Tubal flushing for subfertility (Review)

Mohiyiddeen L, Hardiman A, Fitzgerald C, Hughes E, Mol BWJ, Johnson N, Watson A


Tubal flushing for subfertility.

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[Intervention Review]

Tubal flushing for subfertility

Lamiya Mohiyiddeen¹, Anne Hardiman², Cheryl Fitzgerald³, Edward Hughes³, Ben Willem J Mol⁴, Neil Johnson⁵, Andrew Watson⁶

¹St Mary's Hospital, Manchester, UK. ²Department of O & G, Royal Bolton Hospital, Bolton, UK. ³Department of Obstetrics and Gynaecology, McMaster University, REI Consultant, ONE Fertility, Hamilton, Canada. ⁴The Robinson Institute, School of Paediatrics and Reproductive Health, The University of Adelaide, Adelaide, Australia. ⁵Robinson Research Institute, University of Adelaide, Adelaide, Australia. ⁶Tameside & Glossop Acute Services NHS Trust, Tameside General Hospital, Ashton-Under-Lyne, UK.

Contact address: Lamiya Mohiyiddeen, St Mary’s Hospital, Oxford Road, Manchester, M13 9WL, UK. Lamiya.Mohiyiddeen@cmft.nhs.uk.

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ABSTRACT

Background

Establishing the patency of the fallopian tubes is a commonly undertaken diagnostic investigation for women with subfertility. This is usually achieved by flushing contrast medium through the tubes and taking radiographs. However, it has been noted that many women conceive in the first three to six months after the tubal flushing, which has raised the possibility that tubal flushing could also be a treatment for infertility. There has been debate about which contrast medium should be used (water-soluble or oil-soluble media) as this may influence pregnancy rates.

Objectives

To evaluate the effect of flushing fallopian tubes with oil- or water-soluble contrast media on live birth and pregnancy rates in women with subfertility.

Search methods

We searched the Cochrane Menstrual Disorders and Subfertility Group Specialised Register of trials, MEDLINE, EMBASE, Biological Abstracts, trial registers and reference lists of identified articles. The most recent search was conducted in June 2014.

Selection criteria

Randomised controlled trials (RCTs) comparing tubal flushing with oil-soluble or water-soluble contrast media, or with no treatment, in women with subfertility.

Data collection and analysis

Two authors independently selected the trials, assessed risk of bias and extracted data. We contacted study authors for additional information. The overall quality of the evidence was assessed using GRADE methods.

Main results

Thirteen trials involving 2914 women were included, of whom 2494 were included in the analysis.

Oil-soluble contrast media (OSCM) versus no intervention
The OSCM group had a higher rate of live birth (odds ratio (OR) 3.09, 95% CI 1.39 to 6.91, 1 RCT, 158 women, low quality evidence) and ongoing pregnancy (OR 3.59, 95% CI 2.06 to 6.26, 3 RCTs, 382 women, I² = 0%, low quality evidence) than women who had no intervention. Our findings suggest that among subfertile women with a 17% chance of an ongoing pregnancy if they have no intervention, the rate will increase to between 29% and 55% if they have tubal flushing with OSCM.

**Water-soluble contrast media (WSCM) versus no intervention**

There was no evidence of a difference between the groups in rates of live birth (OR 1.13, 95% CI 0.67 to 1.91, 1 RCT, 334 women, very low quality evidence) or ongoing pregnancy (OR 1.14, 95% CI 0.71 to 1.84, 1 RCT, 334 women, very low quality evidence).

**OSCM versus WSCM**

Two RCTs reported live birth: one found a higher live birth rate in the oil-soluble group and the other found no evidence of a difference between the groups. These studies were not pooled due to very high heterogeneity (I² = 93%). There was no evidence of a difference between the groups in rates of ongoing pregnancy, however there was high heterogeneity (OR 1.44, 95% CI 0.84 to 2.47, 5 RCTs, 1454 women, I² = 76%, random-effects model, very low quality evidence).

**OSCM plus WSCM versus WSCM alone**

There was no evidence of a difference between the groups in rates of live birth (OR 1.06, 95% CI 0.64 to 1.77, 1 RCT, 393 women, very low quality evidence) or ongoing pregnancy (OR 1.23, 95% CI 0.87 to 1.72, 4 RCTs, 633 women, I² = 0%, low quality evidence).

**Authors’ conclusions**

The evidence suggests that tubal flushing with oil-soluble contrast media may increase the chance of pregnancy and live birth compared to no intervention. Findings for other comparisons were inconclusive due to inconsistency and lack of statistical power. There was insufficient evidence on adverse events to reach firm conclusions. Further robust randomised controlled trials are needed.

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**PLAIN LANGUAGE SUMMARY**

**Tubal flushing for subfertility**

**Review question**

Cochrane review authors assessed the evidence to see what effect flushing of the fallopian tubes has on live birth and pregnancy rates in women with subfertility.

**Background**

Blocked fallopian tubes usually means that it is impossible for a woman to conceive as sperm cannot reach the egg in the tube. Establishing whether the tubes are open (patent) is important and requires contrast media (dye) to be pushed through the tubes either at the time of an x-ray (a hysterosalpingogram) or during a laparoscopy (keyhole operation). It has been reported that more women conceive following tubal flushing although it is not clear why this occurs. There has also been debate about which contrast medium should be used (water-soluble or oil-soluble) as this may influence pregnancy rates.

**Study characteristics**

The evidence was current to June 2014. We included randomised controlled trials (RCTs) looking at the effect flushing of the fallopian tubes (with either oil-soluble or water-soluble contrast media) has on live birth and pregnancy rates in women with subfertility. Such women were those who had not been able to conceive after at least six months of unprotected sexual intercourse. We also looked at the rates of adverse events, including miscarriage and ectopic pregnancy (a pregnancy growing outside the womb) after flushing the tubes.

**Key results**

We included 13 RCTs (2914 women). The trials compared oil-soluble and water-soluble media with no intervention and with each other. We found evidence that tubal flushing with oil-soluble media may increase the chances of live birth and ongoing pregnancy, compared to no intervention. Our findings suggest that among subfertile women with a 17% chance of ongoing pregnancy if they...
have no intervention, the rate will increase to between 29% and 55% if they have tubal flushing with oil-based contrast media. We found no evidence of a difference between water-soluble contrast media and no intervention and the contrast media compared one against the other with respect to live birth and pregnancy, though there were few data for most comparisons. There was no evidence of a difference between any of the groups with respect to adverse events, but such events were poorly reported in most studies.

**Quality of the evidence**

The overall quality of the evidence was low or very low for all comparisons. The main limitations were imprecision, risk of bias and inconsistency. There were too few studies to evaluate the risk of publication bias.
<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Illustrative comparative risks* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>No of participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Assumed risk</td>
<td>Corresponding risk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No intervention</td>
<td>OSCM</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Live birth</td>
<td>129 per 1000 (171 to 507)</td>
<td>315 per 1000 (171 to 507)</td>
<td>OR 3.09 (1.39 to 6.91)</td>
<td>158 (1 study)</td>
<td>⊕⊕⊕⊕ low</td>
</tr>
<tr>
<td>Ongoing pregnancy</td>
<td>165 per 1000 (289 to 552)</td>
<td>414 per 1000 (289 to 552)</td>
<td>OR 3.59 (2.06 to 6.26)</td>
<td>382 (3 studies)</td>
<td>⊕⊕⊕⊕ low</td>
</tr>
</tbody>
</table>

Adverse events: There was no evidence of a difference between any of the interventions in rates of adverse events, but such events were poorly reported in most studies.

* The basis for the **assumed risk** is the median control group risk across studies. 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 Study was unblinded but this seems unlikely to influence fertility outcomes
2 Single study with only 32 events
3 Two of the three RCTs did not report methods in adequate detail, and one was at high risk of attrition bias
4 Three small RCTs, total of 77 events
BACKGROUND

Description of the condition

Establishing the patency of the fallopian tubes is a commonly undertaken diagnostic investigation for women with subfertility. This is usually achieved by flushing contrast medium through the tubes and taking radiographs. However, it has been noted that many women conceive in the first three to six months after the tubal flushing, which has raised the possibility that tubal flushing could also be a treatment for subfertility. There has been debate about which contrast medium should be used (water-soluble or oil-soluble media) as this may influence pregnancy rates. A doubling of conception rate after a hysterosalpingogram (HSG) with oily media was reported when compared to those women who had no procedure (Weir 1951). Many reports on the therapeutic aspect of oil-soluble contrast media have been published since the 1960s. However, many of these did not have satisfactory control groups. Various agents have been used primarily for diagnostic purposes in assessing tubal patency, such as methylene blue and oily media in conjunction with laparoscopy and the water-soluble contrast medium (WSCM) and oil-soluble contrast media (OSCM) used for an HSG. Other agents have been used in the past primarily for therapeutic purposes, such as carbon dioxide and oil injection, although these do not form part of current routine practice in most centres (Al-Fadhli 2006).

Description of the intervention

Traditionally HSGs were performed with OSCM. Their use was gradually replaced by WSCM for a number of reasons, (i) WSCM permits better imaging of the tubal mucosal folds and ampullary rugae (internal architecture of the fallopian tubes) than OSCM (Soules 1982); (ii) OSCM have a high viscosity, which results in slow filling of the fallopian tubes often necessitating an inconvenient late film after 24 hours; (iii) OSCM reabsorption is slow, leading to prolonged persistence of OSCM within the pelvic cavity; (iv) if there is accumulation of OSCM within a blocked fallopian tube a chronic inflammatory reaction, called a lipo-granuloma, may occur; this has not been reported in women with patent fallopian tubes and is not known to have long-term consequences (Acton 1988); (v) the potential consequences of intravasation of OSCM into the pelvic blood vessels and lymphatics are allergic reactions or anaphylaxis (Lindequist 1991); and (vi) WSCM are generally cheaper than OSCM.

On the other hand, irrespective of subsequent pregnancy rates, OSCM offer some advantages over WSCM, (i) the slow filling of the fallopian tubes owing to the higher viscosity of OSCM can necessitate a 'late' film but some authorities regard the 24-hour film as an advantage because of the additional information this gives, mainly in the evaluation of adhesions after slow peritoneal spillage (Bateman 1987); and (ii) less pain has been reported with OSCM than with WSCM, probably because of less chemical irritation of the peritoneum (Soules 1982).

One of the earlier descriptions of a possible beneficial therapeutic effect of OSCM came from a radiologist (Gillespie 1965). Gillespie had changed practice from OSCM to WSCM for safety reasons. A decreased pregnancy rate from 41% to 27% over the following 12 months prompted a change back to the use of oily media, and the pregnancy rate rose again to 44%. Other non-randomised controlled studies (Acton 1988; Barwin 1971; DeCherney 1980; Mackey 1971; Yaegashi 1987) supported the hypothesis of the fertility-enhancing effect of OSCM.

With the advent of fluoroscopy, screening severe adverse reactions following the use of oily media in radiology have been reduced (Lindequist 1991). The safety of HSGs with OSCM in this context has been confirmed (Nunley 1987).

Despite data suggesting a fertility-enhancing effect of tubal flushing, particularly with OSCM, this does not form part of routine current practice. There has been a reluctance to embrace this as a standard treatment, possibly relating to the following.

(a) Prior beliefs amongst clinicians which have not, to date, been sufficiently swayed by available data, the criticisms have included: (i) that data on sexual frequency were not available for the 'flushing' versus 'no treatment' trials prior to the RCT by Johnson 2004, hence the notion that the increased pregnancy rate might be due simply to an increased sexual frequency in the group who received treatment. However, Johnson 2004 found no evidence that a change in sexual behaviour in the OSCM treatment group compared to the no treatment group led to an increased pregnancy rate;

(ii) much of the data were from trials where the interventions were performed as diagnostic tests rather than as therapeutic interventions.

(b) A trend towards in vitro fertilisation (IVF) as the panacea for all causes of subfertility.

The first systematic review in this field was published in 1994 (Watson 1994). The original Cochrane Review (Vandekerckhove 1996), first published in 1996, was an expansion and update of that review. There have since been four further updates, in 2002 (Johnson 2002), 2005 (Johnson 2005 (a), Johnson 2005 (c)), 2007 (Johnson 2007) and this current update.

How the intervention might work

There are a number of explanations behind the theory of flushing of the fallopian tubes. These are detailed in the discussion section and include the following.

(i) Flushing out debris from the fallopian tubes, therefore unblocking undamaged tubes. Such debris may not necessarily block the fallopian tube but may hinder conception or embryo transport along the fallopian tube. The observation that lipiodol tubal flushing is effective for women with confirmed tubal patency (Johnson 1996)
2004; Nugent 2002) would support this. Furthermore, there is increasing evidence that some cases of ‘blocked’ fallopian tubes may have been due simply to tubal plugs, dislodged by OSCM, and thus such participants could be classified on the basis of OSCM HSG findings as having unexplained subfertility. Histological examination of resected ‘obstructed’ tubal segments often fails to confirm luminal occlusion (Grant 1971) but amorphous matter has been found within tubal sections (Sulak 1987) and its presence confirmed at falloposcopy (Kerin 1991). Histology of this tissue, obtained by hydrotubating the tube at falloposcopy, has revealed casts of the tube comprised of aggregates of histiocytic-like cells from the mucosal stroma. Observational studies (Capitanio 1991; Novy 1988; Thurmond 1990) have reported a high tubal patency and pregnancy rate after selective transcervical fallopian tube catheterisation under fluoroscopic or hysteroscopic control in patients with previously diagnosed proximal tubal obstruction on HSG with a WSCM or dye laparoscopy. This might be attributable to the ‘flushing out’ of isthmic plugs. Thurmond 1990 achieved tubal patency on at least one side in 86 of 100 consecutive women with subfertility and proximal tubal obstruction, and found that 9 of 20 women who had bilateral cornual blockage and were waiting for tubal surgery or IVF conceived after using the above technique with the majority doing so in the first four cycles after selective tubal catheterisation.

