

Surgery or embolization for varicoceles in subfertile men (Review)

Kroese ACJ, de Lange NM, Collins J, Evers JLH



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[Intervention Review]

Surgery or embolization for varicoceles in subfertile men

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ABSTRACT

Background

A varicocele is a meshwork of distended blood vessels in the scrotum, usually left-sided, due to dilatation of the spermatic vein. Although the concept that a varicocele causes male subfertility has been around for more than 50 years now, the mechanisms by which a varicocele would affect fertility have not yet been satisfactorily explained. Neither is there sufficient evidence to explain the mechanisms by which varicocelectomy would restore fertility. Furthermore, it has been questioned whether a causal relation exists at all between the distension of the pampiniform plexus (a network of many small veins found in the human male spermatic cord) and impairment of fertility.

Objectives

To evaluate the effect of varicocele treatment on live birth and pregnancy rate in subfertile couples where the male has a varicocele.

Search methods

We searched the Cochrane Menstrual Disorders and Subfertility Group Trials Register (12 September 2003 to January 2012), the Cochrane Central Register of Controlled Trials (CENTRAL) in *The Cochrane Library* Issue 1, 2012), MEDLINE (January 1966 to January 2012), EMBASE (January 1985 to January 2012), PsycINFO (to Week 1 2012) and reference lists of articles. In addition, we handsearched specialist journals in the field from their first issue until 2012. We also checked cross-references, references from review articles and contacted researchers in the field.

Selection criteria

Randomised controlled trials (RCTs) were included if they were relevant to the clinical question posed. If they reported pregnancy rates or live birth rates as an outcome measure, and if they reported data in treated (surgical ligation or radiological embolization of the internal spermatic vein) compared to untreated or placebo groups. Two authors independently screened potentially relevant trials. Any differences of opinion were resolved by consensus (none occurred for this review).

Data collection and analysis

Ten studies met the inclusion criteria for the review. For one study we had only data from a published abstract. All ten studies only included men from couples with subfertility problems; one excluded men with sperm counts less than 5 million per mL and one excluded men with sperm counts less than 2 million per mL, with or without progressive motility of less than 10%. Two trials involving

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clinical varicoceles included some men with normal semen analysis. Three studies specifically addressed only men with subclinical varicoceles. Studies were excluded from meta-analysis if they made comparisons other than those specified above.

Main results

The meta-analysis included 894 men. No studies reported live birth. The combined fixed-effect odds ratio (OR) of the 10 studies for the outcome of pregnancy was 1.47 (95% confidence interval (CI) 1.05 to 2.05, very low quality evidence), favouring the intervention. The number needed to treat for an additional beneficial outcome was 17, suggesting benefit of varicocele treatment over expectant management for pregnancy rate in subfertile couples in whom varicocele in the man was the only abnormal finding. Omission of the studies including men with normal semen analysis and subclinical varicocele, some of which had semen analysis improvement as the primary outcome rather than live birth or pregnancy rate, was the subject of a planned subgroup analysis. The outcome of the subgroup analysis (five studies) also favoured treatment, with a combined OR 2.39 (95% CI 1.56 to 3.66). The number needed to treat for an additional beneficial outcome was 7. The evidence was suggestive rather than conclusive, as the main analysis was subject to fairly high statistical heterogeneity ($I^2 = 67\%$) and findings were no longer significant when a random-effects model was used or when analysis was restricted to higher quality studies.

Authors' conclusions

There is evidence suggesting that treatment of a varicocele in men from couples with otherwise unexplained subfertility may improve a couple's chance of pregnancy. However, findings are inconclusive as the quality of the available evidence is very low and more research is needed with live birth or pregnancy rate as the primary outcome.

PLAIN LANGUAGE SUMMARY

Surgery or embolization for varicoceles in subfertile men

Varicocele is a dilatation (enlargement) of the veins along the spermatic cord (the cord suspending the testis) in the scrotum. Dilatation occurs when valves within the veins along the spermatic cord fail and allow retrograde blood flow, causing a backup of blood. The mechanisms by which varicocele might affect fertility have not yet been explained, and neither have the mechanisms by which surgical treatment of the varicocele might restore fertility. This review analysed 10 studies (894 participants) and found evidence (combined odds ratio was 1.47 (95% CI 1.05 to 2.05) to suggest an increase in pregnancy rates after varicocele treatment compared to no treatment in subfertile couples, in whom, apart from poor sperm quality, varicocele in the man was the only abnormal finding. This means that 17 men would need to be treated to achieve one additional pregnancy. However, findings were inconclusive as the quality of the available evidence was very low and more research is needed with live birth or pregnancy rate as the primary outcome.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Varicocele occlusion versus no treatment for varicoceles in subfertile men						
Patient or population: Patients with varicoceles in subfertile men						
Settings:						
Intervention: Varicocele occlusion versus no treatment						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Varicocele occlusion versus no treatment				
Pregnancy rate	173 per 1000	235 per 1000 (180 to 300)	OR 1.47 (1.05 to 2.05)	894 (10 studies)	⊕○○○ very low ^{1,2}	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; OR: Odds ratio;

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹ All of the trials were open label due to very different interventions but there is no evidence that an attempt was made to blind outcome assessors. There were insufficient details provided for allocation concealment, randomisation and selective reporting in almost all of the trials.

² I² statistic was 67%

BACKGROUND

Description of the condition

A varicocele is a meshwork of distended blood vessels in the scrotum, usually left-sided, due to dilatation of the spermatic vein. There are different grades of varicocele as defined by the World Health Organization (WHO): WHO 0: only demonstrable by technical diagnostic methods; WHO I: only palpable/visible during Valsalva manoeuvre; WHO II: palpable when in upright position at room temperature; WHO III: visible when in upright position at room temperature. It has long been uncertain whether it is true or not that a varicocele is “nature’s attempt to heal a diseased testis rather than afflict an otherwise healthy one” (Nieschlag 1995/1998). Although the concept that a varicocele causes male subfertility has been around for more than fifty years now, the mechanisms by which varicoceles would affect fertility have not yet been satisfactorily explained. Neither is there sufficient evidence to explain the mechanisms by which varicocelectomy might restore fertility. Furthermore, it has been questioned whether a causal relationship exists at all between the distension of the pampiniform plexus (a network of many small veins found in the human male spermatic cord) and impairment of fertility.

In a multi-centre study on the investigation and diagnosis of the subfertile couple, the incidence of varicocele in the male partners of subfertile couples was 11.7%. On the other hand, in men with abnormal semen analysis (SA) parameters the incidence of varicocele was 25.4% (WHO 1992). Thus, varicocele is the most frequent single physical abnormality found in subfertile men and occlusion of the left spermatic vein is accepted by many physicians as the treatment of choice for this condition (Nieschlag 1993). Estimates of the incidence of varicocele in men from the general population, however, arrive at a similar figure (15%) (ASRM 2008). Yet varicocele for many years has been associated with abnormalities in semen parameters and implicated as a cause of male subfertility (Dubin 1977). Impaired blood drainage from the testis leading to increased scrotal temperature, hypoxia, increased testicular pressure and reflux of adrenal metabolites and hormones, with deleterious effects on spermatogenesis have been proposed as the etiology (Dubin 1975; Homonnai 1980; Pryor 1987; Segenreich 1986).

Description of the intervention

Varicocelectomy is the surgical correction of a varicocele. There are various methods, the traditional method of treatment being surgical ligation of the internal spermatic vein. Several surgical techniques have been employed but retroperitoneal high ligation (as initially described by Ivanisevitch and modified by Palomo) and trans inguinal ligation (as described by Bernardi) are the most frequently performed. More recently, selective embolization of the

internal spermatic vein with sclerosing solutions (sclerosation), tissue adhesives, or detachable balloons or coils have been used as alternatives. Laparoscopic ligation has also been proposed (Cayan 2009).

How the intervention might work

The mechanisms by which a varicocele might affect fertility have not yet been explained, and neither have the mechanisms by which surgical treatment of the varicocele might restore fertility. Impaired blood drainage from the testis leading to increased scrotal temperature, hypoxia, increased testicular pressure and reflux of adrenal metabolites and hormones, with deleterious effects on spermatogenesis have been proposed as the etiology (Dubin 1975; Homonnai 1980; Pryor 1987; Segenreich 1986).

Why it is important to do this review

Many men with varicocele have normal fertility and investigators have doubted the therapeutic value of treatment of varicocele (Rodriguez 1978; Vermeulen 1985). A review of 50 publications of observational studies including a total of 5471 couples with uncompromised female fertility and a varicocele in the man showed widely varying pregnancy rates of 0% to 50% after treatment, with a weighted mean of 36% (Mordel 1990). This is similar to the 33% spontaneous pregnancy rate in a 1992 review of 20 studies of 2026 couples with completely unexplained subfertility (Taylor 1992). Conclusions regarding the true effect of varicocelectomy on pregnancy rate can only be derived from prospective studies with an unbiased control group: randomised controlled trials (RCTs).

OBJECTIVES

To evaluate the effect of varicocele treatment on live birth and pregnancy rate in subfertile couples where the male has a varicocele.

