Systematic Review and Meta-analysis of Published Prospective Trials. European urology focus 9(1): 154-161 | - Systematic review used as source of primary studies |
| Fallara, Giuseppe, Tang, Stanley, Pang, Karl H et al. (2023) Treatment of Persistent or | - Systematic review used as source of primary studies |

| Study | Code [Reason] |
|---|---|
| Recurrent Varicoceles: A Systematic Review. European urology focus 9(3): 531-540 | |
| Fathi, Atef, Mohamed, Omar, Mahmoud, Osama et al. (2021) The impact of varicocelectomy on sperm DNA fragmentation and pregnancy rate in subfertile men with normal semen parameters: A pilot study. Arab journal of urology 19(2): 186-190 | - Not a relevant study design<br>*Non-randomised study* |
| Feng L, Luo Y HM (2016) Comparison of the effect of ligation of varicocele under lumbar microscope and ligation of laparoscopic varicocele. J Qiqihar Univ Med: 1518-1520 | - Full text paper not available |
| Feng, Rui, Jiang, Jingsong, Cheng, Dexin et al. (2022) Clinical efficacy comparison of sclerosing embolization with 3% polidocanol and the microsurgical subinguinal varicocelectomy in primary varicocele patients. Andrologia 54(10): e14530 | - Not a relevant study design<br>*Non-randomised study* |
| Han, Dayu, Feng, Xin, Guo, Zexin et al. (2023) Combination of High Ligation and Intraoperative Embolization using Polidocanol for Treatment of Varicoceles. Journal of visualized experiments : JoVE | - Study design in PICO<br>*Non-randomised study* |
| Huyghe, E; Faix, A; Methorst, C (2023) [Surgery to improve male fertility]. Progres en urologie : journal de l'Association francaise d'urologie et de la Societe francaise d'urologie 33(13): 681-696 | - Study not reported in English |
| Japari, A. and El Ansari, W. (2024) Varicocele repair for severe oligoasthenoteratozoospermia: Scoping review of published guidelines, and systematic review of the literature. Arab Journal of Urology | - Systematic review, included studies checked for relevance |
| Jargiello, T., Drelich-Zbroja, A., Falkowski, A. et al. (2015) Endovascular transcatheter embolization of recurrent postsurgical varicocele: anatomic reasons for surgical failure. Acta radiologica (Stockholm, Sweden : 1987) 56(1): 63-69 | - Not a relevant study design |
| Kamran, Hooman; Shamohammadi, Iman; Haghpanah, Abdolreza (2024) A closer look: sperm analysis and clinical outcomes of microscopic and loupe-assisted varicocele repair in male infertility due to moderate-to-severe varicocele. International urology and nephrology | - Study design in PICO<br>*Observational study* |
| Kasunic, Daniel, Crebert, Mitchell, Treacy, Patrick-Julien et al. (2024) Comparing the efficacy of different embolisation materials in | - Systematic review, included studies checked for relevance |