(ii) Modulation of peritoneal macrophages (Johnson 1992). OSCM have been shown to alter interleukin and prostaglandin production by peritoneal macrophages (Sawatari 1993) and to modulate peritoneal macrophage activity amongst rats during phagocytosis of sperm (Mikulska 1994).

(iii) Increasing endometrial receptivity by altering endometrial leukocyte populations. The pregnancy-enhancing effect might simply lie at the level of the endometrium. For most couples unsuccessful with IVF treatment, the outcome hinges on failed implantation. It stands to reason that a treatment which substantially increases the likelihood of conception will have some effect on endometrial receptivity. It is possible that endometrial leukocyte populations may be altered and there is increasing evidence that uterine natural killer cells play an important role in the successful development of early pregnancy (Fukui 1999). We now have evidence that uterine dendritic cell populations are influenced by flushing the murine genital tract with the OSCM lipiodol (unpublished observations).

(iv) Other theories with less supporting evidence include ‘straightening’ of tortuous fallopian tubes, disruption of peritubular adhesions, stimulation of tubal ciliary action, improving cervical mucus, and an iodine-induced bacteriostatic action on mucus membranes.

Why it is important to do this review

Tubal flushing is a low-cost minimally invasive investigation which is routinely undertaken during initial assessment of infertile couples. We aimed to establish whether tubal flushing is safe and effective for improving fertility outcomes in subfertile women.

OBJECTIVES

To evaluate the effect of flushing fallopian tubes with oil- or water-soluble contrast media on live birth and pregnancy rates in women with subfertility.

METHODS

Criteria for considering studies for this review

Types of studies
Randomised controlled trials (RCTs) were included. Non-randomised studies and quasi-randomised studies were excluded.

Types of participants
Women with subfertility, defined as inability to achieve pregnancy after at least six months of regular unprotected intercourse.

Types of interventions
Tubal flushing by means of hysterosalpingography (HSG)
Tubal flushing at the time of laparoscopy
Tubal flushing at the time of HyCoSy (hysterosalpingo contrast sonography)
Control groups could receive placebo, no treatment or an alternative type of tubal flushing.

Types of outcome measures

Primary outcomes
1. Live birth per woman
2. Ongoing pregnancy per woman (preferably defined as an ultrasound-confirmed gestational sac at 12 weeks)
Secondary outcomes
3. Miscarriage per pregnancy
4. Ectopic pregnancy per pregnancy
5. Procedural pain, immediate and delayed
6. Short-term adverse events (intravasation, infection, haemorrhage)
7. Image quality, of the uterine cavity and tubal ampulla
8. Long-term complications

Search methods for identification of studies
We searched for all published and unpublished RCTs of tubal flushing for women with subfertility, without language restriction and in consultation with the Menstrual Disorders and Subfertility Group (MDSG) Trials Search Co-ordinator. The most recent search was conducted in June 2014.

Electronic searches
We searched the following electronic databases, trial registers and websites:
- Menstrual Disorders and Subfertility Group (MDSG) Specialised Register of controlled trials
- MEDLINE
- EMBASE
- CENTRAL
- PsycINFO
- Biological Abstracts

The MEDLINE search was combined with the Cochrane highly sensitive search strategy for identifying randomised trials, which appears in the Cochrane Handbook for Systematic Reviews of Interventions (Version 5.0.2, chapter 6, 6.4.11). The EMBASE and PsycINFO searches were combined with trial filters developed by the Scottish Intercollegiate Guidelines Network (SIGN) (http://www.sign.ac.uk/methodology/filters.html#random).

Other electronic sources of trials
Trials registers were searched for ongoing and registered trials:
- National Research Register (NRR) (www2.le.ac.uk/library/find/databases/n/nationalresearchregister);
- Current Controlled Trials (http://www.controlled-trials.com);
- NHS Centre for Reviews and Dissemination (www.crd.york.ac.uk/CRDWeb);

We searched for any trials with the following keywords:
1. hysterosalpingogram, HSG or salpingogram;
2. lipiodol or ethiodol;
3. water-soluble contrast media, WSCM, oil-soluble contrast media or OSCM;
4. tubal flushing.
The search strategies can be found in Appendix 1; Appendix 2; Appendix 3; Appendix 4; Appendix 5; Appendix 6.

Searching other resources
We checked the citation lists of included trials, eligible studies and relevant review articles. We contacted the first or corresponding authors of trials eligible for inclusion to ascertain if they were aware of any ongoing or unpublished trials.
We searched abstract booklets from scientific meetings, including the European Society of Human Reproduction and Embryology, the World Congress of IVF and Reproductive Genetics, the British Fertility Society, the Fertility Society of Australia and the British Congress of Obstetrics and Gynaecology.

Data collection and analysis

Selection of studies
After an initial screen of titles and abstracts retrieved by the search, we retrieved the full texts of all potentially eligible studies. Two review authors (LM and AH) independently selected the trials for inclusion. Differences of opinion were resolved by consensus after consultation with the other review author (AJW).

Data extraction and management
Two of the review authors (LM and AH) independently extracted data, and differences of opinion were resolved by consensus. We sought additional information on trial methodology or actual original trial data from the corresponding authors of trials which appeared to meet the eligibility criteria if aspects of methodology were unclear, or if data were in a form unsuitable for meta-analysis.

Assessment of risk of bias in included studies
Two review authors (LM and AH) independently assessed the included studies using the Cochrane risk of bias assessment tool. Disagreements were resolved by discussion. The conclusions were presented in the 'Risk of bias' table (and for summary see Figure 1 and Figure 2) and incorporated into the interpretation of review findings by means of sensitivity analyses.
Figure 1. Methodological quality graph: review authors’ judgements about each methodological quality item presented as percentages across all included studies.

- Random sequence generation (selection bias)
- Allocation concealment (selection bias)
- Blinding of participants and personnel (performance bias)
- Blinding of outcome assessment (detection bias)
- Incomplete outcome data (attrition bias)
- Selective reporting (reporting bias)
- Other bias

Legend:
- Low risk of bias
- Unclear risk of bias
- High risk of bias
Figure 2. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

<table>
<thead>
<tr>
<th>Study</th>
<th>Random sequence generation (selection bias)</th>
<th>Allocation concealment (selection bias)</th>
<th>Blinding of participants and personnel (performance bias)</th>
<th>Blinding of outcome assessment (detection bias)</th>
<th>Incomplete outcome data (attrition bias)</th>
<th>Selective reporting (reporting bias)</th>
<th>Other bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Al-Fadhli 2006</td>
<td>+</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>
**Measures of treatment effect**

For dichotomous data, the numbers of events in the control and intervention groups of each study were used to calculate Mantel-Haenszel odds ratios (ORs) and 95% confidence intervals (95% CI).

For continuous data (for example procedural pain), mean differences (MDs) and 95% CIs were calculated.

**Unit of analysis issues**

The primary analysis was per woman randomised. Miscarriage and ectopic pregnancy were analysed per 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. Where these were unobtainable, imputation of individual values was undertaken for the primary outcomes only. Live births were assumed not to have occurred in participants with unreported outcomes.

**Assessment of heterogeneity**

Statistical heterogeneity between the results of different studies was examined by checking the results of Chi$^2$ tests and the $I^2$ percentage value. If the $I^2$ was > 50% and Chi$^2$ P value < 0.05, indicating substantial heterogeneity, this was addressed through sensitivity analysis. If $I^2$ was > 80%, then the data were not pooled in a meta-analysis.

If statistical heterogeneity was present, although the results were pooled, reasons for the heterogeneity were sought and the meta-analysis results interpreted cautiously. As part of the heterogeneity assessment we carried out a set of a priori defined subgroup analyses.

**Assessment of reporting biases**

In view of the difficulty in 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. If there were 10 or more studies in an analysis, we planned to use 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**

If the studies were sufficiently similar, we combined the data using a fixed-effect model in the following comparisons.

- Tubal flushing with OSCM versus no treatment.
- Tubal flushing with WSCM versus no treatment.
- Tubal flushing with OSCM versus WSCM.
- Tubal flushing with OSCM and WSCM versus WSCM alone.

An increase in the odds of a particular outcome (which may be beneficial, for example in the case of live birth; or detrimental, for example in the case of a complication) was displayed graphically in the meta-analyses to the right of the centre-line and a decrease in the odds of an outcome was displayed graphically to the left of the centre line.

**Subgroup analysis and investigation of heterogeneity**

Subgroup analysis was performed to determine whether findings differed in studies performed mainly for diagnostic reasons as opposed to studies performed mainly for therapeutic reasons.

If we detected significant heterogeneity (defined as P < 0.05 in the Chi$^2$ heterogeneity test), we explored possible explanations in sensitivity analyses. We used a random-effects model if significant heterogeneity was present.

**Sensitivity analysis**

A priori, we planned the following sensitivity analyses for the primary outcomes:

- a) restricting the analysis to studies at low risk of bias;
- b) using alternative imputation methods;
- c) based on the source of data (whether it was a diagnostic or a therapeutic study);
- d) using risk ratios instead of odds ratios;
- e) using a random-effects model instead of a fixed-effect model.

**Results**

**Description of studies**

**Results of the search**

The 2014 search retrieved 207 discrete articles. Eleven studies were potentially eligible and were retrieved in full text for further consideration. One study (Lindborg 2009) met our inclusion criteria and 10 were excluded. See Characteristics of excluded studies.
Twelve studies were included in previous versions of the review, so the updated version included 13 studies (2582 analysed participants). See Characteristics of included studies. See Figure 3 for details of the screening and selection process.
Figure 3. Study flow diagram.

12 studies included in previous published version of this review (Johnson 2007)

211 records identified through database searching

0 additional records identified through other sources

207 records after duplicates removed

207 records screened

193 records excluded

12 full-text articles assessed for eligibility

11 full-text articles excluded, with reasons

13 studies included in qualitative synthesis

13 studies included in quantitative synthesis (meta-analysis)
Included studies

Types of studies
The 13 included studies were all parallel group RCTs:
• six trials were conducted primarily for therapeutic reasons (Al-Fadhli 2006; Johnson 2004; Letterie 1990; Lindborg 2009; Nugent 2002; Steiner 2003);
• seven trials were conducted primarily for diagnostic reasons (Alper 1986; De Boer 1988; Lindequist 1994; Ogata 1993; Rasmussen 1991; Spring 2000; Yang 1989).

Types of interventions
• Three trials including 382 analysed participants assessed tubal flushing with OSCM versus no treatment (Johnson 2004; Nugent 2002; Ogata 1993).
• One trial assessed tubal flushing with WSCM versus no treatment (Lindborg 2009).
• Six trials with 1483 participants assessed flushing with contrast which included OSCM versus flushing with WSCM alone (OSCM versus WSCM) (Alper 1986; De Boer 1988; Letterie 1990; Lindequist 1994; Rasmussen 1991; Spring 2000).
• Three trials (Al-Fadhli 2006; Steiner 2003; Yang 1989) compared OSCM + WSCM versus WSCM tubal flushing. Spring 2000 also included an arm receiving tubal flushing with both WSCM and OSCM. These four trials included a total of 633 participants for this comparison.

The included studies and their methodological details are summarised in the table Characteristics of included studies.

Types of participants
Women or couples with unexplained infertility were considered eligible for inclusion. Thirteen studies with a total of 2582 analysed participants were included in this review. The number of participants in each study ranged from 34 (Nugent 2002) to 666 (Spring 2000).
The duration of infertility was at least six months in all but three trials where duration of infertility was not specified (Al-Fadhli 2006; Ogata 1993; Yang 1989).
The mean age or age range was not stated in two trials (Ogata 1993; Rasmussen 1991) and the exclusion criteria were not stated in four trial comparisons (Johnson 2004; Letterie 1990; Spring 2000; Spring 2000).
The remaining trials based their exclusion criteria on iodine allergy (Al-Fadhli 2006), bilateral tubal blockage (Alper 1986; Lindborg 2009; Ogata 1993), previous infertility surgery (De Boer 1988), male factor infertility, suspected anovulation (Lindborg 2009), technical difficulties with the HSG (Lindequist 1994; Rasmussen 1991) and causes of infertility other than unexplained (Nugent 2002).

Type of outcome measures

Primary outcomes
Our primary outcomes were live birth and ongoing pregnancy. Four studies reported live birth (Johnson 2004; Lindborg 2009; Rasmussen 1991; Spring 2000). All 13 studies reported ongoing pregnancy.

Secondary outcomes

Excluded studies
Ten studies were excluded from the review: one was not truly randomised with the use of alternate assignment (Schwabe 1983), five were non-randomised comparative studies of HSG with OSCM versus WSCM (Acton 1988; Barwin 1971; DeCherney 1980; Gillespie 1965; Yagushi 1987), one was a three-way non-randomised comparative study of HSG with OSCM versus WSCM versus no treatment (Mackey 1971), and one did not report pregnancy outcomes (Wolf 1989). Another was a recent observational study of pregnancy rates in women undergoing HSG with OSCM (Court 2014). See Characteristics of excluded studies.