METHODS

Criteria for considering studies for this review

Types of studies

Published and unpublished randomised controlled trials were eligible for inclusion. We excluded non-randomised trials as they are associated with a high risk of bias. Trials were eligible if they dealt with the treatment of varicocele in subfertile couples and

contained a control group (no treatment) or placebo group and had the outcome pregnancy rate or live birth rate.

Types of participants

Men with a varicocele (any grade) and normal or abnormal semen analysis, who were part of a couple with otherwise unexplained subfertility. We recorded the grades of varicocele according to WHO criteria (WHO 0: only demonstrable by technical diagnostic methods; WHO I: only palpable/visible during Valsalva manoeuvre; WHO II: palpable when in upright position at room temperature; WHO III: visible when in upright position at room temperature). The clinical findings were confirmed by one of the technical diagnostic methods (such as Doppler ultrasound, phlebography, radioactive scanning or thermography).

Types of interventions

Surgical ligation or embolization versus no treatment or delayed treatment or placebo.

Types of outcome measures

Primary outcomes

1. Live birth.
2. Pregnancy rate.

Secondary outcomes

Adverse events: complications due to varicocelectomy. Semen quality was specified in the original review as a secondary outcome, but later seemed irrelevant in the presence of more clinically meaningful outcomes, and, therefore, was omitted when updating this review.

Search methods for identification of studies

We searched for all published and unpublished RCTs, without language restriction, and in consultation with the Cochrane Menstrual Disorders and Subfertility Group (MDSG) Trials Search Coordinator.

Electronic searches

We searched the following electronic databases, trial registers and web sites: the Cochrane Menstrual Disorders and Subfertility Group Trials Register (from 12 September 2003 to January 2012), the Cochrane Central Register of Controlled Trials (CENTRAL, *The Cochrane Library* Issue 1, 2012), MEDLINE (January 1966 to January 2012), EMBASE (January 1985 to January 2012), PsycINFO (to Week 1 2012) and reference lists of articles.

Please see the appendices [Appendix 1](#); [Appendix 2](#); [Appendix 3](#); [Appendix 4](#); [Appendix 5](#).

Searching other resources

We handsearched reference lists of articles retrieved by the search and contacted experts in the field to obtain additional data. We also handsearched any relevant journals and conference abstracts that were not covered in the MDSG register, in liaison with the Trials Search Coordinator.

Data collection and analysis

Selection of studies

Two review authors (JE and JC) independently scanned the titles and abstracts of articles retrieved by the search and obtained the full text of all potentially eligible studies for the 2009 review. They independently examined the full text articles for compliance with the inclusion criteria and selected studies for inclusion in the previous reviews. Two other authors (AK and NL) updated the search for this review in the same way; corresponding with study investigators, as required, to clarify study eligibility (e.g. with respect to participant eligibility criteria and allocation method), and resolving disagreements by consensus or by discussion with a third author (JE).

Data extraction and management

Two review authors (AK and NL) independently extracted data from eligible studies using a data extraction form designed and pilot-tested by the authors. Any disagreements were resolved by consensus or by discussion with a third author (JE). Data extracted included study characteristics and outcome data ([Characteristics of included studies](#)): method of randomisation; number of men randomised, excluded and analysed; whether they were single centre or multi-centre studies; employed parallel or cross-over design; nature of interventions; the participants (age range, eligibility criteria). We listed details of duration of subfertility, method of investigation of the varicocele, sperm analysis and previous treatment(s) whenever given; blinding of treatment (virtually impossible in studies involving surgery); the use of sequential analysis or factorial design; the performance of a power calculation; duration of follow-up; whether pregnancy was an outcome measure and, if so, how it was diagnosed; how pregnancy results were presented (particularly whether cumulative conception curves with the use of life table analysis were employed); and the source of any funding. We recorded the grades of varicoceles according to WHO criteria (WHO 0: only demonstrable by technical diagnostic methods; WHO I: only palpable/visible during Valsalva manoeuvre; WHO II: palpable when in upright position at room temperature; WHO

III: visible when in upright position at room temperature). For females we recorded age and factors of female infertility (when applicable). Where studies had multiple publications, the main trial report was used as the reference and additional details were derived from secondary papers. We corresponded with study investigators for further data on methods and/or results, as required.

In the preparation of the previous review additional information was obtained from Dr Nieschlag on the randomisation procedure in his study.

Assessment of risk of bias in included studies

Two review authors (AK and NL) independently assessed the included studies for risk of bias using the Cochrane risk of bias assessment tool (www.cochrane-handbook.org) for: allocation (random sequence generation and allocation concealment); blinding of participants and personnel, blinding of outcome assessors; incomplete outcome data; selective reporting; and other bias. Disagreements were resolved by discussion or by a third review author (JE). We have described all judgements fully and presented the conclusions in the Risk of Bias table, which has been incorporated into the interpretation of review findings by means of sensitivity analyses (see below).

Measures of treatment effect

For dichotomous data, we used the numbers of events in the control and intervention groups of each study to calculate the Mantel-Haenszel odds ratios (ORs). We presented 95% confidence intervals (CI) for all outcomes. If data to calculate ORs were not available, we utilised the most detailed numerical data available that facilitated similar analysis of included studies (e.g. test statistics, P values). We compared the magnitude and direction of effect reported by studies with how they were presented in the review, taking account of legitimate differences.

Unit of analysis issues

The primary analysis was per man (from a couple) randomised. Multiple live births/pregnancies were counted as one live birth/pregnancy.

Dealing with missing data

The data were analysed on an intention-to-treat basis as far as possible and attempts were made to obtain missing data from the original investigators. Pregnancy was assumed not to have occurred in couples without a reported outcome or couples who were lost to follow-up. For other outcomes, only the available data were analysed. No imputation was undertaken.

Assessment of heterogeneity

We examined heterogeneity (variations) between the results of different studies by inspecting the scatter in the data points on the graphs and the overlap in their confidence intervals and, more formally, by checking the results of the Chi² tests.

Assessment of reporting biases

In view of the difficulty of detecting and correcting for publication bias and other reporting biases, we aimed to minimise their potential impact by ensuring a comprehensive search for eligible studies and by being alert for duplication of data. There is always the risk of publication bias; however, to our knowledge there are no ongoing trials except the trial included by Dohle (Dohle 2010). If there were 10 or more studies in a primary analysis, we planned to produce a funnel plot to explore the possibility of small study effects (a tendency for estimates of the intervention effect to be more beneficial in smaller studies).

Data synthesis

Where the studies were sufficiently similar, we planned to combine the data using fixed-effect models in the following comparison: varicocele surgery versus no treatment, not further stratified.

In the meta-analysis graphs, an increase in the odds of a particular outcome, which may have been beneficial (e.g. pregnancy/live birth) or detrimental (e.g. adverse events), was displayed to the right of the centre line and a decrease in the odds of an outcome to the left of the centre line.

Subgroup analysis and investigation of heterogeneity

Where data were available, we conducted a subgroup analysis with more strictly defined inclusion criteria: studies that included men with abnormal semen, clinical varicocele and studies that reported live birth/pregnancy as a primary outcome.

If we detected substantial heterogeneity, we planned to explore possible explanations via sensitivity analyses. We planned to take any statistical heterogeneity into account when interpreting the results, especially if there was any variation in the direction of effect.

Sensitivity analysis

We planned to conduct sensitivity analyses for the primary outcomes to determine whether the conclusions were robust to arbitrary decisions made regarding the eligibility and analysis. These analyses included consideration of whether the review conclusions would have differed if:

1. eligibility was restricted to studies without high risk of bias;
2. a random-effects model had been adopted;
3. the summary effect measure was relative risk rather than odds ratio.

Overall quality of the body of evidence: Summary of Findings Table

A Summary of Findings Table was generated using GRADEPRO software. This table evaluated the overall quality of the body of evidence for the main review outcome, using GRADE criteria (study limitations (i.e. risk of bias), consistency of effect, imprecision, indirectness and publication bias).

RESULTS

Description of studies

See: [Characteristics of included studies](#); [Characteristics of excluded studies](#).

Results of the search

In previous versions of this review the search strategy had identified 25 studies. Sixteen studies were excluded. Nine studies met the inclusion criteria. One study was an extension of a previously published study. Therefore, eight studies were left. A further six studies were identified for the update of the review in 2012 ([Abdel-Meguid 2011](#); [Al-Kandari 2007](#); [Al-Said 2008](#); [Dohle 2010](#); [Fayez 2010](#); [Zheng 2009](#)). Four studies were excluded. A total of 10 studies (11 publications) were included for this update with a total of 894 men retained.

Included studies

Study design and setting

Ten studies (11 publications) were included in the review. One study ([Nieschlag 1995/1998](#)) was an extension of a previously published study ([Nieschlag 1995](#)). All studies were randomised controlled trials (RCTs). Seven ([Abdel-Meguid 2011](#); [Breznik 1993](#); [Dohle 2010](#); [Madgar 1995](#); [Nieschlag 1995/1998](#); [Nilsson 1979](#); [Unal 2001](#)) were single centre studies. One ([Krause 2002](#)) was a multi-centre study. For two studies ([Grasso 2000](#); [Yamamoto 1996](#)) it was unclear whether they were single centre or multi-centre studies.