| Study | Code [Reason] |
|---|---|
| improving pain and fertility outcomes in patients with varicoceles: A systematic review. Journal of medical imaging and radiation oncology | |
| Kotb, S., Abdel-Rassoul, M.A., Elkousy, M.M. et al. (2023) Comparison of the pulling technique versus the standard technique in microsurgical subinguinal varicocelectomy: a randomized controlled trial. African Journal of Urology 29(1): 69 | - Comparator in study does not match that specified in protocol<br>*Compares microsurgical subinguinal varicocelectomy using the pulling technique vs. microsurgical subinguinal varicocelectomy using the standard technique* |
| Krause W, Müller HH, Schäfer H et al. (2002) Does treatment of varicocele improve male fertility? results of the 'Deutsche Varikozelenstudie', a multicentre study of 14 collaborating centres. Andrologia 34(3): 164-171 | - Included in Persad 2021 systematic review |
| Li Y, Luo S, Xu Y GX (2011) Laparoscopic and microsurgical treat varicocele the curative effect of recurrent comparison.: 1551-1553 | - Full text paper not available |
| Li, Zixiang, Hu, Simeng, Zhou, Raorao et al. (2022) Comparison of the efficacy and safety of microscopic and laparoscopic surgery for varicocele. World journal of urology 40(1): 299-300 | - Not a relevant study design<br>*Letter to the editor* |
| Liu T, Li J, Huo Z, Zhang H WX (2017) Curative effects of spermatic vein ligation under microscope and laparo- scope for varicocele treatment. Chin J Hum Sex: 8-10 | - Full text paper not available |
| Liu, Qiangzhao, Zhang, Xiaofeng, Zhou, Fenghai et al. (2022) Comparing Endovascular and Surgical Treatments for Varicocele: A Systematic Review and Meta-Analysis. Journal of vascular and interventional radiology : JVIR 33(7): 834-840e2 | - Systematic review used as source of primary studies |
| Mansoor, M., Ali, A., Kumar, N. et al. (2021) Laparoscopic versus open inguinal ligation of varicocele: A study of 60 cases. Pakistan Journal of Medical and Health Sciences 15(10): 3161-3165 | - Not a relevant study design<br>*Participants were allocated to study groups by alternation* |
| Nasser, H.M., Hussein, A., Behairy, G.M. et al. (2020) Impact of percutaneous embolization versus subinguinal microsurgical ligation on semen parameters in primary varicocele patients: comparative study. Egyptian Journal of Radiology and Nuclear Medicine 51(1): 249 | - Not a relevant study design<br>*Non-randomised study* |
| Nieschlag E, Behre HM, Schlingheider A et al. (1993) Surgical ligation vs. angiographic embolization of the vena spermatica: a prospective randomized study for the treatment of varicocele-related infertility. Andrologia 25(5): 233-237 | - Included in Persad 2021 systematic review |

| Study | Code [Reason] |
|---|---|
| Nieschlag E, Hertle L, Fischedick A et al. (1998) Update on treatment of varicocele: counselling as effective as occlusion of the vena spermatica. Human reproduction (Oxford, England) 13(8): 2147-2150 | - Included in Persad 2021 systematic review |
| Nieschlag E, Hertle L, Fischedick A et al. (1995) Treatment of varicocele: counselling as effective as occlusion of the vena spermatica. Human reproduction (Oxford, England) 10(2): 347-353 | - Included in Persad 2021 systematic review |
| Okeke, Chike John, Ojewola, Rufus Wale, Jeje, Emmanuel Ajibola et al. (2023) A comparison of loupe-assisted and non-loupe-assisted subinguinal varicocelectomy. The Nigerian postgraduate medical journal 30(3): 218-225 | - Study does not contain a relevant intervention<br>*The study compares same intervention with and without the loupe* |
| Onozawa M, Endo F, Suetomi T et al. (2002) Clinical study of varicocele: statistical analysis and the results of long-term follow-up. International journal of urology : official journal of the Japanese Urological Association 9(8): 455-461 | - Not a relevant study design<br>*Non-randomised study* |
| Ou, Ningjing, Zhu, Jun, Zhang, Wei et al. (2019) Bilateral is superior to unilateral varicocelectomy in infertile men with bilateral varicocele: Systematic review and meta-analysis. Andrologia 51(11): e13462 | - Systematic review used as source of primary studies |
| Prasad, J.; Daga, R.; Sandhu, P.S. (2024) Comparative study of laparoscopic varicocele ligation versus sub-inguinal varicocelectomy. Journal of Cardiovascular Disease Research 15(4): 1421 | - Study does not contain a relevant population<br>*The study did not specify whether participants were infertile* |
| Qiangzhao, L, Xiaofeng, Z, Fenghai, Z et al. (2022) Comparing radiological and surgical treatments for varicocele: A systematic review and meta-analysis. Journal of vascular and interventional radiology : JVIR | - Systematic review used as source of primary studies |
| Ramirez Calazans, A, Ibarra Rodriguez, M R, Wiesner Torres, S R et al. (2024) Comparing two vascular division techniques in laparoscopic varicocelectomy. A prospective study. Cirugia pediatrica : organo oficial de la Sociedad Espanola de Cirugia Pediatrica 37(2): 75-78 | - Study does not contain a relevant population<br>*Study conducted in 10-15 years old boys* |
| Ramon, Ryan, Warli, Syah Mirsya, Siregar, Ginanda Putra et al. (2024) Varicocele repair in improving spermatozoa, follicle-stimulating hormone, and luteinizing hormone parameters in infertile males with azoospermia: a systematic review and meta-analysis. Asian journal of andrology 26(6): 628-634 | - Systematic review, included studies checked for relevance |