Risk of bias in included studies
See Characteristics of included studies; Figure 1; Figure 2.

Allocation

Sequence generation
Seven trials were rated as at low risk of bias in this domain as they used computer-generated lists or random number tables (Al-Fadhli 2006; Alper 1986; Johnson 2004; Letterie 1990; Lindborg 2009; Spring 2000; Steiner 2003). The method of sequence generation was not adequately described in seven studies, which were rated as at unclear risk of bias (Alper 1986; De Boer 1988; Lindequist 1994; Nugent 2002; Ogata 1993; Rasmussen 1991; Yang 1989).

**Allocation concealment**

Adequate concealment of assigned treatment prior to allocation was reported in three trials (Johnson 2004; Lindborg 2009; Nugent 2002) which were rated as at low risk of bias in this domain. Ten studies did not clearly report an adequate method of allocation concealment and were rated as at unclear risk (Al-Fadhli 2006; Alper 1986; De Boer 1988; Letterie 1990; Lindequist 1994; Ogata 1993; Rasmussen 1991; Spring 2000; Steiner 2003; Yang 1989).

**Blinding**

Only one trial (Yang 1989) was double-blinded, though it was not specifically stated that outcome assessment was blinded. None of the other trials stated that blinding was used, although participant blinding would have been possible in trials where different contrast media were compared. All trials could have been single-blinded for the investigators assessing outcomes. Our primary outcome (live birth and ongoing pregnancy) may not be unduly prone to bias related to lack of blinding, but there may be scope for bias related to more thorough follow up by investigators to find outcomes in couples not attending follow-up clinics. All studies were rated as at unclear risk of bias in this domain.

**Incomplete outcome data**

Randomisation was undertaken some time in advance of the tubal flushing procedure itself (at referral and at scheduling) in four trials (Lindborg 2009; Lindequist 1994; Ogata 1993; Rasmussen 1991) and subsequently a number of participants were withdrawn before they underwent the HSG because they had conceived, changed their mind about undergoing the procedure or participating in the trial, or were subsequently found not to fulfil the criteria for the trial. Randomisation immediately before the procedure was more appropriate.

Withdrawals and losses to follow up after HSG varied from 0% (Nugent 2002; Yang 1989), 1% (Spring 2000), 3% (Johnson 2004), 5% (Steiner 2003), 9% (Rasmussen 1991), 11% (Al-Fadhli 2006), 19% (Alper 1986), 21% (Lindequist 1994), 22% (Lindborg 2009), 28% (Letterie 1990) and 37% (Ogata 1993) of participants who underwent the procedure; this was unclear for one trial (De Boer 1988). The highest withdrawal rate of 37% (Ogata 1993) was due to the fact that women underwent the HSG (or not) before any results of their other investigations were known, and only women with proof of ovulation in all four cycles of follow up were retained in the analysis. Incompleteness or loss to follow up accounted for approximately one half of the withdrawals in the other trials.

Other than in the trials where all randomised participants were analysed, it was impossible to recalculate the treatment effect based on the originally randomised groups (using the intention-to-treat principle). It was not obvious that the intention-to-treat principle was the best approach for analysis given the poor design (randomisation before eligibility established) of some of the trials. However, it is generally recommended to minimize bias in the design, conduct and analysis of RCTs of effectiveness. Only two trials (Johnson 2004; Nugent 2002) performed an intention-to-treat analysis. Only one trial (Alper 1986) specified outcome details for participants withdrawn from each randomised group. Recalculation of the OR including these participants had little effect on the conclusions of this trial (OR 1.31, 95% CI 0.51 to 3.04 for all participants versus OR 1.31, 95% CI 0.56 to 3.09 after exclusion).

**Selective reporting**

All studies reported live birth or pregnancy, or both. However, five studies failed to report any adverse events (Al-Fadhli 2006; De Boer 1988; Ogata 1993; Steiner 2003; Yang 1989) and one did not clearly report how pregnancy was ascertained (Letterie 1990). These studies were rated as at unclear risk of selective reporting, while others were rated as at low risk.

**Other potential sources of bias**

We found no potential sources of within-study bias in the included studies.

**Effects of interventions**

See: Summary of findings for the main comparison Tubal flushing with oil-soluble contrast media (OSCM) versus no intervention; Summary of findings 2 Tubal flushing with water-soluble contrast media (WSCM) versus no intervention; Summary of findings 3 Tubal flushing with oil-soluble contrast media (OSCM) versus water-soluble contrast media (WSCM); Summary of findings 4 Tubal flushing with oil-soluble plus water-soluble contrast media (OSCM + WSCM) versus WSCM only

(1) Tubal flushing with OSCM versus no treatment

**Primary outcomes**

1.1 Live birth
Only one study (Johnson 2004) making this comparison reported live birth. Tubal flushing with OSCM was associated with a significant increase in the odds of ongoing pregnancy (OR 3.09, 95% CI 1.39 to 6.91, 1 RCT, 158 women). See Analysis 1.1; Figure 4.

**Figure 4. Forest plot of comparison: 1 OSCM versus no intervention, outcome: 1.1 Live birth.**

### 1.2 Ongoing pregnancy

Three studies (Johnson 2004; Nugent 2002; Ogata 1993) making this comparison reported ongoing pregnancy (OR 3.59, 95% CI 2.06 to 6.26, 3 RCTs, 382 women, I² = 0%). See Analysis 1.2.

**Subgroup analysis**

Findings were similar in trials either with a diagnostic or with a therapeutic focus.

- In trials where the intervention was intended primarily as a diagnostic test (Ogata 1993): pregnancy OR 3.48 (95% CI 1.42 to 8.52).
- In trials where the intervention was intended primarily as a therapy (Johnson 2004; Nugent 2002): pregnancy OR 3.67 (95% CI 1.81 to 7.44).

**Sensitivity analyses**

None of the planned sensitivity analyses substantially altered the main findings.

**Secondary outcomes**

### 1.3 Miscarriage per pregnancy

Only one study (Johnson 2004) reported miscarriage rate per pregnancy. There was no evidence of a difference between the groups (OR 1.00, 95% CI 0.16 to 6.25, 1 RCT, 42 pregnancies). See Analysis 1.3.

### 1.4 Ectopic pregnancy

Only one study (Johnson 2004) reported ectopic pregnancy. There was no evidence of a difference between the groups (OR 1.58, 95% CI 0.06 to 41.34, 1 RCT, 42 pregnancies). See Analysis 1.5.

### 1.5 Procedural pain, immediate and delayed

This outcome was not reported.

### 1.6 Short-term adverse events (intravasation, infection, haemorrhage)

One study (Johnson 2004) reported 2 cases of asymptomatic intravasation without sequelae in the OSCM group (n = 73) and no other adverse events. Nugent 2002 also stated there were no adverse events. The remaining studies in this group did not report on these outcomes.

### 1.7 Image quality, of the uterine cavity and tubal ampulla

This outcome was not reported.

### 1.8 Long-term complications

Two studies in this group (Johnson 2004; Nugent 2002) stated that there were no long-term complications. This outcome was not reported in the remaining studies.

(2) Tubal flushing with WSCM versus no treatment

Only one study made this comparison (Lindborg 2009): women undergoing hysterosalpingo contrast sonography (HyCoSy) as a part of subfertility investigation were included.
Primary outcomes

2.1 Live birth
There was no evidence of a difference between the groups in live
birth rates (OR 1.13, 95% CI 0.67 to 1.91, 1 RCT, 334 women).
See Analysis 2.1; Figure 5.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>WSCM Events</th>
<th>Total Events</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lindberg 2009</td>
<td>38</td>
<td>168</td>
<td></td>
<td>1.10</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>168</td>
<td>168</td>
<td>1.10</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>38</td>
<td>34</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity</td>
<td>Not applicable</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect Z = 0.47 (p = 0.64)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 5. Forest plot of comparison: 2 WSCM versus no intervention, outcome: 2.1 Live birth.

2.2 Ongoing pregnancy
There was no evidence of a difference between the groups in on-
going pregnancy rates (OR 1.14, 95% CI 0.71 to 1.84, 1 RCT,
334 women). See Analysis 1.2.

Sensitivity analyses
Use of risk ratios did not affect the findings for this comparison.

Secondary outcomes

2.3 Miscarriage
There was no evidence of a difference between the groups in mis-
carriage rates (OR 1.12, 95% CI 0.42 to 2.96, 1 RCT, 40 preg-
nancies). See Analysis 2.3.

2.4 Ectopic pregnancy
There was no evidence of a difference between the groups in ec-
topic pregnancy rates (OR 0.90, 95% CI 0.05 to 14.76, 1 RCT,
40 pregnancies). See Analysis 2.4.

2.5 Procedural pain, immediate and delayed
This outcome was not reported.

2.6 Short-term adverse events (intravasation, infection, haemorrhage)
There was one case of pelvic infection (n = 149) requiring treat-
ment with intravenous antibiotics.

2.7 Image quality, of the uterine cavity and tubal ampulla
This outcome was not reported.

2.8 Long-term complications
This outcome was not reported.

(3) Tubal flushing with OSCM versus WSCM
Five studies made this comparison (Alper 1986; De Boer 1988;
Lindequist 1994; Rasmussen 1991; Spring 2000).

Primary outcomes

3.1 Live birth
Two studies reported this outcome (Rasmussen 1991; Spring
2000). They were not pooled due to extreme statistical hetero-
genesis (I^2 = 94%).
One of these studies (Rasmussen 1991) reported a higher live birth
rate in the OSCM group (OR 3.45, 95% CI 1.97 to 6.03, 1
RCT, 398 women). The other found no difference between the
groups (OR 0.92, 95% CI 0.60 to 1.40, 1 RCT, 533 women,
random-effects model). No obvious explanation was found for this inconsistency in findings, although age differences at baseline in one of the studies (Spring 2000) may have favoured WSCM to some degree. See Analysis 3.1; Figure 6.

Figure 6. Forest plot of comparison: 3 OSCM versus WSCM, outcome: 3.1 Live birth.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>OSCM</th>
<th>WSCM</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rasmussen 1991</td>
<td>30</td>
<td>90</td>
<td>3.45 [1.97, 6.03]</td>
</tr>
<tr>
<td>Spring 2000</td>
<td>24</td>
<td>54</td>
<td>0.02 [0.00, 1.43]</td>
</tr>
</tbody>
</table>

3.2 Ongoing pregnancy

All five studies reported ongoing pregnancy. There was no evidence of a difference between the groups (OR 1.44, 95% CI 0.84 to 2.47, 5 RCTs, 1454 women, $I^2 = 76\%$, random-effects model). The high heterogeneity was mainly due the effects of one study (Rasmussen 1991) that found a benefit for WSCM. Heterogeneity reduced to $I^2 = 24\%$ when this study was excluded from the analysis, and the overall finding of no difference between the groups did not change. See Analysis 3.2. No obvious reason for the heterogeneity was identified.

Subgroup analysis

All studies making this comparison were conducted primarily for diagnostic reasons.

Sensitivity analyses

None of the sensitivity analyses affected the findings for this comparison.

Secondary outcomes

3.3 Miscarriage

One study (Spring 2000) reported miscarriage. There was no evidence of a difference between the groups (OR 0.82 95% CI 0.40, 1.64, 1 RCT, 158 pregnancies). See Analysis 2.3.

3.4 Ectopic pregnancy

One study (Spring 2000) reported ectopic pregnancy. There was no evidence of a difference between the groups (OR 0.56, 95% CI 0.12 to 2.13, 1 RCT, 158 pregnancies). See Analysis 2.4.

3.5 Procedural pain, immediate and delayed

One study (Rasmussen 1991) reported the incidence of any post-procedural pain. Pain was less frequently reported in the OSCM group (OR 0.13, 95% CI 0.08 to 0.22, 1 RCT, 417 women). See Analysis 3.5.

A second study (Alper 1986) measured procedural pain 15 minutes after the intervention and found no difference between the groups on a scale of 0 to 5 (MD -0.30, 95% CI -0.78 to 0.18, 1 RCT, 106 women). See Analysis 3.6.

3.6 Short-term adverse events (intravasation, infection, haemorrhage)

The odds of the complication intravasation were higher with OSCM (OR 5.05, 95% CI 2.27 to 11.22, 3 RCTs, 768 women, $I^2 = 0\%$) (De Boer 1988; Lindequist 1994; Rasmussen 1991). There was no evidence of a difference between the groups in the odds of infection (OR 0.21, 95% CI 0.03 to 1.62, 2 RCTs, 662 women) or post-procedure bleeding (OR 0.65, 95% CI 0.40 to 1.06, 2 RCTs, 662 women, $I^2 = 0\%$) (Lindequist 1994; Rasmussen 1991).

No serious complications were reported in these studies.

3.7 Image quality, of the uterine cavity and tubal ampulla

The odds of obtaining a satisfactory image were lower for OSCM than for WSCM, for both the uterine cavity (Peto OR 0.18, 95% CI 0.12 to 0.26) and the tubal ampulla (Peto OR 0.05, 95% CI 0.04 to 0.07) (De Boer 1988; Lindequist 1994; Rasmussen 1991).

3.8 Long-term complications

This outcome was not reported.
(4) Tubal flushing with OSCM + WSCM versus WSCM
Four studies made this comparison (Al-Fadhli 2006; Spring 2000; Steiner 2003; Yang 1989).