Participants

Ten studies included 449 men with varicocele in the intervention groups and 445 men with varicocele in the control groups. All men were from couples with otherwise unexplained subfertility. Two studies of men with clinical varicocele also included normospermic varicocele patients ([Breznik 1993](#); [Nilsson 1979](#)). One study excluded men with sperm counts of less than 5 million per mL ([Madgar 1995](#)) and one study ([Krause 2002](#)) excluded men with less than 2 million per mL, with or without less than 10% progressive motility. Three studies included men with subclinical

varicocele only ([Grasso 2000](#); [Unal 2001](#); [Yamamoto 1996](#)). One study ([Breznik 1993](#)) included clinical as well as subclinical varicocele. Four studies excluded azoospermia ([Abdel-Meguid 2011](#); [Dohle 2010](#); [Krause 2002](#); [Nilsson 1979](#)). The mean of men age was 28.4 to 38 years (range 21 to 52 years). Nine studies included only couples with infertility persisting longer than one year. The duration of infertility was not mentioned in one study ([Breznik 1993](#)). Seven studies mentioned no obvious causes of female infertility, one included also couples with treatable female infertility ([Krause 2002](#)). Two studies did not mention female infertility ([Grasso 2000](#); [Unal 2001](#)).

Interventions

One of 10 studies compared embolization/surgical repair versus no treatment ([Breznik 1993](#)).

Two of 10 studies compared embolization versus no treatment ([Krause 2002](#)) or counselling only ([Nieschlag 1995/1998](#)).

One of 10 studies compared surgical repair (ligation) versus clomiphene citrate ([Unal 2001](#)).

Six of 10 studies compared surgical repair (ligation) versus no treatment, and one compared surgical repair versus delayed treatment ([Madgar 1995](#)).

Studies comparing treatment with counselling only were included and the outcome of the counselling-only group ([Nieschlag 1995/1998](#)) was considered together with those of the no-treatment groups from other trials. The study that compared varicocele treatment with clomiphene citrate ([Unal 2001](#)) was included since for this indication clomiphene citrate was judged no more effective than vitamin C ([Abel 1982](#)). In this study ([Unal 2001](#)), the control group pregnancy rate was the lowest of all trials.

Outcomes

No studies reported live birth.

Five of 10 studies reported pregnancy rate as primary outcome ([Abdel-Meguid 2011](#); [Breznik 1993](#); [Dohle 2010](#); [Madgar 1995](#); [Nieschlag 1995/1998](#)).

Three of 10 studies reported pregnancy rate as secondary outcome ([Nilsson 1979](#); [Unal 2001](#); [Yamamoto 1996](#)).

One of 10 studies reported conception rate as primary outcome ([Krause 2002](#)).

One of 10 studies reported paternity as secondary outcome ([Grasso 2000](#)).

Excluded studies

Sixteen studies were excluded in previous reviews with a further four excluded in the present update. The predominant reason for exclusion was their comparing two or more technical procedures (different types of surgery and embolization) without the inclusion of an untreated comparison group.

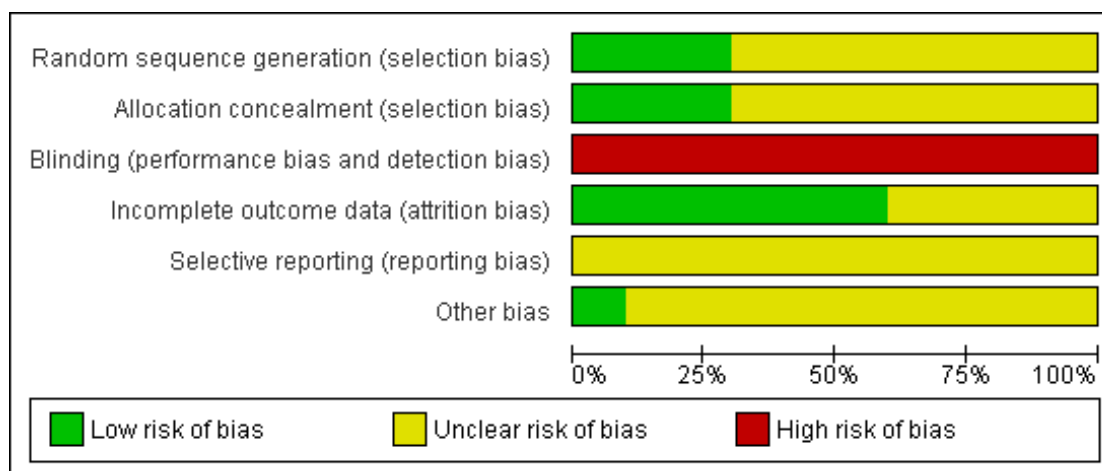
Risk of bias in included studies

See additional table and figures 'Risk of bias of studies' ([Figure 1](#); [Figure 2](#)). One trial ([Madgar 1995](#)) used a randomised postponement-of-treatment design, and only data from the period before treatment in the controls have been included in the present review. Only the corresponding data (from the first 12 months following varicocelectomy) have been used for the immediate intervention group of this study.

Figure 1. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding (performance bias and detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Abdel-Meguid 2011	+	+	-	+	?	?
Breznik 1993	?	?	-	+	?	?
Dohle 2010	?	?	-	?	?	?
Grasso 2000	?	?	-	+	?	?
Krause 2002	+	+	-	+	?	?
Madgar 1995	?	?	-	+	?	?
Nieschlag 1995/1998	+	+	-	?	?	?
Nilsson 1979	?	?	-	+	?	+
Unal 2001	?	?	-	?	?	?
Yamamoto 1996	?	?	-	?	?	?

Figure 2. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.



Allocation

Overall, although the included studies all contained a statement about random allocation, these were not high quality studies. Their poor methodological quality and their clinical and statistical heterogeneity should be taken into account. Three out of 10 studies (Abdel-Meguid 2011; Krause 2002; Nieschlag 1995/1998) described a strategy for concealment of the allocation sequence. Two out of 10 studies (Abdel-Meguid 2011; Krause 2002) included a power calculation in the Methods section. Four out of 10 studies used computer randomisation (Abdel-Meguid 2011; Dohle 2010; Krause 2002; Nieschlag 1995/1998) and were at low risk of selection bias. Six out of 10 studies did not state randomisation (Breznik 1993; Grasso 2000; Madgar 1995; Nilsson 1979; Unal 2001; Yamamoto 1996). These studies were at unclear risk of selection bias.

Blinding

Ten out of 10 studies were partly surgical, none was (single or double) blinded. Blinding is virtually impossible in surgical trials, unless sham surgery is performed. Blinding is not likely to make a difference to the outcomes (pregnancy and live birth rate). All studies were at unclear risk of bias.

Incomplete outcome data

The number of drop-outs after randomisation and the losses to follow up were considerable (1.3% to 54%) in six of 10 studies (Abdel-Meguid 2011; Breznik 1993; Dohle 2010; Krause 2002; Nieschlag 1995/1998; Yamamoto 1996), and went unmentioned in four of 10 studies (Grasso 2000; Madgar 1995; Nilsson 1979; Unal 2001). These studies were considered to be at high risk of attrition bias.

Selective reporting

For infertility interventions, live birth and the surrogates pregnancy rate and clinical pregnancy rate are by far the most important outcomes and no other outcomes were consistently reported.

Other potential sources of bias

Five out of 10 studies reported no baseline differences (Abdel-Meguid 2011; Dohle 2010; Krause 2002; Madgar 1995; Nieschlag 1995/1998), one of the 10 studies reported no difference in baseline age (Unal 2001), four out of 10 studies did not report if there were baseline differences (Breznik 1993; Grasso 2000; Nilsson 1979; Yamamoto 1996). These studies were at unclear risk of bias. The period of untreated follow-up was 12 to 40 months in one study (Unal 2001), 12 months in seven studies (Abdel-Meguid 2011; Grasso 2000; Krause 2002; Madgar 1995; Nieschlag 1995/1998; Yamamoto 1996) and > 36 months in the

other two (Breznik 1993; Nilsson 1979). Studies with an untreated follow-up duration of more than 12 months can report unjustifiably higher pregnancy rates, which is also a source of bias. Three of the 10 studies (Krause 2002; Madgar 1995; Nieschlag 1995/1998) did not offer or allow for an intention-to-treat analysis. One of the 10 studies (Dohle 2010) performed an intention-to-treat analysis, five of the 10 studies (Breznik 1993; Grasso 2000; Nilsson 1979; Unal 2001; Yamamoto 1996) did not describe their analysis in sufficient detail to estimate the role of attrition.

Effects of interventions

See: [Summary of findings for the main comparison Varicocele occlusion versus no treatment for varicoceles in subfertile men](#)

Primary outcomes

1. Live birth

No studies reported the outcome live birth rate.

2. Pregnancy

The OR comparing treatment (intervention) to no treatment (or counselling/clomiphene citrate) for pregnancy rate was 1.47 (95% CI 1.05 to 2.05, $P = 0.03$, 894 men, 181 pregnancies, $I^2 = 67%$) (Figure 3) which suggests a statistically significant benefit for treatment. The number needed to treat to benefit was 17. However, the overall quality of the evidence was rated as very low (Summary of findings for the main comparison) and there was substantial heterogeneity ($I^2 = 67%$). A funnel plot for this outcome was not suggestive of publication bias (Figure 4).