| Study | Code [Reason] |
|---|---|
| Ramzan, M., Farooq, M.A., Uzair, M. et al. (2024) A COMPARATIVE STUDY OF LAPAROSCOPIC VERSUS OPEN HIGH LIGATION OF VARICOCELE. Journal of Population Therapeutics and Clinical Pharmacology 31(8): 1476 | - Study design in PICO<br>*Unclear whether it is a RCT or Quasi-RCT as detailed information on randomisation process or participant allocation process not provided* |
| Santos, M. and Lopez, P.J. (2022) Laparoscopic varicocele. Urology Video Journal 16: 100194 | - Not a relevant study design<br>*An abstract and a video* |
| Sasson, Daniel C and Kashanian, James A (2020) Varicoceles. JAMA 323(21): 2210 | - Conference abstract |
| Sautter T, Sulser T, Suter S et al. (2002) Treatment of varicocele: a prospective randomized comparison of laparoscopy versus antegrade sclerotherapy. European urology 41(4): 398-400 | - Included in Persad 2021 systematic review |
| Shah, Bhushan; Bajaj, Jayant; Vijendra, Adithya R (2024) Beyond the Incision: A Comparative Study of Suprainguinal and Inguinal Varicocele Surgeries. Cureus 16(8): e67073 | - Comparator in study does not match that specified in protocol<br>*Inguinal approach (open) vs. Suprainguinal approach (open)* |
| Shahzad, S., Shahid, M.W., Mughal, M.A. et al. (2021) Comparison of open sub-inguinal and microscopic sub-inguinal varicocelectomy for improvement of sperm parameters. Pakistan Journal of Medical and Health Sciences 15(10): 2882-2885 | - Study does not contain relevant outcomes<br>*Study examines the improvement in sperm count and motility* |
| Soetandar, Alwin, Noegroho, Bambang Sasongko, Siregar, Safendra et al. (2022) Microsurgical varicocelectomy effects on sperm DNA fragmentation and sperm parameters in infertile male patients: A systematic review and meta-analysis of more recent evidence. Archivio italiano di urologia, andrologia : organo ufficiale [di] Societa italiana di ecografia urologica e nefrologica 94(3): 360-365 | - Systematic review used as source of primary studies |
| Sun XL, Wang JL, Peng YP, Gao QQ, Song T, Yu W EA (2018) Bilateral is superior to unilateral varicocelectomy in infertile males with left clinical and right subclinical varicocele: a prospective randomized controlled study. Int Urol Nephrol: 205-210 | - Comparator in study does not match that specified in protocol<br>*Bilateral varicocelectomy vs. Unilateral varicocelectomy* |
| Syarief, A.N., Rahman, I.A., Setiawan, M.R. et al. (2023) The Influence of Number of Ligated Veins in Varicocele Patients Undergoing Microsurgical Varicocelectomy in Postoperative Pain and Sperm Parameters Outcome. Medical archives (Sarajevo, Bosnia and Herzegovina) 77(4): 299 | - Systematic review, included studies checked for relevance |
| Syarief, Ahmad Nurfakhri, Rahman, Ilham Akbar, Sangadji, Agung Ravi Saputra et al. | - Study does not contain a relevant population<br>*Participants are adolescents (mean age 13.7 y.)* |