Primary outcomes

4.1 Live birth
One study reported live birth (Spring 2000). There was no evidence of a difference between the groups (OR 1.06, 95% CI 0.64 to 1.77, 1 RCT, 393 women). See Analysis 4.1; Figure 7.

Figure 7. Forest plot of comparison: 4 OSCM + WSCM versus WSCM, outcome: 4.1 Live birth.

4.2 Ongoing pregnancy
Four studies reported ongoing pregnancy (Al-Fadhli 2006; Spring 2000; Steiner 2003; Yang 1989). There was no evidence of a difference between the groups (OR 1.23, 95% CI 0.87 to 1.72, 4 RCTs, 633 women). See Analysis 4.2.

Subgroup analysis
Findings did not differ substantially when the studies were subgrouped into therapeutic and diagnostic studies.

4.3 Miscarriage
There was no evidence of a difference between the groups in miscarriage rates (OR 1.14, 95% CI 0.53 to 2.48, 1 RCT, 393 women) (Spring 2000).

4.4 Ectopic pregnancy
There were no significant differences in ectopic pregnancy (OR 0.48, 95% CI 0.05 to 4.38, 2 RCTs, 422 women) (Letterie 1990; Spring 2000).

4.5 Procedural pain, immediate and delayed
This outcome was not reported.

4.6 Short-term adverse events (intravasation, infection, haemorrhage)
This outcome was not reported.

4.7 Image quality, of the uterine cavity and tubal ampulla
This outcome was not reported.

4.8 Long-term complications
This outcome was not reported.

Secondary outcomes

4.9 Proximal tube patency
This outcome was not reported.
Subgroup analysis
A subgroup analysis for whether the intervention was performed by HSG or laparoscopy did not significantly alter the outcome for either pregnancy rate after tubal flushing at laparoscopy (Peto OR 1.93, 95% CI 0.85 to 4.38) or hysterosalpingography (Peto OR 1.18, 95% CI 0.82 to 1.70).
**ADD I T I O N A L S U M M A R Y OF F I N D I N G S**

Tubal flushing with water-soluble contrast media (WSCM) versus no intervention

**Population:** Women with subfertility  
**Intervention:** Tubal flushing with WSCM versus no intervention

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Illustrative comparative risks* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>No of participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Assumed risk</td>
<td>Corresponding risk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No intervention</td>
<td>WSCM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Live birth</td>
<td>205 per 1000</td>
<td>226 per 1000 (147 to 330)</td>
<td>OR 1.13 (0.67 to 1.91)</td>
<td>334 (1 study)</td>
<td>⊕⊕⊕⊕ very low1,2</td>
</tr>
<tr>
<td>Ongoing pregnancy</td>
<td>265 per 1000</td>
<td>291 per 1000 (204 to 399)</td>
<td>OR 1.14 (0.71 to 1.84)</td>
<td>334 (1 study)</td>
<td>⊕⊕⊕⊕ very low1,2</td>
</tr>
</tbody>
</table>

Adverse events  
There was no evidence of a difference between any of the interventions in rates of adverse events, but such events were poorly reported in most studies

---

* The basis for the **assumed risk** is the median control group risk across studies. 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 High risk of attrition bias. Unblinded, but this seems unlikely to influence fertility outcomes
2 Wide confidence intervals compatible with appreciable benefit, harm or no effect. Low event rates (72 births, 93 pregnancies)
**Tubal flushing with oil-soluble contrast media (OSCM) versus water-soluble contrast media (WSCM) versus no intervention**

**Population:** Women with subfertility  
**Intervention:** Tubal flushing with OSCM versus WSCM

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Illustrative comparative risks* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>No of participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>WSCM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Corresponding risk</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Assumed risk</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Live birth</td>
<td>See comment</td>
<td>See comment</td>
<td>Not estimable</td>
<td></td>
<td>High heterogeneity (I-squared 96%): studies unsuitable for pooling. One study shows benefit for OSCM, the other shows no effect. No conclusions could be drawn</td>
</tr>
<tr>
<td>Ongoing pregnancy</td>
<td>208 per 1000 (181 to 393)</td>
<td>OR 1.44 (0.84 to 2.47)</td>
<td>1454 (5 studies)</td>
<td>⊕⊕⊕⊕ very low</td>
<td>A study in the Cochrane database showed no difference in pregnancy rates between the two groups. The other studies showed no difference in pregnancy rates.</td>
</tr>
<tr>
<td>Adverse events</td>
<td>There was no evidence of a difference between any of the interventions in rates of adverse events, but such events were poorly reported in most studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* The basis for the **assumed risk** is the median control group risk across studies. 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.
High heterogeneity ($I^2 76\%$), largely attributable to a single study. No obvious reason for heterogeneity identified.

Wide confidence intervals compatible with substantial benefit from OSCM or with no effect.

No explanation was provided.
## Tubal flushing with oil-soluble plus water-soluble contrast media (OSCM + WSCM) versus water-soluble contrast media (WSCM)

**Population:** Women with subfertility  
**Intervention:** Tubal flushing with OSCM + WSCM versus WSCM

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Illustrative comparative risks* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>No of participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Assumed risk</td>
<td>Corresponding risk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>WSCM</td>
<td>OSCM + WSCM</td>
<td>Live birth</td>
<td>208 per 1000 (144 to 317)</td>
<td>218 per 1000 (144 to 317)</td>
</tr>
<tr>
<td></td>
<td>Ongoing pregnancy</td>
<td>317 per 1000 (288 to 444)</td>
<td>363 per 1000 (288 to 444)</td>
<td>OR 1.23 (0.87 to 1.72)</td>
<td>633 (4 studies)</td>
</tr>
<tr>
<td>Adverse events</td>
<td>There was no evidence of a difference between any of the interventions in rates of adverse events, but such events were poorly reported in most studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* The basis for the assumed risk is the median control group risk across studies. 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 Method of allocation concealment not described
2 Wide confidence intervals compatible with substantial benefit, harm or no effect from the intervention. Single study, only 83 events
3 Confidence intervals compatible with substantial benefit in the OCSM plus WSCM group, or with no effect; total of 227 events
DISCUSSION

Summary of main results

The results of this systematic review give some evidence that tubal flushing with OSCM increases the pregnancy rate compared to no treatment. Our findings suggest that among women with a 17% chance of ongoing pregnancy if they have no intervention, the rate will increase to 29% to 35% if they have tubal flushing with OSCM. Findings for other comparisons were inconclusive due to inconsistency and lack of statistical power.

There was no evidence of a difference between any of the groups with respect to adverse events, but such events were poorly reported in most studies.

The success rates of fertility treatments are best assessed in terms of live birth, and only 4 of the 13 studies included in this review assessed live birth as an outcome measure. Outcome measures should also include multiple pregnancy rates and treatment complications.

Overall completeness and applicability of evidence

The evidence was limited by small sample sizes for several comparisons, especially for the outcome of live birth. It is also not entirely clear which women are most likely to benefit from the intervention. The 24-month follow up of an RCT included in this meta-analysis (Johnson 2007) provided evidence of the effectiveness of lipiodol flushing for women with unexplained infertility. The initial trial showed a positive effect of lipiodol in women with mild endometriosis at six months follow up (Johnson 2004). The follow-up study showed no enhanced fertility beyond six months in women with endometriosis, but suggested a sustained and consistent enhanced fertility up to 24 months in women with pure unexplained infertility. However, another RCT suggests that the most pronounced effect might be apparent in the subgroup of women with endometriosis who have normal patent fallopian tubes (Johnson 2004). Pregnancy rate and live birth were similar in the follow-up study (Brent 2006) of the first 100 women receiving lipiodol as a treatment.

Data on adverse events were scanty and in most cases unsuitable for pooling. There needs to be a proper evaluation of complications associated with these procedures.

Quality of the evidence

The overall quality of the evidence was low or very low for all comparisons. The main limitations were imprecision, risk of bias and heterogeneity. There were too few studies in any one comparison to evaluate the risk of publication bias. See Summary of findings for the main comparison; Summary of findings 2; Summary of findings 3; Summary of findings 4.

The risk of bias in most of the primary studies was unclear or high for most domains, and only three described satisfactory methods of allocation concealment. Most were unblinded. As noted above, this may not have unduly influenced findings for live birth and pregnancy but could influence the assessment of adverse events.

The possibility that increased sexual frequency in a non-blinded trial is a contributory factor to improved fertility is also a possible source for bias in unblinded trials. One trial (Johnson 2004) collected sexual frequency data and showed that there was no difference in subsequent sexual frequency for those randomised to tubal flushing compared to no treatment.

The source of funding was not stated in nine trials. In the remaining four trials, two were not industry supported (Lindborg 2009; Spring 2000) and in two studies it was stated only that products were supplied free of charge (Letterie 1990; Rasmussen 1991).

Potential biases in the review process

We are unaware of any potential biases in our review process.

Agreements and disagreements with other studies or reviews

Studies comparing OSCM with WSCM have shown a consistent and homogeneous therapeutic effect of oily media in previous meta-analyses (Vandekerckhove 1993). Results from non-randomised studies have also suggested that OSCM tubal flushing increases pregnancy rates and that the pregnancy rate following OSCM tubal flushing exceeds that following WSCM tubal flushing (Watson 1994). The greatest effect of OSCM tubal flushing occurred in women with unexplained subfertility (Watson 1994).

Authors’ conclusions

Implications for practice

The evidence suggests that tubal flushing with oil-soluble contrast media may increase the chance of pregnancy and live birth compared to no intervention. Findings for other comparisons were inconclusive due to inconsistency and lack of statistical power. There was no evidence of a difference between any of the groups with respect to adverse events, but such events were poorly reported in most studies.

Tubal flushing with oily media such as lipiodol could represent a simple, less invasive and cost-effective alternative to other modalities of treatment for couples where the woman has normal patent fallopian tubes. Moreover, it is less likely than other options to increase the risk of multiple pregnancy. We suggest that there is a strong argument for adopting this approach as a treatment for
unexplained infertility. For safety reasons, we believe it is important for such procedures to be performed only under fluoroscopic control and in women with previously confirmed bilateral tubal patency.

Implications for research
Further robust randomised trials comparing oil-soluble versus water-soluble media or no treatment should be undertaken, with live birth as the primary outcome. Comparative data on adverse events should also be reported. Further scientific research on the OSCM-related improvement in fecundity may clarify its mechanism of working and explain some cases of hitherto ‘unexplained’ infertility. To investigate the potential advantages of flushing with OSCM a randomised controlled trial comparing this approach with IVF and intrauterine insemination for women with subfertility (either unexplained or with proven appropriately staged endometriosis) seems a logical next step. Future trials should take into account the timing and frequency of intercourse.

ACKNOWLEDGEMENTS
The authors acknowledge the contributions of these previous authors:

- Patrick Vandekerckhove was the primary author of the original review, was involved in trial selection and data extraction of trials for the updated review and critically reviewed the updated review in 2007
- Tasuku Harada and Richard Lilford were authors of the original review and commented on the updated review in 2007.

We would like to acknowledge members of the editorial office in Auckland for assistance with updates.

REFERENCES

References to studies included in this review

Al-Fadhli 2006  [published data only]

Alper 1986  [published data only]

De Boer 1988  [published data only]

Johnston 2004  [published data only]


Letterie 1990  [published data only]

Lindborg 2009  [published data only]

Lindequist 1994  [published data only]

Nugent 2002  [published data only]

Ogata 1993  [published data only]

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Rasmussen 1991 (published data only)


Spring 2000 (published data only)

Steiner 2003 (published data only)

Yang 1989 (published data only)

References to studies excluded from this review

Acton 1988 (published data only)

Barwin 1971 (published data only)

Court 2014 (published data only)

DeCherney 1980 (published data only)

Gillespie 1965 (published data only)

Mackey 1971 (published data only)

Perquin 2006 (published data only)

Schwabe 1983 (published data only)

Wolf 1989 (published data only)

Yaegashi 1987 (published data only)

References to ongoing studies

Dreyer 2014 (published data only)

Additional references

Bateman 1987

Brent 2006

Capitanio 1991

Fukui 1999

Grant 1971

Johnson 1992
Johnson J, Montoya I, Olive D. Ethiodol oil contrast medium inhibits macrophage phagocytosis and adherence.