Figure 3. Forest plot of comparison: I Varicocele occlusion versus no treatment, outcome: I.I Pregnancy rate.

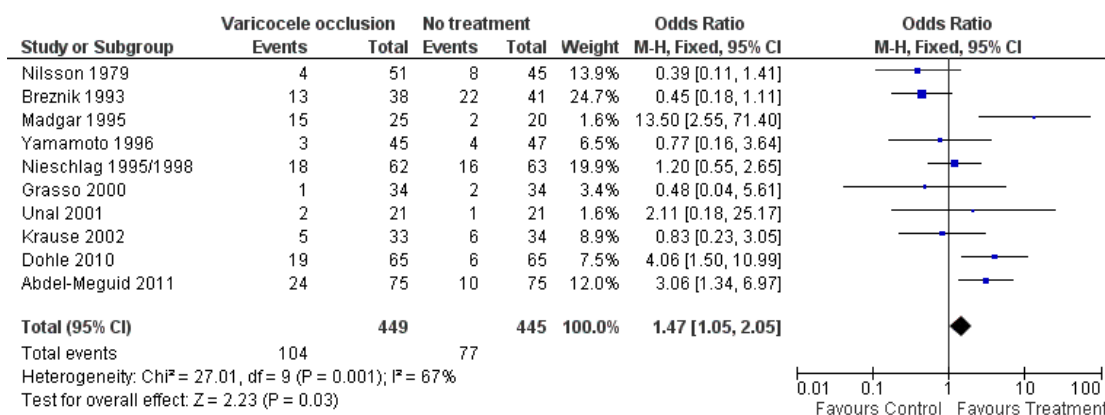
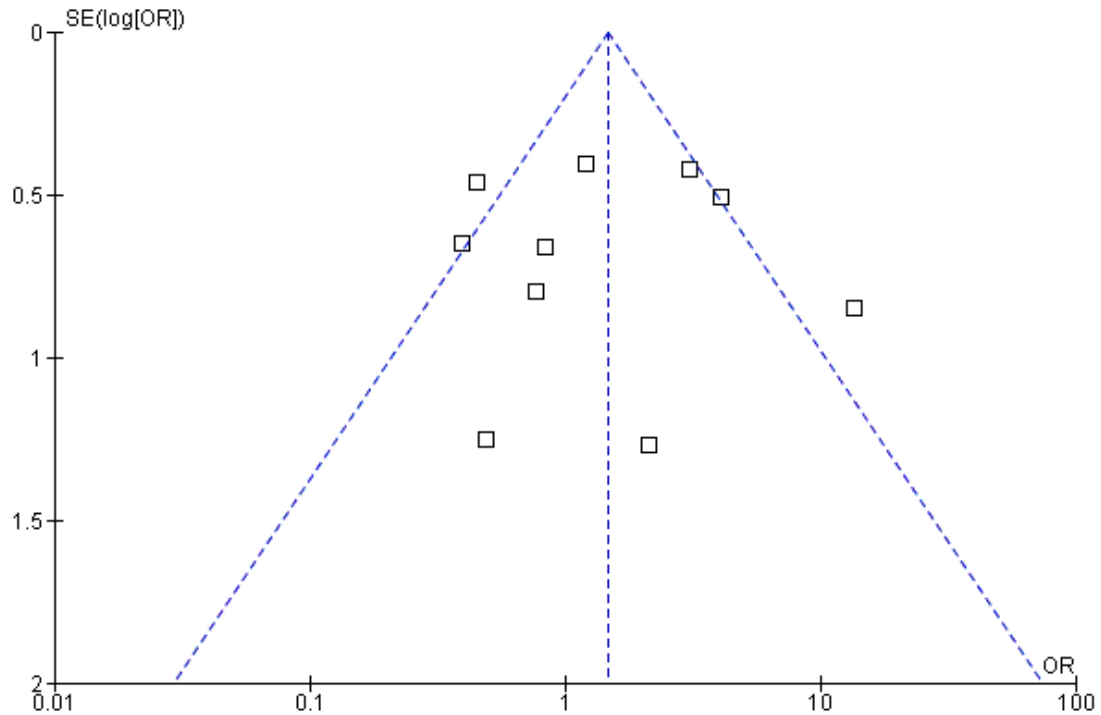
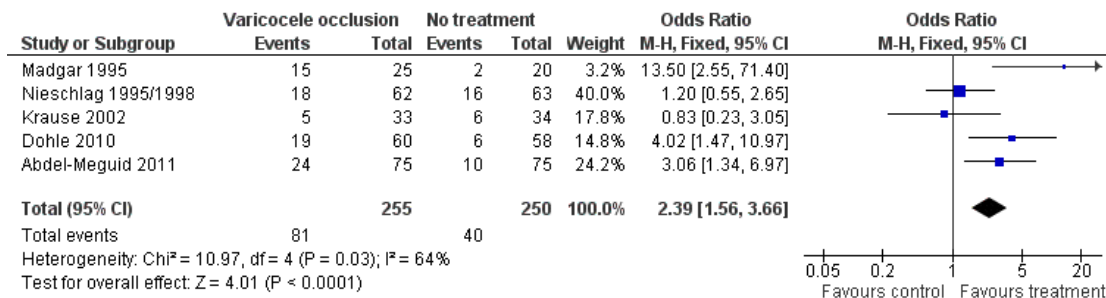


Figure 4. Funnel plot of comparison: I Varicocele occlusion versus no treatment, outcome: I.I Pregnancy rate.



The subgroup analysis consisted of five trials, which were restricted to men with clinical varicoceles, an abnormal semen analysis (azoospermia excluded) and pregnancy rate as the primary outcome (Abdel-Meguid 2011; Dohle 2010; Krause 2002; Madgar 1995; Nieschlag 1995/1998). In the results of the subgroup analysis, the OR comparing treatment to no treatment was 2.39 (95% CI 1.56 to 3.66, $P = 0.03$, 505 men, 121 pregnancies, $I^2 = 64%$) (Figure 5) which also significantly favoured treatment. The number needed to treat to benefit was 7. Excluding unpublished data (Dohle 2010) the combined OR favouring treatment was 2.11 (95% CI 1.13 to 3.38), number needed to treat was 8.

Figure 5. Forest plot of comparison: 2 Varicocele occlusion versus no treatment in men with abnormal semen analysis, clinical varicocele and primary outcome pregnancy rate, outcome: 2.1 Pregnancy rate.



Sensitivity analyses

1. When analysis was restricted to studies that reported acceptable methods of randomisation and allocation concealment (Abdel-Meguid 2011; Krause 2002; Nieschlag 1995/1998) there was no significant difference between the groups, though the lower confidence interval was 1.00 (OR 1.67, 95% CI 1.00 to 2.78, P = 0.05, 342 men, 79 pregnancies, I² = 48%).

2. When a random-effects model was used there was no significant difference between the groups, though heterogeneity remained substantial (OR 1.38, 95% CI 0.70 to 2.71, P = 0.36, I² = 67%).

3. When risk ratio rather than odds ratio was reported, the statistical significance of the findings did not change (RR 1.34, 95% CI 1.03 to 1.74, P = 0.03).

Secondary outcomes

Adverse events

One study included the outcome adverse events (Abdel-Meguid 2011). No events were reported.

DISCUSSION

Summary of main results

The findings of the original review (2009) failed to offer evidence that treatment of a varicocele in men from couples with otherwise unexplained subfertility improves the chance of spontaneous pregnancy. The findings of this updated review, supplemented by two studies (Abdel-Meguid 2011; Dohle 2010) suggest that pregnancy rates may improve after treatment of varicocele. The combined OR of the 10 studies was 1.47 (95% CI 1.05 to 2.05, P < 0.03), favouring treatment over no treatment. We excluded studies which

involved men with normal semen analysis (and azoospermia) and subclinical varicocele, some of which had semen analysis improvement as the primary outcome rather than pregnancy rate (Breznik 1993; Grasso 2000; Nilsson 1979; Unal 2001; Yamamoto 1996), and performed a subgroup analysis. So the subgroup consisted of five trials, which were restricted to men with clinical varicocele, an abnormal semen analysis and pregnancy rate as the primary outcome. This subgroup analysis also favoured treatment over no treatment, with a combined OR of 2.39 (95% CI 1.56 to 3.66). Statistical heterogeneity was fairly high for the primary analysis (67%). Moreover, findings were sensitive to the choice of statistical model and a random-effects model found no significant difference between the groups. Restriction to higher quality studies also found no significant difference between the groups, though this analysis included only 79 men and results bordered on statistical significance.

The present review suggests a benefit from treatment of varicocele for subclinical and clinical varicocele in subfertile men with normal and abnormal semen analysis and with otherwise unexplained subfertility. However, our findings are not conclusive as the overall quality of the evidence was very low.

Overall completeness and applicability of evidence

No studies reported live birth, but the included studies did report pregnancy rates. There was discussion in the review team about the applicability of studies which included men with normal semen analysis and subclinical varicocele and a primary outcome other than live birth or pregnancy. For this reason we performed a subgroup analysis of studies which were restricted to men with clinical varicoceles, an abnormal semen analysis (azoospermia excluded) and pregnancy rate as the primary outcome. This subgroup analysis agreed with the findings of the main analysis.