| Study | Code [Reason] |
|---|---|
| (2023) A systematic review and meta-analysis on the efficacy of internal spermatic artery ligation during laparoscopic varicocelectomy in children and adolescents: Is it safe?. Archivio italiano di urologia, andrologia : organo ufficiale [di] Societa italiana di ecografia urologica e nefrologica 95(3): 11627 | |
| Söylemez H, Penbegül N, Atar M, Bozkurt Y, Sancaktutar AA AB (2012) Comparison of Laparoscopic and Microscopic Subinguinal Varicocelectomy in terms of Postoperative Scrotal Pain. JSLS 16: 212-217 | - Study design in PICO<br>*Non-randomised study* |
| Wang, Hai and Ji, Zhi-Gang (2020) Microsurgery Versus Laparoscopic Surgery for Varicocele: A Meta-Analysis and Systematic Review of Randomized Controlled Trials. Journal of investigative surgery : the official journal of the Academy of Surgical Research 33(1): 40-48 | - Systematic review used as source of primary studies |
| Wang, Qun; Liu, Yanhong; Wang, Libo (2020) Open, Laparoscopic, and Microsurgical Varicocelectomy for Male Infertility: a Systematic Review and Meta-analysis. Indian Journal of Surgery 82(4): 478-485 | - Systematic review used as source of primary studies |
| Wang, Xinkun, Chen, Tong, Qiu, Junfeng et al. (2020) Effects of Primary Varicocele and Related Surgery in Male Infertility: A Meta-Analysis. Frontiers in surgery 7: 586153 | - Systematic review used as source of primary studies |
| Wang, Y., Song, Y., Qin, C. et al. (2023) Comparison between Microsurgical Varicocelectomy with and without Testicular Delivery for Treatment of Varicocele: An Updated Systematic Review and Meta-Analysis. Andrologia 2023: 7348578 | - Systematic review, included studies checked for relevance |
| Warli, Syah Mirsya, Nabil, Rizky An, Kadar, Dhirajaya Dharma et al. (2024) A comparison between the efficacy and complication of laparoscopic and microsurgical varicocelectomy: Systematic review and meta-analysis. Urology annals 16(2): 113-119 | - Systematic review, included studies checked for relevance |
| Yavetz H, Levy R, Papo J et al. (1992) Efficacy of varicocele embolization versus ligation of the left internal spermatic vein for improvement of sperm quality. International journal of andrology 15(4): 338-344 | - Included in Persad 2021 systematic review |
| Zhang, Gaoyue, Li, Jianying, Xu, Zhiming et al. (2024) Microscopic Varicocelectomy under Local Anesthesia as the Treatment of Varicocele. Journal of visualized experiments : JoVE | - Study design in PICO<br>*Non-randomised study* |

## Excluded economic studies

**Table 7: Excluded health economic studies and reason for their exclusion**

| Study | Code [Reason] |
|---|---|
| ***Excluded in the final sift*** | |
| Boeri, Luca; Fulgheri, Irene; Cristina, Marco et al. (2022) Varicocoele embolization with sclerosing agents leads to lower radiation exposure and procedural costs than coils: Data from a real-life before and after study. Andrology; 2022; vol. 10 (no. 4); 694-701 | - Total costs for both interventions were presented but there was no explanation as to how these costs were estimated or obtained<br><br>- Cost comparison study based on retrospective data with 116 men included |
| Clements, Warren; Chenoweth, Abigail; Morphett, Laura et al (2024) A cost outcome study of varicocoele embolisation and future pregnancy in an Australian public hospital setting.. Journal of medical imaging and radiation oncology; 2024; vol. 68 (no. 3); 282-288 | - Cost comparison study was based on retrospective data with 18 people included |
| ***Excluded at full text review (2nd sift)*** | |
| Wickham, Azadeh; Vu, Dan; El-Arabi, Ahmad; Gatti, John M (2021) Adolescent Varicocelectomy: Success at What Cost? Clinical Outcome and Cost Comparison of Surgical Ligation and Percutaneous Embolization. Journal of laparoendoscopic & advanced surgical techniques. Part A; 2021; vol. 31 (no. 8); 942-946 | - Wrong perspective – US |
| Vu Tan, L; Phuc Cam Hoang, N; Ba Tien Dung, M et al. (2023) Spontaneous pregnancies post-microsurgical varicocelectomy in infertile men with severe oligozoospermia: a preliminary vietnamese report. La Clinica terapeutica; 2023; vol. 174 (no. 2); 126-131 | - Not an economic evaluation |
| Jing, Ye-Xiang; Wang, Rui-Hua; Liu, Zhao-Xuan; Meng, Qing-Yi (2020) Analysis of internal spermatic vein embolization through catheter versus laparoscopic high ligation in treatment of left varicocele. Vascular; 2020; vol. 28 (no. 5); 583-590 | - Wrong perspective – non-OECD |