**Johnson 2005 (c)**


**Kerin 1991**


**Lindequist 1991**


**Mikulska 1994**


**Novy 1988**


**Nunley 1987**


**Sawatari 1993**


**Soules 1982**


**Sulak 1987**


**Thurmond 1990**


**Vandekerckhove 1993**


**Watson 1994**


**Weir 1951**


**References to other published versions of this review**

**Johnson 2002**


**Johnson 2005 (a)**


**Johnson 2007**


**Vandekerckhove 1996**


* Indicates the major publication for the study
## Characteristics of included studies  
*ordered by study ID*

### Al-Fadhli 2006

<table>
<thead>
<tr>
<th>Methods</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Method of randomisation: computer-generated random table</td>
<td></td>
</tr>
<tr>
<td>Allocation concealment: not mentioned</td>
<td></td>
</tr>
<tr>
<td>Blinding: not mentioned</td>
<td></td>
</tr>
<tr>
<td>Analysis: power calculation suggested a requirement for 27 women per contrast group and 39 recruited per group</td>
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</tr>
<tr>
<td>Intention-to-treat analysis not performed but possible from the data</td>
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</tr>
<tr>
<td>Study setting: McGill University Health Center, Montreal, Quebec, Canada</td>
<td></td>
</tr>
<tr>
<td>Duration of study: September 2002 to September 2004</td>
<td></td>
</tr>
<tr>
<td>Duration of follow up: 6 months</td>
<td></td>
</tr>
<tr>
<td>Withdrawals:</td>
<td></td>
</tr>
<tr>
<td>88 women recruited and randomised</td>
<td></td>
</tr>
<tr>
<td>1 woman in the lipiodol group excluded (underwent an ovarian cystectomy during the same laparoscopy)</td>
<td></td>
</tr>
<tr>
<td>9 withdrawn after randomisation (4 lost to follow up and 5 had IVF immediately after the laparoscopy with dye sufflation)</td>
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</tr>
<tr>
<td>78 women analysed</td>
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<tr>
<td>Source of funding not stated</td>
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<tr>
<td>Number of participants: 88</td>
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<tr>
<td>Mean age: 32 years (SD 0.6) WSCM; 31 years (SD 0.5) OSCM</td>
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<tr>
<td>Inclusion criteria: infertile women, duration of infertility not mentioned</td>
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<tr>
<td>Investigative work-up: early follicular FSH &lt; 10 IU/L, normal semen analysis (criteria not mentioned), ovulatory confirmation by mid-luteal phase progesterone &gt; 25 mmol/L, patent fallopian tubes at HSG. Included women had normal laparoscopic findings or stage I or II endometriosis</td>
<td></td>
</tr>
<tr>
<td>Exclusion criteria: iodine allergy</td>
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<td>Breakdown by cause of infertility not specified</td>
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<tr>
<td>Previous fertility treatments not specified</td>
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<table>
<thead>
<tr>
<th>Interventions</th>
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<tbody>
<tr>
<td>Tubal flushing during laparoscopy, after sufflation with WSCM methylene blue dye: OSCM lipiodol (ultra-fluid; Guerbet/Ezem, Canada, Montreal, Quebec) versus WSCM saline</td>
<td></td>
</tr>
<tr>
<td>A volume of 10 ml of contrast medium was used</td>
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</tr>
<tr>
<td>Timing not specified with menstrual cycle</td>
<td></td>
</tr>
<tr>
<td>Co-interventions: excision of endometriosis during the laparoscopy was performed in 20 patients (11 WSCM + OSCM, 9 WSCM)</td>
<td></td>
</tr>
<tr>
<td>Primarily intended as therapeutic procedure</td>
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</table>

<table>
<thead>
<tr>
<th>Outcomes</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy rate (method of diagnosis not specified)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Notes</th>
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</thead>
<tbody>
<tr>
<td>Unclear whether the assigned treatment was adequately concealed prior to allocation</td>
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<table>
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<tr>
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### Al-Fadhli 2006 (Continued)

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<th>Support for judgement</th>
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<td>Low risk</td>
<td>Computer-generated randomisation</td>
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<td>No mention of allocation concealment</td>
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<td>Mentions no blinding</td>
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</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Unclear risk</td>
<td>No mention</td>
</tr>
<tr>
<td>All outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Unclear risk</td>
<td>Withdrawals and losses to follow up totalled 11%</td>
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<tr>
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<td></td>
<td></td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>Failed to report pain or adverse effects</td>
</tr>
<tr>
<td>Other bias</td>
<td>Low risk</td>
<td>No other potential bias identified</td>
</tr>
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</table>

### Alper 1986

<table>
<thead>
<tr>
<th>Methods</th>
<th>Randomisation: random number table</th>
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<td>Allocation concealment: not mentioned</td>
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<tr>
<td></td>
<td>Blinding: not mentioned</td>
</tr>
<tr>
<td></td>
<td>Trial design: parallel group</td>
</tr>
<tr>
<td></td>
<td>Analysis: power calculation not mentioned. Intention-to-treat analysis not performed</td>
</tr>
<tr>
<td></td>
<td>Study setting: single-centre; Ottowa Civic Hospital, Ottowa, Canada</td>
</tr>
<tr>
<td></td>
<td>Duration of trial: 8 months</td>
</tr>
<tr>
<td></td>
<td>Duration of follow up: 6 months</td>
</tr>
<tr>
<td></td>
<td>Withdrawals: 13 (9.9%) withdrawn after HSG; 12 (9.2%) lost to follow up</td>
</tr>
<tr>
<td></td>
<td>131 women recruited and randomised</td>
</tr>
<tr>
<td></td>
<td>106 women analysed</td>
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<table>
<thead>
<tr>
<th>Participants</th>
<th>No of women: 106 analysed</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Mean age: mean age 29.3 years (SD 4.6) WSCM; 29.1 years (SD 2.9) OSCM</td>
</tr>
<tr>
<td></td>
<td>Cause of infertility: Primary or secondary infertility for more than 12 months (mean or range of duration of pre-existing infertility not stated, but duration and proportion of primary to secondary similar in two groups)</td>
</tr>
<tr>
<td></td>
<td>Investigative work-up: semen analysis, PCT, BBT and endometrial biopsy; diagnostic laparoscopy prior to HSG in most women</td>
</tr>
<tr>
<td></td>
<td>Breakdown specified by cause for infertility</td>
</tr>
<tr>
<td></td>
<td>Previous fertility treatments not specified</td>
</tr>
<tr>
<td></td>
<td>Women with bilateral tubal blockage withdrawn after HSG; no other exclusions specified</td>
</tr>
</tbody>
</table>
Alper 1986  (Continued)

| Interventions | HSG with OSCM ethiodol (Savage Laboratories, Missouri City, USA) versus WSCM Renographin (ER Squibb & Sons, Princeton, USA)  
A volume of 10 to 20 ml of contrast medium was used  
Timing: any day of menstrual cycle  
No co-interventions  
Primarily intended as diagnostic procedure  
|
|----------------|------------------------------------------------------------------------------------------------------------------|
| Outcomes       | Pregnancy (diagnosis based on urine hCG or serum beta-hCG plus ultrasound, all the patients had pregnancies confirmed by ultrasound)  
Volume of contrast medium used  
Pain during HSG  
Intravasation  
|
| Notes          | Unclear whether the assigned treatment was adequately concealed prior to allocation  
|
| **Risk of bias** | **Authors’ judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | Low risk | Random number table used  
|
| Allocation concealment (selection bias) | Unclear risk | No mention of allocation concealment  
|
| Blinding of participants and personnel (performance bias) | Unclear risk | No mention of blinding in the text although this could have been possible  
|
| Blinding of outcome assessment (detection bias) | Unclear risk | No blinding mentioned for the outcome assessment  
|
| Incomplete outcome data (attrition bias) | High risk | Follow up and withdrawals from the study totalled 19%  
|
| Selective reporting (reporting bias) | Low risk | No selective reporting identified  
|
| Other bias | Low risk | No other potential bias identified  

### Methods

- **Randomisation:** not stated
- **Allocation concealment:** not stated
- **Blinding:** not stated
- **Analysis:** not mentioned, intention-to-treat analysis not done
- **Study setting:** St Radboud University Hospital, Nijmegen, Holland
- **Duration of trial:** February 1985 to October 1986
- **Duration of follow up:** 6 months
- **Withdrawals:** none

### Participants

- **Number of participants:** 175
- **Mean age:** 29 years (19 to 44)
- **Primary or secondary infertility for more than six months; mean infertility duration 37 (SD 26.2) months
- **Investigative work-up:** normal PCT or sperm penetration test, or both, and BBT
- **Breakdown by cause for infertility:** unexplained only
- **Previous fertility treatments not specified other than exclusion for women with previous infertility surgery**

### Interventions

- **HSG with OSMC ethiodol (Guerbet, France) versus WSCM iopamidol (Bracco, Italy)
- A volume of 10 ml contrast medium was used
- **Timing:** day 6 to 13 of menstrual cycle
- **No co-interventions
- Primarily intended as diagnostic procedure**

### Outcomes

- **Pregnancy rate (diagnosis based on ultrasound, although ultrasound criteria not specified)
- Quality of visualisation of uterine cavity
- Quality of visualisation of ampullary tubal folds
- Time for contrast medium to disperse from pelvis**

### Notes

- Unclear whether the assigned treatment was adequately concealed prior to allocation

### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Randomisation method not mentioned</td>
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<tr>
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<td>Unclear risk</td>
<td>No mention of allocation concealment</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>Unclear risk</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Unclear risk</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Unclear risk</td>
<td>Rates of loss to follow up and withdrawals from the study were unclear</td>
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</table>
### De Boer 1988 (Continued)

<table>
<thead>
<tr>
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<th>Failed to report pain or adverse effects</th>
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</thead>
<tbody>
<tr>
<td>Other bias</td>
<td>Low risk</td>
<td>No other potential bias identified</td>
</tr>
</tbody>
</table>

### Johnson 2004

**Methods**
- **Randomisation:** two computer-generated random number sequences (A - women with unexplained infertility; B - women with endometriosis in the context of otherwise unexplained infertility)
- **Allocation concealment:** sequentially numbered sealed opaque envelopes
- **Blinding:** no blinding
- **Trial design:** parallel group
- **Analysis:** power calculation and intention-to-treat (ITT) analysis done
- **Study setting:** single-centre, University of Auckland Dept O & G with Fertility Plus, National Women's Hospital, Auckland, New Zealand
- **Duration of trial:** 3 years
- **Duration of follow up:** 6 months
- **Withdrawals:** none
- Two separate randomisation schedules were used for the endometriosis and unexplained infertility subpopulations
- **Time of randomisation:** on same cycle as HSG, usually several days before HSG
- Not blinded
- 158 women recruited and randomised
- No exclusions before HSG
- No withdrawals
- 2 protocol breaches
- 3 women lost to follow up
- 158 women analysed on ITT basis
- **Duration of follow up:** 6 months
- **Single-centre:** University of Auckland Dept O & G with Fertility Plus, National Women's Hospital, Auckland, New Zealand

**Participants**
- **No of women:** 158
- **Mean age:** 33.9 years (SD 2.9) for OSCM; 33.5 years (SD 3.8) for control
- **Inclusion criteria:** unexplained infertility (or endometriosis where fallopian tubes and ovaries unaffected by endometriotic disease) of duration > 12 months, full investigation for the cause complete, age 18 to 39 years, biochemistry as below; confirmed bilateral tubal patency
- **Cause of infertility:** unexplained primary or secondary infertility (primary 54.8% OSCM, 60.0% no treatment) for more than 12 months (mean duration of pre-existing infertility 54.8 months)
- **Investigative work-up:** normal semen analysis by WHO criteria, early follicular FSH < 10 IU/l, ovulatory confirmation by serum progesterone > 25 mmol/l, normal fallopian tubes at laparoscopy and dye insufflation or HSG
- **Breakdown by cause for infertility:** pure unexplained 61%, endometriosis with normal fallopian tubes and ovaries 39%, all other causes for infertility excluded
- **Previous fertility treatments:** IVF 34%, IUI 44%, empirical clomiphene 60%, women with endometriosis having previous surgical treatment 60%
**Interventions**

- HSG with OSCM lipiodol versus no treatment
- Timed after menses but prior to Day 12
- Information sheet on fertile phase of the cycle given to both groups; no other co-interventions
- Primarily intended as therapeutic procedure

**Outcomes**

- **Primary outcome:**
  1) clinical pregnancy (diagnosis based on positive pregnancy test and intrauterine gestation sac on ultrasound)
  2) live birth
- **Secondary outcome:**
  1) miscarriage
  2) ectopic pregnancy
  3) fetal death > 20 weeks
  4) termination
  5) multiple pregnancy
  6) adverse events

**Notes**

- Assigned treatment was clearly adequately concealed prior to allocation

**Risk of bias**

<table>
<thead>
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<th>Authors' judgement</th>
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<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Computer-generated random number sequences</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>Allocation concealment: sequentially numbered sealed opaque envelopes</td>
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<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>Unclear risk</td>
<td>Not possible to blind participants since the treatment involved HSG and control had no treatment</td>
</tr>
<tr>
<td>All outcomes</td>
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<td></td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Unclear risk</td>
<td>No blinding of executor of the assignment or the assessor at follow up</td>
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<tr>
<td>All outcomes</td>
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<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Low risk</td>
<td>Losses to follow up and withdrawals totalled 3%</td>
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<td>All outcomes</td>
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<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>There is no indication that the study reported selected outcomes</td>
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<tr>
<td>Other bias</td>
<td>Low risk</td>
<td>No other potential bias identified</td>
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</table>
**Letterie 1990**

**Methods**
- Randomisation: random number scheme
- Allocation concealment: no mention of this
- Blinding: no mention of this
- Trial design: parallel group
- Analysis: power calculation not mentioned; intention-to-treat analysis not feasible
- Study setting: Single-centre; Tripler Army Medical Centre, Honolulu, Hawaii, USA
- Duration of study: not mentioned
- Duration of follow up: 12 months
- Withdrawals: 11 withdrawn after randomisation (8 inadequate follow up and 3 "inadequate coital exposure")