Quality of the evidence

The clinical and statistical heterogeneity of the studies and the small numbers should be taken into account, and the overall quality of the evidence was rated as very low ([Summary of findings for the main comparison](#)). Moreover, our findings were sensitive to choice of statistical model, and were only of borderline significance when analysis was restricted to higher quality studies. This suggests that the benefit found for treatment of varicocele should be interpreted very cautiously. A funnel plot for the outcome of pregnancy rate ([Figure 4](#)) was not suggestive of publication bias.

Potential biases in the review process

The decision to include studies which included normozoospermic men from infertile couples ([Breznik 1993](#); [Nilsson 1979](#); [Unal 2001](#); [Yamamoto 1996](#)) was disputable, but was based on their apparently representing a category of patients for whom varicocelectomy is deemed appropriate. Given their allocation by randomisation these men were evenly distributed between the experimental group and the controls. Also, the decision to include studies which accepted men with subclinical varicocele ([Breznik 1993](#); [Grasso 2000](#); [Nilsson 1979](#); [Unal 2001](#); [Yamamoto 1996](#)) is disputable. The American Urology Association (AUA) and the American Society for Reproductive Medicine (ASRM) state that normospermia and subclinical varicocele are no indication for surgical treatment. A literature search regarding the relationship between grade of varicocele and the response to varicocelectomy showed different outcomes, ranging from no improvement of semen analysis after treatment of subclinical varicocele to significant improvement. However, live birth or pregnancy rate were not outcomes in these studies. This was a reason to perform a subgroup analysis with the exclusion of these studies ([Breznik 1993](#); [Grasso 2000](#); [Nilsson 1979](#); [Unal 2001](#); [Yamamoto 1996](#)).

We included two studies ([Nieschlag 1995/1998](#); [Unal 2001](#)) comparing clomiphene citrate and counselling (respectively) to treatment, since for the sake of this review both interventions may be regarded as 'placebo' compared to surgery or embolization. The OR comparing counselling only or clomiphene citrate to no treatment for pregnancy rate was 1.27 (95% CI 0.70 to 2.32, $P = 0.43$, 445 men, 77 pregnancies), which was not significant.

Agreements and disagreements with other studies or reviews

This review covers a long period of time. Especially in the early years, study methodology was far from perfect. Addition of new, better studies to the review has allowed for performing a subgroup analysis of the higher quality studies. Although the findings of our previous meta-analysis were consistent with those of non-Cochrane reviews at the time ([Cocuzza 2008](#); [French 2008](#);

[Marmar 2007](#)), the present updated review suggests that there might be some value in varicocelectomy in selected patients.

AUTHORS' CONCLUSIONS

Implications for practice

Surgical or radiological treatment of varicocele in subfertile men with clinical varicocele and abnormal semen analysis may be of benefit, but the evidence is not conclusive. The value of surgical or radiological treatment in subfertile men with subclinical varicocele and normal semen analysis is disputable, as the number needed to treat to benefit was 17.

Implications for research

The ideal trial design would be to compare, in a randomised fashion, a sham operation with the actual procedure; any other design is potentially biased by the placebo effect of having had the operation performed; and surgery is a strong placebo indeed. However, for such a trial design it would be difficult to obtain ethical committee approval since it would put the control group at risk of surgical and anaesthetic complications without any possibility of benefit ([Hargreave 1997](#)). Since all studies included in the present review essentially considered invasive treatment, in none had the investigator, patient, or assessor been blinded to the procedure performed. However, the outcome measures of this review, live birth and pregnancy rate, were unambiguous. Therefore, apart from the placebo effect, no other negative factors of the lack of blinding were presumed to affect the conclusions drawn.

The studies included in the present review of varicocele treatment are heterogeneous. This indicates a need for a large, properly conducted RCT of varicocele treatment in men with varicocele and sperm defects, from couples with otherwise unexplained subfertility. The authors realise, however, that it will become increasingly difficult to conduct such a study, since the introduction of in vitro fertilisation (IVF) and intracytoplasmic sperm injection (ICSI) in the fertility clinic will make many men reluctant to take the risk of being allocated to the no-treatment arm of such a study, when at the same time a robust treatment of proven effectiveness is readily available in the form of IVF/ICSI. The issue will be further compounded by the fact that many couples tend to delay their first pregnancy nowadays, and are likely to feel that they have not much time left to spend on expectant management once they have decided, in their mid- to late thirties, to seek professional help for their fertility problem.

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Patrick Vandekerckhoven was involved in preparing the 2001 version of this review.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Abdel-Meguid 2011

Methods	Randomised clinical trial. 251 men eligible, 150 randomised, 75 to varicocelectomy, 75 to no treatment. All men received allocated intervention. 2 men lost to follow-up. 5 excluded from analysis	
Participants	Married, overall healthy men 20-39 years of age, who had had infertility for more than 1 year of unprotected intercourse. Clinical palpable unilateral or bilateral varicocele (grades 1-3) and impaired semen quality (sperm concentration < 20 million/mL and/or progressively motile sperm < 50% and/or morphologically normal sperm < 30%) . Exclusion: normal semen parameters, azoospermia, an abnormal hormonal profile, additional causes of infertility, significant medical diseases, smoking, occupational heat exposure, associated female factor infertility, female age > 35 years, unstable marriage. Mean age men 29.3 and 28.4 years in no treated and treated groups, respectively. Mean age women not stated	
Interventions	Subinguinal microsurgical varicocelectomy VERSUS no treatment	
Outcomes	Pregnancy rate. Method of diagnosis not specified. Duration of follow-up 12 months	
Notes	Single centre trial	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random allocation sequence was computer generated
Allocation concealment (selection bias)	Low risk	An independent research assistant
Blinding (performance bias and detection bias) All outcomes	High risk	
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 men lost to FU, 5 excluded from analysis
Selective reporting (reporting bias)	Unclear risk	Unclear
Other bias	Unclear risk	Method of diagnosis not specified

Breznik 1993

Methods	Randomised clinical trial. 96 men (of an unspecified number of eligibles) were randomised, 17 excluded (18%; all accounted for), 79 eventually analysed (38 treated, 41 controls). Five couples achieving pregnancy before surgery were transferred to the no treatment group. This has been corrected for this review (see notes). More detailed intention-to-treat analysis not possible
Participants	Men with subclinical (thermography, phlebography) and clinical varicoceles (WHO I-III). Definition and duration of subfertility not stated. Age and infertility work up not stated. Female causes and previous treatment excluded. Men with azoospermia were excluded, men with normospermia were included
Interventions	High ligation of spermatic vein(s) (Palomo), sclerosation of spermatic vein, or Gianturco spiral embolization VERSUS no treatment
Outcomes	Pregnancy rate. Method of diagnosis not specified. Duration of follow-up 48 months (12 months in 1 treated patient)
Notes	13 pregnancies in 38 women (34%) of treated men and 22 in 41 (54%) of non-treated men; however, 5 couples with pregnancy before surgery had been transferred to no treatment group. Correction results in 18/43 (42%) and 17/36 (47%) pregnancies, respectively. 25 of 79 included men had normospermia

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information given
Allocation concealment (selection bias)	Unclear risk	Unspecified
Blinding (performance bias and detection bias) All outcomes	High risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	82 % FU complete
Selective reporting (reporting bias)	Unclear risk	No information given
Other bias	Unclear risk	Unclear description of inclusion and exclusion criteria. Method of diagnosis of pregnancy not specified. No intention-to-treat analysis

Dohle 2010

Methods	Randomised clinical trial. 416 men eligible, 130 randomised, 65 men to treatment and 65 to no treatment. 12 (9%) lost to follow up, not accounted for. Number of exclusions not noted. Intention-to-treat analysis was performed
Participants	Men with no other abnormalities than clinical varicocele (confirmed by ultrasound) and subnormal semen analysis. Duration of subfertility > 1 year. Definition subfertility not stated. Age women < 36 years. Exclusion: azoospermia, obvious female subfertility causes. Mean age men 32.9 and 32.7 years, mean age women 29.6 and 29.3 years in treated and no treated groups, respectively. Baseline characteristics comparable
Interventions	Surgical repair (not specified) VERSUS delayed treatment after 1 year (ART or varicocele repair)
Outcomes	Pregnancy rate. Method of diagnosis not specified
Notes	Data of a published abstract completed by contact with the author. The study will be published later this year. The study started as a multi-centre trial, but turned into a single centre trial because of lack of included patients

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not assessable because of incomplete study data
Allocation concealment (selection bias)	Unclear risk	Not assessable because of incomplete study data
Blinding (performance bias and detection bias) All outcomes	High risk	
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not assessable because of incomplete study data
Selective reporting (reporting bias)	Unclear risk	Not assessable because of incomplete study data
Other bias	Unclear risk	Not assessable because of incomplete study data

Grasso 2000

Methods	Randomised clinical trial. 68 men randomised of an unspecified number of eligibles. All agreed not to resort to ART for 12 months
Participants	Men with subclinical (Doppler ultrasound) varicocele (Hirsch grade I left varicocele) and abnormal semen analysis: oligo- astheno- or teratozoospermia of varying degrees. Clinical varicocele excluded. Definition of subfertility not stated. Duration > 1 year. Female subfertility causes and previous treatment not stated
Interventions	Left spermatic vein ligation (Palomo) VERSUS no treatment.
Outcomes	Primary: Sperm analysis. Secondary: Paternity. Method of diagnosis not specified. Duration of follow-up 12 months
Notes	Only men aged > 30 years old (range 30 to 38) included. 1 pregnancy in 34 women (2.9%) of treated men and 2 in 34 (5.9%) of non-treated men