# Appendix K Research recommendations – full details

## Research recommendation for review question: What is the clinical and cost effectiveness of surgical and radiological treatments for fertility problems associated with varicocele?

### K.1 Research recommendation

What is the clinical and cost effectiveness of radiological, surgical and microsurgical treatment for male factor fertility problems associated with clinically detected varicocele and reduced semen parameters on improving live births from spontaneous conception?

### K.2 Why this is important

There is some evidence showing higher pregnancy rates following surgical and radiological treatment for male factor fertility problems in those with clinical varicocele and abnormal semen analysis. However, most of the RCT evidence does not report live birth as an outcome. There is also uncertainty about the relative effectiveness of surgical and radiological treatments, and cost effectiveness particularly of microsurgical treatment. Given that varicocele is a common cause of male factor fertility problems and is a reversible condition, examining the clinical and cost effectiveness of surgical and radiological treatment should allow the best treatment to be offered to improve the chance of live birth.

### K.3 Rationale for research recommendation

**Table 8: Research recommendation rationale**

| | |
|---|---|
| **Importance to 'patients' or the population** | Varicocele is a common cause of male factor fertility problems and is a reversible condition. Determining the most clinical and cost-effective treatment for clinical varicocele could enable couples to conceive spontaneously who would otherwise not be able to |
| **Relevance to NICE guidance** | This guideline recommends that surgical or radiological treatment is considered for male factor fertility problems associated with clinically detected varicocele and abnormal semen parameters. However, uncertainty about the relative clinical and cost-effectiveness of different treatments did not allow for greater specificity or strength in terms of the treatment recommended |
| **Relevance to the NHS** | The outcome of this research could increase the treatment options for male factor fertility problems associated with varicocele |
| **National priorities** | Improved treatment options for male factor fertility problems that may enable spontaneous conception |
| **Current evidence base** | There is some RCT evidence showing higher pregnancy rates following surgical or radiological treatment for male factor fertility problems. However, the evidence for the primary outcome of live birth is sparse and equivocal |
| **Equality considerations** | None known |

*RCT: randomised controlled trial*

### K.1.4 Modified PICO table

**Table 9: Research recommendation modified PICO table**

| | |
|---|---|
| **Population** | People with male factor fertility problems associated with clinically detected varicocele and reduced semen parameters who are trying to conceive spontaneously with a partner with no significant female factor fertility problems |
| **Intervention** | • Radiological treatment<br>  ○ Varicocele embolisation<br>  ○ Sclerotherapy<br>• Surgical treatment<br>  ○ Laparoscopic varicocelectomy<br>  ○ Open varicocelectomy<br>• Microsurgical varicocelectomy |
| **Comparator** | Head-to-head comparison of radiological, surgical and microsurgical interventions (above) |
| **Outcome** | Live birth; clinical pregnancy; varicocele recurrence; motile sperm concentration; adverse events (hydrocele formation; pain; haematoma; infection; testicular atrophy); cost-effectiveness |
| **Study design** | RCT with economic analysis |
| **Timeframe** | Follow-up to pregnancy loss or live birth |
| **Additional information** | None |

*RCT: randomised controlled trial*