**Participants**
- No of patients: 29
  - Mean age: 27 (SD 3.5) years OSCM; 25 (SD 4.1) years WSCM (not significant)
  - Cause of infertility: unexplained infertility of mean duration 24 (SD 14.5) months OSCM; 28 (SD 13.9) months WSCM; inclusion criterion > 12 months
  - Inclusion criteria: ovulatory status as documented by biphasic basal body temperature with a 14-day luteal phase; serum progesterone > 3ng/ml or in phase secretory endometrium on biopsy, or both; normal semen analysis; normal pelvic anatomy and bilateral patent tubes
  - Exclusion criteria: iodine allergy; evidence of endometriosis, tubal disease or pelvic adhesions
  - Breakdown by cause: not done
  - Investigative work-up: normal semen analysis; ovulatory confirmation based on BBT and serum progesterone or secretory phase, or both; normal prolactin, thyroxine and TSH; normal pelvis and bilateral tubal patency at laparoscopy
  - Breakdown by cause for infertility: unexplained only
  - Previous fertility treatments not specified
  - Exclusions specified: where cause for infertility diagnosed; iodine allergy

**Interventions**
- Tubal flushing during laparoscopy, after standard dye studies, with OSCM ethiodol (Savage Laboratories) versus WSCM Conray-60 (Mallinckrodt Inc.)
  - A volume of 20 ml of contrast medium was used
  - Timing not specified with menstrual cycle
  - No co-interventions
  - Primarily intended as therapeutic procedure

**Outcomes**
- Pregnancy (diagnostic criteria not specified)
- Ectopic pregnancy

**Notes**
- Unclear whether the assigned treatment was adequately concealed prior to allocation

**Risk of bias**

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<th>Authors' judgement</th>
<th>Support for judgement</th>
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<td>Random number scheme</td>
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<tr>
<td>Allocation concealment (selection bias)</td>
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<td>No mention in the paper</td>
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### Letterie 1990  
(Continued)

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<tbody>
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<td>Unclear risk</td>
<td>No mention of this in the paper</td>
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<tr>
<td>(performance bias)</td>
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<tr>
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</tr>
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<td>Some aspects like how the pregnancy test was confirmed not clearly mentioned</td>
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### Lindborg 2009

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<td>Blinding: not done</td>
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<td>Analysis: intention-to-treat analysis done</td>
</tr>
<tr>
<td>Trial design: parallel group</td>
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<tr>
<td>Study setting: Reproductive unit at Sahlgrenska University, Gothenburg, Sweden</td>
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<tr>
<td>Duration of study: December 2001 to May 2006</td>
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<td>Duration of follow up: 6 months</td>
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<td>Number of participants: 334</td>
</tr>
<tr>
<td>Mean age: 31.9 yrs</td>
</tr>
<tr>
<td>Inclusions: at least 1 year of subfertility, already scheduled for HyCoSy</td>
</tr>
<tr>
<td>Exclusions: &gt; 40 yrs, severe male infertility, severe tubal pathology, suspected anovulation (menstrual period &gt; 35 days)</td>
</tr>
<tr>
<td>Breakdown for cause: 63% primary infertility, mean duration of infertility 2.1 yrs</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>All received transvaginal scan prior to use of contrast medium (hydrosalpinx contraindication)</td>
</tr>
<tr>
<td>Saline injected into uterine cavity to achieve distension, WSCM (Echovist, Bayer AG) instilled to evaluate tubal patency</td>
</tr>
<tr>
<td>Maximum 15 ml used</td>
</tr>
<tr>
<td>Categorical statement made for each tube (patent, occluded, unclear)</td>
</tr>
<tr>
<td>All received oral antibiotic postprocedure</td>
</tr>
<tr>
<td>Timing not specified with menstrual cycle</td>
</tr>
<tr>
<td>No co-interventions</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome clinically pregnancy defined sonographically as visible fetal sac within 6 months</td>
</tr>
<tr>
<td>Live birth</td>
</tr>
<tr>
<td><strong>Miscarriage</strong></td>
</tr>
<tr>
<td>----------------</td>
</tr>
</tbody>
</table>

### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Computer-generated randomisation</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>Sealed opaque envelopes envelopes used</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
<td>Unclear risk</td>
<td>Not blinded</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) All outcomes</td>
<td>Unclear risk</td>
<td>Physicians aware of allocation</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>High risk</td>
<td>Losses to follow up and withdrawals totalled 22%</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>There is no indication that the study has reported selected outcomes</td>
</tr>
<tr>
<td>Other bias</td>
<td>Low risk</td>
<td>No other potential bias identified</td>
</tr>
</tbody>
</table>

### Lindequist 1994

| **Methods** | | |
|--------------|---------------------------------------------------------------|
| Method of randomisation: not stated | **Allocation concealment: not mentioned** |
| Blinding: not mentioned | **Analysis: no mention of power calculation, intention-to-treat analysis not performed nor possible** |
| Study design: parallel group | **Study setting: Odense University Hospital, Odense, Denmark** |
| Duration of study: September 1989 to April 1991 | **Duration of follow up: 20 to 39 months** |
| Withdrawals: 307 recruited and randomised, 60 patients excluded prior to HSG or lost to follow up, 5 withdrawn after HSG | |

| **Participants** | | |
|------------------|---------------------------------------------------------------|
| No of participants: 242 | **Mean age: 29.9 yrs OSCM (21 t0 43); 29.5 yrs WSCM (20 to 40)** |
| Inclusions: primary or secondary infertility for more than 12 months; secondary 48 (40%) OSCM, 42 (35%) WSCM | |
Exclusion criteria: pregnant prior to HSG; HSG declined; technical difficulties leading to unsuccessful HSG; HSG not performed by authors; infertility < 12 months
Mean duration of pre-existing infertility 41 months OSCM, 40 months WSCM
Breakdown by cause for infertility not specified
Previous fertility treatments not specified

Interventions
HSG with OSCM lipiodol (Laboratories Guerbet, France) versus HSG with WSCM Iotrolan
A volume of 5 to 10 ml of contrast medium was used
Timed between end of menses and Day 10
No co-interventions
Primarily intended as diagnostic procedure

Outcomes
Pregnancy (method of diagnosis not specified, but data extracted from Danish Patient Database to complete information with respect to pregnancy)
Image quality
Pain
Infection
Haemorrhage

Notes
Unclear whether the assigned treatment was adequately concealed prior to allocation

Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
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</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
<td>Unclear risk</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) All outcomes</td>
<td>High risk</td>
<td>All examinations and evaluations performed by authors</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>High risk</td>
<td>Losses to follow up and withdrawals totalled 21%</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>Pregnancy information from Danish database</td>
</tr>
<tr>
<td>Other bias</td>
<td>Low risk</td>
<td>No other potential bias identified</td>
</tr>
</tbody>
</table>
### Methods
- **Method of randomisation:** third party sealed envelopes with allocation inside
- **Allocation concealment:** adequate
- **Blinding:** not blinded
- **Analysis:** power calculation specified a requirement for 180 recruits but trial terminated early owing to slow recruitment rate and running out of time
- **Intention-to-treat analysis performed**
- **Study setting:** Leeds General Infirmary and Princess Royal Hospital, Hull, UK
- **Duration of study:** 10 months
- **Duration of follow up:** 6 months
- **Withdrawals:** nil

### Participants
- **Number of participants:** 34
- **Mean age:** 30.6 years (eligibility criterion < 36 years).
- **Inclusion criteria:** unexplained primary or secondary infertility (proportion of primary and secondary not stated) for more than 12 months (mean duration of pre-existing infertility 49 months)
- **Investigative work-up:** normal semen analysis by WHO criteria, ovulatory confirmation by serum progesterone or serial scanning, normal fallopian tubes at laparoscopy and dye insufflation or HSG
- **Breakdown by cause for infertility:** unexplained only, all other causes for infertility excluded
- **Previous fertility treatments not specified**

### Interventions
- **HSG with OSCM lipiodol versus no treatment**
- **Timing with menstrual cycle not specified**
- **Information sheet on fertile phase of the cycle given to both groups; no other co-interventions**
- **Primarily intended as therapeutic procedure**

### Outcomes
- **Pregnancy rate (diagnosis based on positive pregnancy test)**
- **Viable pregnancy (diagnosis based on fetal heart on ultrasound)**
- **Adverse events**

### Notes
- Assigned treatment was clearly adequately concealed prior to allocation

### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Not described</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>Third party sealed envelope entry</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>Unclear risk</td>
<td>No mention</td>
</tr>
<tr>
<td>All outcomes</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### **Nugent 2002** *(Continued)*

<table>
<thead>
<tr>
<th>Bias Type</th>
<th>Risk Level</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Unclear risk</td>
<td>No mention</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Low risk</td>
<td>All participants apparently included in analysis</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>No selective reporting identified</td>
</tr>
<tr>
<td>Other bias</td>
<td>Low risk</td>
<td>No other potential bias identified</td>
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</table>

### **Ogata 1993**

<table>
<thead>
<tr>
<th>Section</th>
<th>Details</th>
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<tr>
<td><strong>Methods</strong></td>
<td>Method of randomisation: not stated</td>
</tr>
<tr>
<td></td>
<td>Allocation concealment: not stated</td>
</tr>
<tr>
<td></td>
<td>Blinding: not mentioned</td>
</tr>
<tr>
<td></td>
<td>Analysis: no mention of power calculation. Intention-to-treat analysis not done nor possible</td>
</tr>
<tr>
<td></td>
<td>Study setting: University of Kyusyu, Fukuoka, Japan</td>
</tr>
<tr>
<td></td>
<td>Study duration: November 1989 to February 1991</td>
</tr>
<tr>
<td></td>
<td>Duration of follow up: 4 months</td>
</tr>
<tr>
<td></td>
<td>Withdrawals: ? exclusions after randomisation before HSG</td>
</tr>
<tr>
<td></td>
<td>? withdrawals after HSG: only women who had 4 ovulatory cycles were analysed</td>
</tr>
<tr>
<td></td>
<td>? losses to follow up</td>
</tr>
<tr>
<td><strong>Participants</strong></td>
<td>Number of participants: 302 randomised (148 versus 154). Those who failed to complete the four ovulatory cycles of observation were excluded, so only 190 were included in analysis (105 versus 85)</td>
</tr>
<tr>
<td></td>
<td>Mean age: not specified; said to be similar between the 2 groups</td>
</tr>
<tr>
<td></td>
<td>Inclusion criteria: primary or secondary infertility (proportion not specified) having first visit to infertility clinic; duration of infertility not specified but said to be similar between the 2 groups</td>
</tr>
<tr>
<td></td>
<td>Investigative work-up: not specified, but rate of male infertility and PCT results said to be similar between the 2 groups</td>
</tr>
<tr>
<td></td>
<td>Breakdown by cause for infertility not specified</td>
</tr>
<tr>
<td></td>
<td>Previous fertility treatments not specified</td>
</tr>
<tr>
<td></td>
<td>No exclusion criteria specified</td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td>HSG with oil-soluble contrast medium lipiodol (Ultra-Fluid) versus no HSG (the HSG was delayed for 4 months until after the analysis)</td>
</tr>
<tr>
<td></td>
<td>Volume of contrast medium not specified</td>
</tr>
<tr>
<td></td>
<td>Timing with respect to menstrual cycle not specified</td>
</tr>
<tr>
<td></td>
<td>No co-interventions</td>
</tr>
<tr>
<td></td>
<td>Primarily intended as diagnostic procedure</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>Pregnancy (method of diagnosis not specified)</td>
</tr>
</tbody>
</table>
Notes
Unclear whether the assigned treatment was adequately concealed prior to allocation

Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>No mention of randomisation process</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>Unclear risk</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Unclear risk</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>High risk</td>
<td>Losses to follow up and withdrawals totalled 37% (102/302)</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>Failed to report pain or adverse effects</td>
</tr>
<tr>
<td>Other bias</td>
<td>Low risk</td>
<td>No other potential bias identified</td>
</tr>
</tbody>
</table>

Rasmussen 1991

Methods
Method of randomisation: not stated
Allocation concealment: not stated
Blinding: no mention
Analysis: intention-to-treat analysis not done or not possible, no mention of power calculation
Study setting: Odense University Hospital, Odense, Denmark
Duration of study: 1985 to 1988
Duration of follow up: 9 months
Withdrawals: 507 recruited and randomised, 78 excluded prior to HSG, 31 withdrawn after HSG, 14 lost to follow up (out of 207 in total)

Participants
Number of participants: 398
Mean age: not stated
Inclusion: primary or secondary infertility for more than 12 months (mean or range of duration of pre-existing infertility not stated)
Exclusion criteria: pregnant prior to HSG; HSG declined; technical difficulties leading to unsuccessful HSG; HSG not performed by authors
Investigative work-up: not stated
Breakdown by cause for infertility not specified
Previous fertility treatments not specified
### Interventions

HSG with OSCM lipiodol (Laboratories Guerbet, France) versus 3 types of WSCM: iohexol (Omnipaque 350, Nycomed, Oslo), ioxaglate (Hexabrix 320, Laboratoire Guerbet, France), diatrizoate (Urografin, Schering, Berlin). As there were no outcome differences between the 3 groups using WSCM, they were combined in the analysis of results.

A volume of 5 to 10 ml of contrast medium was used.

Timing with menstrual cycle not specified.

No co-interventions.

Primarily intended as diagnostic procedure.

### Outcomes

Pregnancy (method of diagnosis not specified).

Other outcomes of this trial (reported image quality, pain, infection, haemorrhage and intravasation) are reported in a separate publication (Lindequist 1991).

### Notes

Unclear whether the assigned treatment was adequately concealed prior to allocation.