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information given
Allocation concealment (selection bias)	Unclear risk	No information given
Blinding (performance bias and detection bias) All outcomes	High risk	
Incomplete outcome data (attrition bias) All outcomes	Low risk	No information given
Selective reporting (reporting bias)	Unclear risk	No information given
Other bias	Unclear risk	Only men aged > 30 years old (range 30 to 38) included. Unclear description of inclusion and exclusion criteria

Krause 2002

Methods	Randomised clinical trial. 67 men randomised, of an unspecified number of eligibles: 33 to sclerosation, 34 to no treatment. 36 (54%) lost to follow up, 2 dropped out directly after randomisation. 31 completed study. Intention-to-treat analysis performed
Participants	Men from couples with > 1 year subfertility, with clinical varicoceles only. Definition subfertility not stated. Exclusion: subclinical varicoceles; symptomatic varicoceles; genital disease (e.g. cryptorchidism); severe general disease; use of drugs with effects on sperm; sperm count < 2 million per mL; progressive motility < 10%; > 1 million per mL leucocytes; volume < 1 mL; untreated or untreatable female subfertility. Mean age men

Krause 2002 (Continued)

	32.2 years; women 29.7 years. Loss to follow up 54%, unaccounted for
Interventions	Retrograde or antegrade sclerosation VERSUS no treatment.
Outcomes	Conception rate. Method of diagnosis: Ultrasound. Duration of follow-up 12 months
Notes	Multi-centre trial, scheduled to include 460 men. Discontinued after 3 years because of poor recruitment (70 men in 15 centres). Intention-to-treat analysis was performed; however, only 42 out of 67 men (63%) were treated as randomised. Very poor follow-up

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number generator, provided by telephone after registration
Allocation concealment (selection bias)	Low risk	Conducted remotely
Blinding (performance bias and detection bias) All outcomes	High risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	46% FU complete, loss to follow up not accounted for.
Selective reporting (reporting bias)	Unclear risk	No information given
Other bias	Unclear risk	Prospective, correction of power, selection bias

Madgar 1995

Methods	Randomised clinical trial, postponement-of-treatment study, part of unpublished WHO study #84902. 210 new patients, 57 eligible, 45 men randomised, 25 to treatment group, 20 to no-treatment
Participants	Inclusion: visible or palpable left varicocele, abnormal SA (< 20 million/mL, WHO) . Exclusion: SA < 5 million/mL, accessory gland infection, abnormal FSH, LH or T. Definition subfertility and work up according to WHO, duration > 12 months. Age 28. 7 years in either group. Female factors excluded. Previous treatment not mentioned
Interventions	Surgical high ligation of spermatic vein(s) (modified Palomo) VERSUS delayed surgery (for 12 months)
Outcomes	Pregnancy rate. Method of diagnosis not specified. Duration of follow-up 12 months

Madgar 1995 (Continued)

Notes	Only pre-treatment part in control patients taken into account for present review	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information given
Allocation concealment (selection bias)	Unclear risk	Unspecified
Blinding (performance bias and detection bias) All outcomes	High risk	
Incomplete outcome data (attrition bias) All outcomes	Low risk	As allocated, minus losses to FU (not noted)
Selective reporting (reporting bias)	Unclear risk	No information given
Other bias	Unclear risk	No information given

Nieschlag 1995/1998

Methods	Randomised clinical trial. 226 eligible: 203 randomised, 23 opted for assisted reproduction. 125 completed study: 62 treated by ligation/embolization, 63 received counselling only. 78 (38%) drop-outs after randomisation, all accounted for. Intention-to-treat analysis not performed
Participants	Men from couples with > 1 year subfertility; regular, unprotected intercourse; Valsalva-positive varicocele (WHO grade I: N = 66, grade II: N = 43, grade III: N = 16) and subnormal (WHO) semen analysis. Exclusion: history of maldescended testes, infections, anti-sperm antibodies, general disease, chronic medication, obvious female subfertility causes (anovulation, endometriosis, tubal blockage). Mean age men 33, women 30.5 yrs in counselling. Loss to follow up accounted for
Interventions	Radiological embolization or surgical ligation VERSUS counselling only. Radiological embolization: by Histacryl tissue adhesive. Surgical ligation: by high retroperitoneal ligation according to Bernardi (1942). All men in the treatment and no-treatment groups were re-investigated and counselled after 3, 6, 9 and 12 months
Outcomes	Pregnancy rate. Method of diagnosis not specified. Duration of follow-up 12 months
Notes	During study period WHO definition of normal morphology cut-off changed from 50% to 30%. Since patient assignment was random all study groups affected equally (mean date of entry into study not different) The only significant difference for achieving pregnancy was the female age at admittance

Nieschlag 1995/1998 (Continued)

	to the study regardless of treatment modality: 28.8 years (pregnant) versus 31.1 years (not pregnant) (P < 0.05)	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number generator, before first patient entered study, provided in opaque envelopes
Allocation concealment (selection bias)	Low risk	Adequate, by third party
Blinding (performance bias and detection bias) All outcomes	High risk	
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information given
Selective reporting (reporting bias)	Unclear risk	No information given
Other bias	Unclear risk	This study was first published in 1995 and then continued and published again in 1998 because of insufficient power

Nilsson 1979

Methods	Randomised clinical trial. 96 men included of 165 eligible, excluded: 69 men. 51 men treated by surgical ligation, 45 to control group. Loss to follow up and drop-outs not mentioned
Participants	Inclusion: men with unilateral varicocele of couples with primary subfertility. Exclusion: previous genital or inguinal surgery, mumps orchitis during/after puberty, uni- or bilateral cryptorchidism (treated or untreated), azoospermia, anti-sperm antibodies, raised FSH, female subfertility factors (ovulatory inadequacy, tubal blockage, cervical hostility) . Diagnosis of varicocele: clinical. Duration of subfertility 2-8 yrs. Mean age treated men 31 yrs, controls 30 yrs, age women not stated
Interventions	Surgical ligation of internal spermatic vein(s) (modified Palomo) and cremasteric vein(s) (if varicosity of that system as well) VERSUS no treatment. Co-interventions specifically stated to have been avoided
Outcomes	Primary outcome: sperm analysis. Secondary outcome: pregnancy rate. Method of diagnosis of pregnancy not specified. Duration follow-up: mean 53 months (range 36 to 74 months)

Nilsson 1979 (Continued)

Notes	Varicocele patients from subfertile couples were included, irrespective of semen analysis results. Normospermia was not an exclusion criterion, 26% men had sperm counts < 20 million/mL. Old study (more than 30 years)	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information given
Allocation concealment (selection bias)	Unclear risk	Unspecified
Blinding (performance bias and detection bias) All outcomes	High risk	
Incomplete outcome data (attrition bias) All outcomes	Low risk	FU complete
Selective reporting (reporting bias)	Unclear risk	No information given
Other bias	Low risk	Duration of subfertility has a broad range and is extensive (> 24 months): selection bias. Follow-up period for pregnancy rate is extensive (36-74 months)

Unal 2001

Methods	Randomised clinical trial. 42 men randomised, 21 to surgery, 21 to clomiphene citrate. Number eligible not stated. Method of randomisation not stated. Inclusion criteria well described, exclusion criteria not stated	
Participants	Inclusion: men with left subclinical (Doppler ultrasound) varicocele and normal testicular size. Definition of subfertility not stated. Duration > 1 year. Fertility work up, female fertility and age not stated. Oligoasthenospermia to normospermia are included	
Interventions	Surgical ligation of the spermatic vein VERSUS clomiphene citrate for 6 months (50 mg/day)	
Outcomes	Seminal improvement. Pregnancy rate was a secondary outcome. Duration of follow-up 12-40 months	
Notes	Men taking clomiphene citrate in control group. Normospermia was not an exclusion criteria. Only left subclinical varicocele were included	

Risk of bias

Unal 2001 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information given
Allocation concealment (selection bias)	Unclear risk	Unspecified
Blinding (performance bias and detection bias) All outcomes	High risk	
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	FU not mentioned
Selective reporting (reporting bias)	Unclear risk	No information given
Other bias	Unclear risk	Follow-up period for pregnancy rate is extensive (12-40 months). Small study population

Yamamoto 1996

Methods	Randomised clinical trial. Method of randomisation not stated. 92 were randomised, 45 to treatment, 47 to no-treatment group. Intention-to-treat analysis not performed. Inclusion criteria well described, exclusion criteria not stated
Participants	Inclusion: left subclinical varicocele, defined as a thermographic difference of > 0.3 degree Celsius and no clinical varicocele. No patients reported previous cryptorchidism, hydrocoele, testicular trauma, or surgery of the urogenital tract. Definition subfertility not stated, duration 1-5 yrs. Mean age men 32 (range 24-37) yrs. Age women not stated. Infertility work up included history, physical examination, BBT, endocrinology, and HSG (in selected patients)
Interventions	High ligation of the internal spermatic vein(s) VERSUS no treatment
Outcomes	Sperm analysis. Secondary outcome was pregnancy rate. Method of diagnosis of pregnancy not specified. Duration follow-up 12 months
Notes	Men with normospermia have been included in this study. Method of diagnoses of varicocele is disputable

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unclear

Yamamoto 1996 (Continued)

Allocation concealment (selection bias)	Unclear risk	Unspecified
Blinding (performance bias and detection bias) All outcomes	High risk	Not used
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	As allocated, minus losses to FU.
Selective reporting (reporting bias)	Unclear risk	91% FU complete
Other bias	Unclear risk	Method of diagnosis of pregnancy not specified. Duration of subfertility has a broad range and is extensive

Dr Nieschlag provided additional information on the allocation concealment procedure in his study.

Abbreviations: ART = Assisted Reproductive Technology; BBT = Basal Body Temperature; FSH = Follicle Stimulating Hormone; FU = Follow-Up; HSG = Hysterosalpingography; LH = Luteinising Hormone; SA = Semen Analysis; T = Testosterone; yrs = years

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Al-Kandari 2007	RCT with three arms: open inguinal, laparoscopic, and subinguinal microscopic surgery
Al-Said 2008	RCT with three arms: open inguinal, laparoscopic, and subinguinal microscopic surgery
Barbalias 1998	RCT of four different venous embolization approaches
Cavallini 2003	RCT with three arms: surgery, cinnoxiam, and placebo. Pregnancy rates not reported
Cayan 2000	RCT of high ligation surgery versus microsurgical high inguinal varicocelectomy
De Rose 2003	RCT with three arms: surgery, surgery and menotropin, or menotropin
Fayez 2010	RCT with three arms: compared outcome and complications of three simple varicocelectomy techniques
Grasso 1995	RCT of bilateral versus unilateral occlusion of spermatic veins in men with bilateral varicoceles
Khan 2003	RCT of high versus low ligation procedures
Laven 1992	RCT in adolescents. Follow-up of testicular volume, semen analysis. No pregnancy rates

(Continued)

Matsuda 1993	RCT of artery preservation versus ligation
Nieschlag 1993	RCT of surgical ligation versus embolization. Semen analysis, pregnancy rates
Paduch 1997	RCT in adolescents. Follow-up of testicular volume. No semen analysis, no pregnancy rates
Podkamenev 2002	RCT of laparoscopy versus open surgery
Sautter 2002	RCT of laparoscopy versus sclerotherapy
Sayfan 1992	RCT of three techniques of varicocele repair: percutaneous embolization, high ligation of the internal spermatic vein(s), and trans inguinal ligation of the internal and external spermatic vein(s)
Yamamoto 1995a	RCT in adolescents. Follow-up of testicular volume, semen analysis
Yamamoto 1995b	RCT of spermatic artery preservation versus ligation
Yavetz 1992	RCT of embolization versus surgical ligation
Zheng 2009	RCT with two arms: bilateral varicolectomy versus left varicolectomy in patients with left clinical and right subclinical varicocele

DATA AND ANALYSES

Comparison 1. Varicocele occlusion versus no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pregnancy rate	10	894	Odds Ratio (M-H, Fixed, 95% CI)	1.47 [1.05, 2.05]

Comparison 2. Varicocele occlusion versus no treatment in men with abnormal semen analysis, clinical varicocele and primary outcome pregnancy rate

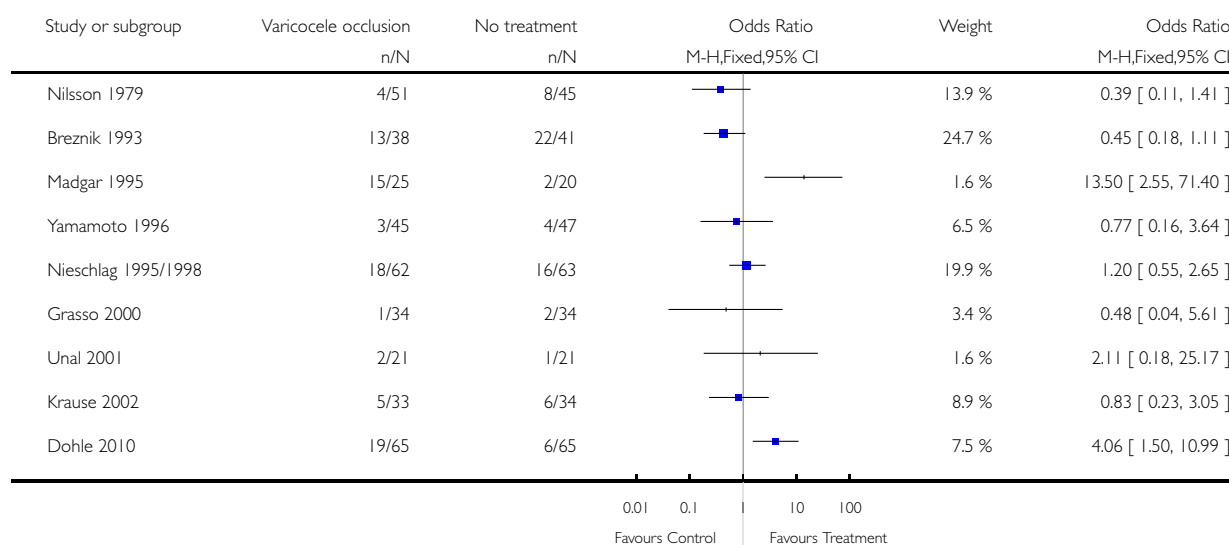
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pregnancy rate	5	505	Odds Ratio (M-H, Fixed, 95% CI)	2.39 [1.56, 3.66]

Analysis 1.1. Comparison 1 Varicocele occlusion versus no treatment, Outcome 1 Pregnancy rate.

Review: Surgery or embolization for varicoceles in subfertile men

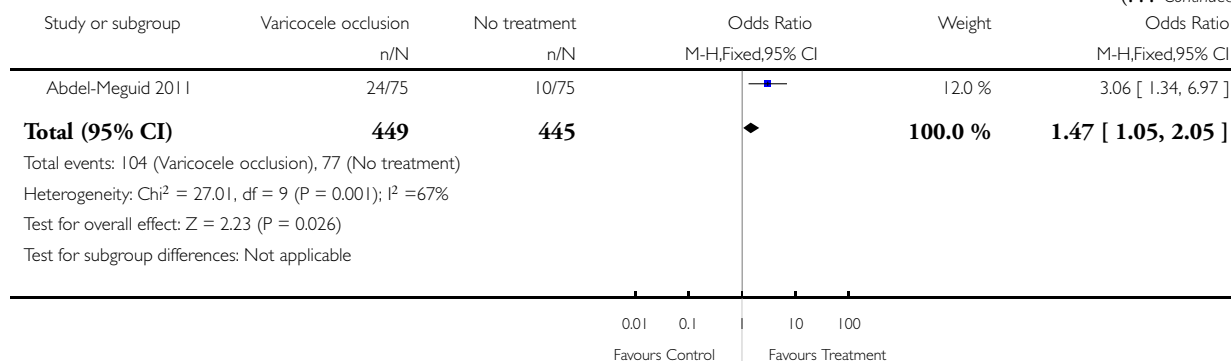
Comparison: 1 Varicocele occlusion versus no treatment

Outcome: 1 Pregnancy rate



(Continued ...)

(... Continued)

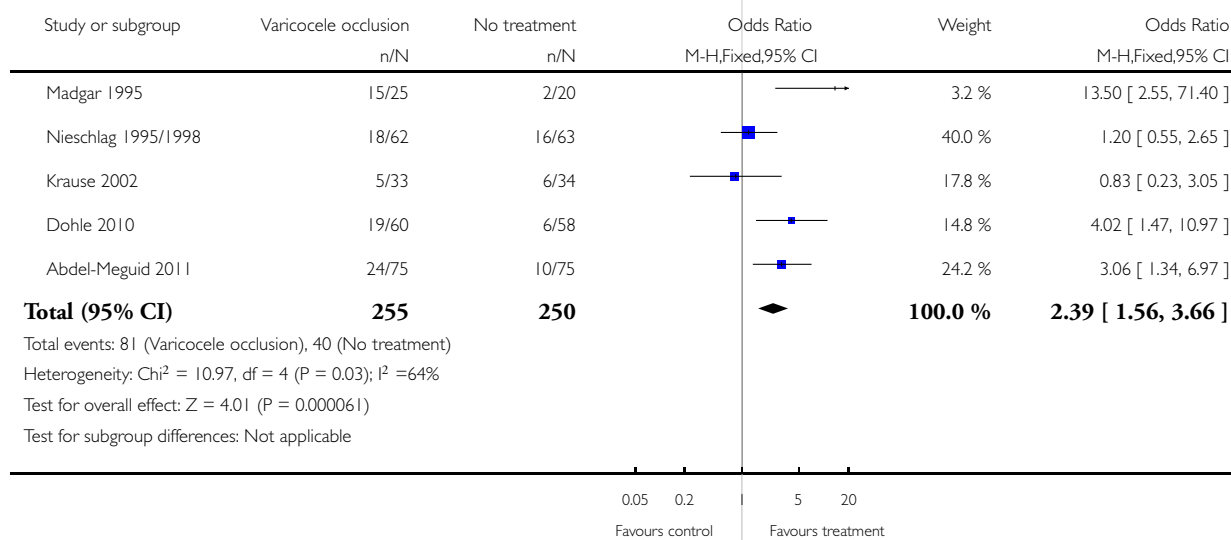


Analysis 2.1. Comparison 2 Varicocele occlusion versus no treatment in men with abnormal semen analysis, clinical varicocele and primary outcome pregnancy rate, Outcome 1 Pregnancy rate.