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Not stated</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>Unclear risk</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Unclear risk</td>
<td>No mention to suggest this</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Unclear risk</td>
<td>Losses to follow up and withdrawals totalled 9%</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>No selective reporting identified</td>
</tr>
<tr>
<td>Other bias</td>
<td>Low risk</td>
<td>No other potential bias identified</td>
</tr>
</tbody>
</table>
## Methods

Method of randomisation: computer-generated random numbers in blocks of 9 at each site  
Allocation concealment: adequate  
Blinding: not mentioned  
Analysis: power calculation suggested a requirement for 257 women per contrast group (achieved for 2 groups and recruitment abandoned for third group owing to difficulty recruiting)  
Intention-to-treat analysis not performed  
Study setting: 10 centres co-ordinated by the Kaiser Permanente Medical Care Program Infertility Work Group, California, USA  
Duration of study: December 1993 to July 1996  
Duration of follow up: 12 months  
Withdrawals: 673 recruited and randomised, 7 lost to follow-up

## Participants

Number of participants: 666  
Mean age: 29.3 yrs (SD 4.6) years WSCM; 29.1 yrs (SD 2.9) years OSCM  
Inclusion criteria: primary or secondary infertility (OSCM 35.0%, WSCM 37.1%, WSCM + OSCM 34.8% primary infertility). Mean duration of infertility: OSCM 3.13 (SD 3.03) years, WSCM 3.15 (SD 3.18) years, WSCM + OSCM 3.09 (SD 3.61); eligibility criterion > 12 months  
Investigative work-up: not specified  
Breakdown by cause for infertility not specified  
Previous fertility treatments not specified  
Exclusion criteria: nil

## Interventions

HSG with OSCM ethiodol (Savage Laboratories, Melville, USA) versus WSCM diatrizoate and iodipamide (Bracco Diagnostics, New Brunswick, USA) versus both WSCM and OSCM  
Volume WSCM mean 9.4 (range 2 to 75) ml; OSCM mean 8.6 (range 1 to -55) ml; both - WSCM mean 8.2 (range 1 to 30) ml and OSCM mean 6.0 (range 1 to 20) ml  
Timing with menstrual cycle not specified  
Co-interventions: artificial insemination performed in 25.3% OSCM; 24.6% WSCM; 24.8% WSCM + OSCM  
Primarily intended as diagnostic procedure

## Outcomes

Pregnancy (diagnostic criteria not specified)  
Live birth  
Miscarriage  
Ectopic pregnancy

## Notes

Assigned treatment was clearly adequately concealed prior to allocation

### Risk of bias

**Bias** | **Authors' judgement** | **Support for judgement**
--- | --- | ---
Random sequence generation (selection bias) | Low risk | Random number scheme
### Steiner 2003

**Methods**
- Method of randomisation: computer-generated random numbers
- Allocation concealment: not concealed
- Analysis: no power calculation, intention to treat analysis not done
- Blinding: not done
- Study setting: University of Carolina, USA
- Duration of study: August 1996 to November 2000
- Duration of follow up: 18 months
- Withdrawals: 698 recruited, 642 excluded, 3 lost to follow up

**Participants**
- Number of participants: 56
- Mean age: 32.9 (SD 3.4) years WSCM; 32.6 (SD 3.6) years WSCM + OSCM
- Inclusion criteria: primary or secondary infertility (WSCM 57.5%, WSCM + OSCM 46.7% primary infertility)
- Mean duration of infertility: WSCM 2.9 (SD 3.0) years, WSCM + OSCM 2.8 (SD 2.3) years; eligibility criterion > 12 months
- Exclusion criteria: iodine allergy, non-patent tubes, refusal to participate
- Investigative work-up: not specified
- Breakdown by cause for infertility specified but data for subpopulations could not be extracted
- Previous fertility treatments not specified

---

### Tubal flushing for subfertility (Review)

- Spring 2000  
  (Continued)

<table>
<thead>
<tr>
<th>Risk of bias category</th>
<th>Unclear risk</th>
<th>Not mentioned</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>Unclear risk</td>
<td>Not blinded</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Unclear risk</td>
<td>Same clinician provided patient details, carried out HSG and reported the results</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Low risk</td>
<td>Losses to follow up and withdrawals totalled 1%</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>No selective reporting identified</td>
</tr>
<tr>
<td>Other bias</td>
<td>High risk</td>
<td>Interventions not delivered as planned: 25/133 women randomised to receive both WSCM and OSCM did not receive OSCM due to tubal abnormalities shown on WSCM. Groups unequal at baseline: younger women (aged 20 to 24) more likely to be assigned to WSCM, women aged 35 to 39 more likely to be assigned to OSCM</td>
</tr>
</tbody>
</table>
Interventions
HSG with WSCM Sinografin (Bracco Diagnostics, New Brunswick, USA) versus WSCM Sinografin + OSCM ethiodol (Savage Laboratories, Melville, USA)
Timing with menstrual cycle not specified
Co-interventions: ovulatory medication used in 61.5% WSCM; 53.3% WSCM + OSCM
Primarily intended as therapeutic procedure

Outcomes
Pregnancy (self report or positive blood or urine pregnancy test)
Time to conception

Notes
Allocation was not concealed from physicians; patients were informed of allocation after randomisation before treatment

Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Computer-generated number scheme</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>No allocation concealment done</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>Unclear risk</td>
<td>Not blinded</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Unclear risk</td>
<td>Clinicians reporting the outcome were aware of the allocation</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Low risk</td>
<td>Losses to follow up and withdrawals totalled 5%</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>Failed to report pain or adverse effects</td>
</tr>
<tr>
<td>Other bias</td>
<td>Low risk</td>
<td>No other potential bias identified</td>
</tr>
</tbody>
</table>
### Yang 1989

#### Methods
- Method of randomisation: not stated.
- Allocation concealment: unclear
- Blinding: double blind
- Analysis: no mention of power calculation, intention-to-treat analysis not done
- Study setting: Mackay Memorial Hospital, Taipei, Japan
- Duration of study: October 1986 to March 1987
- Duration of follow up: 8 months
- Withdrawals: nil

#### Participants
- Number of participants: 109
- Participant age: range 22 to 44 years; mean age WSCM 30.1 years, WSCM + OSCM 30.0 years
- Inclusion criteria: primary or secondary infertility for more than 12 months (mean or range of duration of pre-existing infertility not stated)
- Exclusion criteria: not mentioned
- Investigative work-up: not stated
- Breakdown specified by cause for infertility
- Previous fertility treatments not specified

#### Interventions
- HSG with WSCM Telebrix Hystero (Laboratories Guerbet) versus WSCM Telebrix Hstero followed by OSCM lipiodol Ultrafluide (Laboratories Guerbet)
- A volume of 10 ml WSCM and 5 ml OSCM were used
- Timing with menstrual cycle not specified
- No co-interventions
- Primarily intended as diagnostic procedure

#### Outcomes
- Pregnancy (method of diagnosis not specified)

#### Notes
- Unclear whether the assigned treatment was adequately concealed prior to allocation

### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
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<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>The method of randomisation not stated</td>
</tr>
<tr>
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<td>Unclear risk</td>
<td>Not stated</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
<td>Low risk</td>
<td>States it is double blinded</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) All outcomes</td>
<td>Unclear risk</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>Low risk</td>
<td>All participants included in analysis</td>
</tr>
</tbody>
</table>
### Characteristics of excluded studies  
**[ordered by study ID]**

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acton 1988</td>
<td>Non-randomised study comparing HSG with OSCM versus WSCM in 420 women</td>
</tr>
<tr>
<td>Barwin 1971</td>
<td>Non-randomised study comparing HSG with OSCM versus WSCM in 248 women</td>
</tr>
<tr>
<td>Court 2014</td>
<td>Non-randomised observational study looking at pregnancy rates in 100 patients undergoing HSG using OSCM</td>
</tr>
<tr>
<td>DeCherney 1980</td>
<td>Non-randomised study comparing HSG with OSCM versus WSCM in 339 women</td>
</tr>
<tr>
<td>Gillespie 1965</td>
<td>Non-randomised study comparing HSG with OSCM versus WSCM in 271 women</td>
</tr>
<tr>
<td>Mackey 1971</td>
<td>Non-randomised study of HSG with OSCM versus WSCM versus no treatment in 523 women. (Showed no therapeutic effect of HSG with WSCM (OR 0.87, 95% CI 0.47 to 1.59), but a significantly higher pregnancy rate after HSG with OSCM (OR 1.60, 95% CI 1.09 to 2.35))</td>
</tr>
<tr>
<td>Perquin 2006</td>
<td>Randomised controlled trial comparing hysterosalpingography prior to laparoscopy and dye in 344 women</td>
</tr>
<tr>
<td>Schwabe 1983</td>
<td>Described as 'pseudo-randomised' with alternate assignment (thus not a truly randomised trial and therefore excluded), studied HSG with OSCM versus WSCM in 198 women (121 analysed). (Showed no significant difference in the odds of pregnancy for OSCM versus WSCM (OR 2.00, 95% CI 0.74 to 5.45))</td>
</tr>
<tr>
<td>Wolf 1989</td>
<td>Double-blind RCT of HSG with Iotrolan (WSCM) versus Iohexol versus diatrizoate assessing image quality and pain, but not pregnancy outcomes, in 60 women. A potential therapeutic effect on subsequent pregnancy outcomes could not therefore be studied</td>
</tr>
<tr>
<td>Yaegashi 1987</td>
<td>Non-randomised study of HSG with OSCM versus WSCM in 224 women. The details of this study were confirmed after commissioning a translation from the original Japanese publication</td>
</tr>
</tbody>
</table>
## Characteristics of ongoing studies  [ordered by study ID]  

### Dreyer 2014

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trial name or title</strong></td>
<td>H2Olie study</td>
</tr>
<tr>
<td><strong>Methods</strong></td>
<td>Randomised single-blind parallel trial comparing oil-based contrast medium with water-based contrast medium for tubal flushing</td>
</tr>
</tbody>
</table>
| **Participants**                 | **Inclusion**  
1. Age between 18 up to and including 39 years  
2. Subfertility of at least one year  
3. Chlamydia antibody titer (CAT) negative  
4. Low risk of tubal pathology according to the medical history  
5. Valid indication for HSG in the fertility work-up or before intrauterine insemination treatment  
**Exclusions**  
1. Endocrinopathological diseases as: PCOS, Cushing syndrome, adrenal hyperplasia, hyperprolactinemia, acromegaly, hypothalamic amenorrhea, hypothyroidy, diabetes mellitus type 1  
2. Known or high risk for tubal pathology, CAT positive  
3. Known contrast (iodine) allergy  
4. Male subfertility defined as a post-wash total motile sperm count $< 3 \times 10^6$ spermatozoa/ml  
5. If not willing or able to sign the consent form |
| **Interventions**                | Tubal flushing with oil-based contrast medium versus water-based contrast medium                                                                                                                           |
| **Outcomes**                     | Primary: ongoing pregnancy rates  
Secondary: live birth rates, miscarriages, ectopic pregnancy and pain scores                                                                                                                         |
| **Starting date**                | 1/12/2011                                                                                                                                                                                             |
| **Contact information**          | K Dreyer: k.dreyer@vumc.nl,  
Department of Reproductive Medicine VU University Medical Center PK 6Z K180 De Boelelaan 1118, 1081 HV, Amsterdam, The Netherlands, +31 (0)20 4445277 |
| **Notes**                        | Data collection complete at November 2014; results expected at ESHRE 2015  
Funding: VU University Medical Center  
NTR3270 accessed 25/11/2014 |
### DATA AND ANALYSES

#### Comparison 1. OSCM versus no intervention

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Live birth</td>
<td>1</td>
<td>158</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>3.09 [1.39, 6.91]</td>
</tr>
<tr>
<td>2 Ongoing Pregnancy</td>
<td>3</td>
<td>382</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>3.59 [2.06, 6.26]</td>
</tr>
<tr>
<td>3 Miscarriage per pregnancy</td>
<td>1</td>
<td>42</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>1.0 [0.16, 6.25]</td>
</tr>
<tr>
<td>4 Procedural pain</td>
<td>0</td>
<td>0</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>0.0 [0.0, 0.0]</td>
</tr>
<tr>
<td>5 Ectopic pregnancy per pregnancy</td>
<td>1</td>
<td>42</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>1.58 [0.06, 41.34]</td>
</tr>
<tr>
<td>6 Intravasation</td>
<td>0</td>
<td>0</td>
<td>Peto Odds Ratio (Peto, Fixed, 95% CI)</td>
<td>0.0 [0.0, 0.0]</td>
</tr>
<tr>
<td>7 Infection</td>
<td>0</td>
<td>0</td>
<td>Peto Odds Ratio (Peto, Fixed, 95% CI)</td>
<td>0.0 [0.0, 0.0]</td>
</tr>
<tr>
<td>8 Haemorrhage</td>
<td>0</td>
<td>0</td>
<td>Peto Odds Ratio (Peto, Fixed, 95% CI)</td>
<td>0.0 [0.0, 0.0]</td>
</tr>
<tr>
<td>9 Long term complications</td>
<td>0</td>
<td>0</td>
<td>Peto Odds Ratio (Peto, Fixed, 95% CI)</td>
<td>0.0 [0.0, 0.0]</td>
</tr>
</tbody>
</table>