Review: Surgery or embolization for varicoceles in subfertile men

Comparison: 2 Varicocele occlusion versus no treatment in men with abnormal semen analysis, clinical varicocele and primary outcome pregnancy rate

Outcome: 1 Pregnancy rate



APPENDICES

Appendix 1. Cochrane Central Register of Controlled Trials

- 1 exp Varicocele/ (77)
- 2 Varicocele\$.tw. (111)
- 3 exp Infertility, Male/ (468)
- 4 (male adj1 infertil\$).tw. (158)
- 5 (male adj1 subfertil\$).tw. (41)
- 6 varicocele\$.tw. (3)
- 7 or/1-6 (618)
- 8 exp Urology/ (54)
- 9 varicolectom\$.tw. (47)
- 10 varicolectom\$.tw. (1)
- 11 exp Ligation/ (412)
- 12 ligation\$.tw. (910)
- 13 embolisation\$.tw. (57)
- 14 surg\$.tw. (60132)
- 15 embolization\$.tw. (477)
- 16 vessel seal\$.tw. (44)
- 17 or/8-16 (61282)
- 18 7 and 17 (108)
- 19 limit 18 to yr="2010 -Current" (9)

Appendix 2. EMBASE

- Embase <1980 to 2012 Week 01>
- 1 exp Varicocele/ (4700)
 - 2 Varicocele\$.tw. (4215)
 - 3 or/1-2 (5181)
 - 4 exp urologic surgery/ or exp male genital system surgery/ (338184)
 - 5 varicolectom\$.tw. (886)
 - 6 varicolectom\$.tw. (7)
 - 7 or/4-6 (338610)
 - 8 3 and 7 (1344)
 - 9 Clinical Trial/ (822753)
 - 10 Randomized Controlled Trial/ (295130)
 - 11 exp randomization/ (55336)
 - 12 Single Blind Procedure/ (14625)
 - 13 Double Blind Procedure/ (102446)
 - 14 Crossover Procedure/ (31558)
 - 15 Placebo/ (190575)
 - 16 Randomized controlled trial\$.tw. (67654)
 - 17 Rct.tw. (8276)
 - 18 random allocation.tw. (1079)
 - 19 randomly allocated.tw. (16046)
 - 20 allocated randomly.tw. (1726)
 - 21 (allocated adj2 random).tw. (691)
 - 22 Single blind\$.tw. (11391)
 - 23 Double blind\$.tw. (120428)
 - 24 ((treble or triple) adj blind\$).tw. (255)
 - 25 placebo\$.tw. (163626)
 - 26 prospective study/ (179865)

27 or/9-26 (1166955)
28 case study/ (14372)
29 case report.tw. (212369)
30 abstract report/ or letter/ (804273)
31 or/28-30 (1026844)
32 27 not 31 (1133220)
33 8 and 32 (179)
34 (2011\$ or 2012\$).em. (1366496)
35 33 and 34 (37)

Appendix 3. MEDLINE(R)

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>

1 exp Varicocele/ (3408)
2 Varicocele\$.tw. (3534)
3 exp Infertility, Male/ (20691)
4 (male adj1 infertil\$).tw. (5278)
5 (male adj1 subfertil\$).tw. (373)
6 varicocele\$.tw. (59)
7 or/1-6 (24616)
8 exp Urology/ (7198)
9 varicolectom\$.tw. (699)
10 varicocoelectom\$.tw. (4)
11 exp Ligation/ (16491)
12 ligation\$.tw. (47877)
13 embolisation\$.tw. (2791)
14 surg\$.tw. (1142476)
15 embolization\$.tw. (25646)
16 vessel seal\$.tw. (259)
17 or/8-16 (1212312)
18 7 and 17 (2899)
19 randomized controlled trial.pt. (317479)
20 controlled clinical trial.pt. (83325)
21 randomized.ab. (233136)
22 placebo.tw. (135645)
23 clinical trials as topic.sh. (157091)
24 randomly.ab. (171635)
25 trial.ti. (99764)
26 (crossover or cross-over or cross over).tw. (51915)
27 or/19-26 (777505)
28 (animals not (humans and animals)).sh. (3551249)
29 27 not 28 (717881)
30 18 and 29 (146)
31 (2010\$ or 2011\$ or 2012\$).ed. (1973860)
32 30 and 31 (13)

Appendix 4. PsycINFO

PsycINFO <1806 to January Week 2 2012>

- 1 Varicoc\$.tw. (15)
- 2 (male adj1 infertil\$.tw. (88)
- 3 (male adj1 subfertil\$.tw. (4)
- 4 or/1-3 (106)
- 5 exp Surgery/ (34790)
- 6 varicoelectom\$.tw. (1)
- 7 varicocoelectom\$.tw. (0)
- 8 ligation\$.tw. (856)
- 9 emboli?ation\$.tw. (157)
- 10 surg\$.tw. (27775)
- 11 vessel seal\$.tw. (0)
- 12 or/5-11 (53401)
- 13 4 and 12 (6)

Appendix 5. Keywords for electronic searches

The following key words were used

Keywords CONTAINS “varicocele” or “varicocele” or “male factor subfertility” or “male factor” or “male infertility” or “male subfertility” or Title CONTAINS “varicocele” or “varicocele” or “male factor subfertility” or “male factor” or “male infertility” or “male subfertility”

AND

Keywords CONTAINS “ligation” or “ligation of spermatic vein” or “Ligasure vessel sealing” or “artery ligation” or “vein ligation” or “veinembolization” or “surgery” or “Surgical” or “surgical ligation” or “*Surgical-Procedures,-Laparoscopic” or “varicocele-embolization” or “varicocele ligation” or “varicocele-outcome” or “varicolectomy” or “varicocoelectomy” or “varicocoelectomy” or “varicocoelectomy” or “embolisation” or “embolization” or Title CONTAINS “ligation” or “ligation of spermatic vein” or “Ligasure vessel sealing” or “artery ligation” or “vein ligation” or “veinembolization” or “surgery” or “Surgical” or “surgical ligation” or “*Surgical-Procedures,-Laparoscopic” or “varicocele-embolization” or “varicocele ligation” or “varicocele-outcome” or “varicolectomy” or “varicocoelectomy” or “varicocoelectomy” or “varicocoelectomy” or “embolisation” or “embolization”

WHAT'S NEW

Last assessed as up-to-date: 22 January 2012.

Date	Event	Description
12 September 2012	New citation required and conclusions have changed	2 studies added; results of updated review suggest evidence of slight benefit from treatment
2 February 2012	New search has been performed	Anja Kroese and Natascha de Lange added to authoring team

HISTORY

Protocol first published: Issue 2, 1995

Review first published: Issue 1, 2001

Date	Event	Description
21 October 2008	Amended	ROB figures added
22 April 2008	Amended	Converted to new review format.
22 April 2008	New citation required but conclusions have not changed	Jane Clarke added to authoring team
15 January 2008	New citation required and conclusions have changed	Substantive amendment
22 November 2007	New search has been performed	Two new studies found and excluded
25 October 2007	New search has been performed	Search string revised and re run

CONTRIBUTIONS OF AUTHORS

Anja Kroese participated in the screening of the literature, the initial data abstraction and the data management, the analysis and interpretation of the data, and the preparation of the manuscript.

Natascha de Lange participated in the screening of the literature, the initial data abstraction and data management, the analysis and interpretation of the data, and the preparation of the manuscript.

John Collins participated in the initial review and all updates. He also participated in the preparation of the manuscript of this review

Johannes Evers participated in the screening of the literature, the initial data abstraction and data management, the analysis and interpretation of the data, and the preparation of the manuscript of all previous reviews. He also participated in the preparation of the manuscript of this review.

DECLARATIONS OF INTEREST

No conflicts of interest exist.

SOURCES OF SUPPORT

Internal sources

- Internal support, Not specified.
MDSG editorial base

External sources

- New Source of support, Not specified.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Live birth was made a primary rather than a secondary outcome.

NOTES

In the 2004 update three new RCTs were added to the Included Studies section of the review, one ongoing study was added to the Ongoing Studies section, and further detail was added to the narrative sections of the review.

In the 2008 update two new RCTs were considered for inclusion that were excluded.

In the 2009 update no new RCTs were included.

INDEX TERMS

Medical Subject Headings (MeSH)

*Embolization, Therapeutic; Infertility, Male [etiology; surgery; *therapy]; Outcome Assessment (Health Care); Pregnancy Rate; Randomized Controlled Trials as Topic; Sperm Count; Varicocele [complications; surgery; *therapy]

MeSH check words

Female; Humans; Male; Pregnancy