#### Comparison 2. WSCM versus no intervention

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Live birth</td>
<td>1</td>
<td>334</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.10 [0.73, 1.66]</td>
</tr>
<tr>
<td>2 Ongoing Pregnancy</td>
<td>1</td>
<td>334</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>1.14 [0.71, 1.84]</td>
</tr>
<tr>
<td>3 Miscarriage per pregnancy</td>
<td>1</td>
<td>93</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>1.01 [0.35, 2.90]</td>
</tr>
<tr>
<td>4 Ectopic pregnancy</td>
<td>1</td>
<td>93</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>0.90 [0.05, 14.76]</td>
</tr>
<tr>
<td>5 Procedural pain</td>
<td>0</td>
<td>0</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>0.0 [0.0, 0.0]</td>
</tr>
<tr>
<td>6 Intravasation</td>
<td>0</td>
<td>0</td>
<td>Peto Odds Ratio (Peto, Fixed, 95% CI)</td>
<td>0.0 [0.0, 0.0]</td>
</tr>
<tr>
<td>7 Infection</td>
<td>0</td>
<td>0</td>
<td>Peto Odds Ratio (Peto, Fixed, 95% CI)</td>
<td>0.0 [0.0, 0.0]</td>
</tr>
<tr>
<td>8 Haemorrhage</td>
<td>0</td>
<td>0</td>
<td>Peto Odds Ratio (Peto, Fixed, 95% CI)</td>
<td>0.0 [0.0, 0.0]</td>
</tr>
<tr>
<td>9 Long term complications</td>
<td>0</td>
<td>0</td>
<td>Peto Odds Ratio (Peto, Fixed, 95% CI)</td>
<td>0.0 [0.0, 0.0]</td>
</tr>
</tbody>
</table>

#### Comparison 3. OSCM versus WSCM

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Live birth</td>
<td>2</td>
<td></td>
<td>Odds Ratio (M-H, Random, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>2 Ongoing pregnancy</td>
<td>5</td>
<td>1454</td>
<td>Odds Ratio (M-H, Random, 95% CI)</td>
<td>1.44 [0.84, 2.47]</td>
</tr>
<tr>
<td>3 Miscarriage per pregnancy</td>
<td>1</td>
<td>158</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>0.82 [0.40, 1.64]</td>
</tr>
<tr>
<td>4 Ectopic pregnancy</td>
<td>1</td>
<td>158</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>0.56 [0.10, 3.12]</td>
</tr>
<tr>
<td>5 Any postprocedural pain (dichotomous variable)</td>
<td>1</td>
<td>417</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>0.13 [0.08, 0.22]</td>
</tr>
<tr>
<td>6 Procedural pain (continuous variable)</td>
<td>1</td>
<td>106</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>-0.30 [-0.78, 0.18]</td>
</tr>
</tbody>
</table>
Comparison 4. OSCM + WSCM versus WSCM

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Live birth</td>
<td>1</td>
<td>393</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>1.06 [0.64, 1.77]</td>
</tr>
<tr>
<td>2 Ongoing Pregnancy</td>
<td>4</td>
<td>633</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>1.23 [0.87, 1.72]</td>
</tr>
<tr>
<td>3 Miscarriage per pregnancy</td>
<td>1</td>
<td>130</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>1.14 [0.53, 2.48]</td>
</tr>
<tr>
<td>4 Ectopic pregnancy</td>
<td>2</td>
<td>422</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>0.48 [0.05, 4.38]</td>
</tr>
<tr>
<td>5 Procedural pain</td>
<td>0</td>
<td>0</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>0.0 [0.0, 0.0]</td>
</tr>
<tr>
<td>6 Intravasation</td>
<td>0</td>
<td>0</td>
<td>Peto Odds Ratio (Peto, Fixed, 95% CI)</td>
<td>0.0 [0.0, 0.0]</td>
</tr>
<tr>
<td>7 Infection</td>
<td>0</td>
<td>0</td>
<td>Peto Odds Ratio (Peto, Fixed, 95% CI)</td>
<td>0.0 [0.0, 0.0]</td>
</tr>
<tr>
<td>8 Haemorrhage</td>
<td>0</td>
<td>0</td>
<td>Peto Odds Ratio (Peto, Fixed, 95% CI)</td>
<td>0.0 [0.0, 0.0]</td>
</tr>
<tr>
<td>9 Long term complications</td>
<td>0</td>
<td>0</td>
<td>Peto Odds Ratio (Peto, Fixed, 95% CI)</td>
<td>0.0 [0.0, 0.0]</td>
</tr>
</tbody>
</table>

Analysis 1.1. Comparison I OSCM versus no intervention, Outcome 1 Live birth.

Review: Tubal flushing for subfertility

Comparison: I OSCM versus no intervention

Outcome: 1 Live birth

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>OSCM (n/N)</th>
<th>No intervention (n/N)</th>
<th>Odds Ratio M-H,Fixed,95% CI</th>
<th>Weight</th>
<th>Odds Ratio M-H,Fixed,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Johnson 2004</td>
<td>23/73</td>
<td>11/85</td>
<td>3.09 [1.39, 6.91]</td>
<td>100.0%</td>
<td>3.09 [1.39, 6.91]</td>
</tr>
</tbody>
</table>

Total (95% CI) 73 85

Total events: 23 (OSCM), 11 (No intervention)
Heterogeneity: not applicable
Test for overall effect: \(Z = 2.76\) (\(P = 0.0058\))
Test for subgroup differences: Not applicable

Tubal flushing for subfertility (Review)
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Analysis 1.2. Comparison 1 OSCM versus no intervention, Outcome 2 Ongoing Pregnancy.

Review: Tubal flushing for subfertility

Comparison: 1 OSCM versus no intervention

Outcome: 2 Ongoing Pregnancy

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>OSCM n/N</th>
<th>No intervention n/N</th>
<th>Odds Ratio M-H,Fixed,95% CI</th>
<th>Weight</th>
<th>Odds Ratio M-H,Fixed,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Johnson 2004</td>
<td>28/73</td>
<td>14/85</td>
<td>3.16 [1.50, 6.63]</td>
<td>56.1 %</td>
<td></td>
</tr>
<tr>
<td>Nugent 2002</td>
<td>5/17</td>
<td>0/17</td>
<td>2.40 [0.78, 304.61]</td>
<td>4.1 %</td>
<td></td>
</tr>
<tr>
<td>Ogata 1993</td>
<td>25/105</td>
<td>7/85</td>
<td>3.48 [1.42, 8.52]</td>
<td>41.5 %</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>195</td>
<td>187</td>
<td>3.59 [2.06, 6.26]</td>
<td>100.0 %</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 58 (OSCM), 21 (No intervention)
Heterogeneity: Chi² = 1.03, df = 2 (P = 0.60); I² = 0.0%
Test for overall effect: Z = 4.50 (P < 0.00001)
Test for subgroup differences: Not applicable

Analysis 1.3. Comparison 1 OSCM versus no intervention, Outcome 3 Miscarriage per pregnancy.

Review: Tubal flushing for subfertility

Comparison: 1 OSCM versus no intervention

Outcome: 3 Miscarriage per pregnancy

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>OSCM n/N</th>
<th>No intervention n/N</th>
<th>Odds Ratio M-H,Fixed,95% CI</th>
<th>Weight</th>
<th>Odds Ratio M-H,Fixed,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Johnson 2004</td>
<td>4/28</td>
<td>2/14</td>
<td>1.00 [0.16, 6.25]</td>
<td>100.0 %</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>28</td>
<td>14</td>
<td>1.00 [0.16, 6.25]</td>
<td>100.0 %</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 4 (OSCM), 2 (No intervention)
Heterogeneity: not applicable
Test for overall effect: Z = 0.0 (P = 1.0)
Test for subgroup differences: Not applicable
### Analysis 1.5. Comparison 1 OSCM versus no intervention, Outcome 5 Ectopic pregnancy per pregnancy.

Review: Tubal flushing for subfertility  
Comparison: 1 OSCM versus no intervention  
Outcome: 5 Ectopic pregnancy per pregnancy

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>OSCM n/N</th>
<th>No intervention n/N</th>
<th>Odds Ratio M-H,Fixed,95% CI</th>
<th>Weight</th>
<th>Odds Ratio M-H,Fixed,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Johnson 2004</td>
<td>1/28</td>
<td>0/14</td>
<td>1.58 [0.06, 41.34]</td>
<td>100.0%</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>28</td>
<td>14</td>
<td></td>
<td>100.0%</td>
<td>1.58 [0.06, 41.34]</td>
</tr>
</tbody>
</table>

Total events: 1 (OSCM), 0 (No intervention)  
Heterogeneity: not applicable  
Test for overall effect: Z = 0.28 (P = 0.78)  
Test for subgroup differences: Not applicable

### Analysis 2.1. Comparison 2 WSCM versus no intervention, Outcome 1 Live birth.

Review: Tubal flushing for subfertility  
Comparison: 2 WSCM versus no intervention  
Outcome: 1 Live birth

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>WSCM n/N</th>
<th>No intervention n/N</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lindborg 2009</td>
<td>38/168</td>
<td>34/166</td>
<td>1.10 [0.73, 1.66]</td>
<td>100.0%</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>168</td>
<td>166</td>
<td></td>
<td>100.0%</td>
<td>1.10 [0.73, 1.66]</td>
</tr>
</tbody>
</table>

Total events: 38 (WSCM), 34 (No intervention)  
Heterogeneity: not applicable  
Test for overall effect: Z = 0.47 (P = 0.64)  
Test for subgroup differences: Not applicable
### Analysis 2.2. Comparison 2 WSCM versus no intervention, Outcome 2 Ongoing Pregnancy.

**Review:** Tubal flushing for subfertility  
**Comparison:** 2 WSCM versus no intervention  
**Outcome:** 2 Ongoing Pregnancy

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>WSCM n/N</th>
<th>No intervention n/N</th>
<th>Odds Ratio M-H,Fixed,95% CI</th>
<th>Weight</th>
<th>Odds Ratio M-H,Fixed,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lindborg 2009</td>
<td>49/168</td>
<td>44/166</td>
<td>1.14 [0.71, 1.84]</td>
<td>100.0%</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>168</strong></td>
<td><strong>166</strong></td>
<td></td>
<td><strong>100.0%</strong></td>
<td><strong>1.14 [0.71, 1.84]</strong></td>
</tr>
</tbody>
</table>

Total events: 49 (WSCM), 44 (No intervention)  
Heterogeneity: not applicable  
Test for overall effect: Z = 0.54 (P = 0.59)  
Test for subgroup differences: Not applicable

### Analysis 2.3. Comparison 2 WSCM versus no intervention, Outcome 3 Miscarriage per pregnancy.

**Review:** Tubal flushing for subfertility  
**Comparison:** 2 WSCM versus no intervention  
**Outcome:** 3 Miscarriage per pregnancy

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>WSCM n/N</th>
<th>No intervention n/N</th>
<th>Odds Ratio M-H,Fixed,95% CI</th>
<th>Weight</th>
<th>Odds Ratio M-H,Fixed,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lindborg 2009</td>
<td>9/49</td>
<td>8/44</td>
<td>1.01 [0.35, 2.90]</td>
<td>100.0%</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>49</strong></td>
<td><strong>44</strong></td>
<td></td>
<td><strong>100.0%</strong></td>
<td><strong>1.01 [0.35, 2.90]</strong></td>
</tr>
</tbody>
</table>

Total events: 9 (WSCM), 8 (No intervention)  
Heterogeneity: not applicable  
Test for overall effect: Z = 0.02 (P = 0.98)  
Test for subgroup differences: Not applicable
### Analysis 2.4. Comparison 2 WSCM versus no intervention, Outcome 4 Ectopic pregnancy.

**Review:** Tubal flushing for subfertility

**Comparison:** 2 WSCM versus no intervention

**Outcome:** 4 Ectopic pregnancy

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>WSCM 1/49 (n/N)</th>
<th>No intervention 1/44 (n/N)</th>
<th>Odds Ratio M-H,Fixed,95% CI (Odds Ratio)</th>
<th>Weight (Odds Ratio)</th>
<th>Total 100.0% (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lindborg 2009</td>
<td></td>
<td></td>
<td>1.00 [0.05, 14.76]</td>
<td>100.0%</td>
<td>0.90 [0.05, 14.76]</td>
</tr>
</tbody>
</table>

**Total events:** 1 (WSCM), 1 (No intervention)

**Heterogeneity:** not applicable

**Test for overall effect:** Z = 0.08 (P = 0.94)

**Test for subgroup differences:** Not applicable

### Analysis 3.1. Comparison 3 OSCM versus WSCM, Outcome 1 Live birth.

**Review:** Tubal flushing for subfertility

**Comparison:** 3 OSCM versus WSCM

**Outcome:** 1 Live birth

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>OSCM 30/98 (n/N)</th>
<th>WSCM 34/300 (n/N)</th>
<th>Odds Ratio M-H,Random,95% CI (Odds Ratio)</th>
<th>Odds Ratio M-H,Random,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rasmussen 1991</td>
<td></td>
<td></td>
<td>3.45 [1.97, 6.03]</td>
<td></td>
</tr>
<tr>
<td>Spring 2000</td>
<td>53/273</td>
<td>54/260</td>
<td>0.92 [0.60, 1.40]</td>
<td></td>
</tr>
</tbody>
</table>

**Test for overall effect:** Z = 0.08 (P = 0.94)

**Test for subgroup differences:** Not applicable
### Analysis 3.2. Comparison 3 OSCM versus WSCM, Outcome 2 Ongoing pregnancy.

**Review:** Tubal flushing for subfertility

**Comparison:** 3 OSCM versus WSCM

**Outcome:** 2 Ongoing pregnancy

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>OSCM</th>
<th>WSCM</th>
<th>Odds Ratio</th>
<th>Weight</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H,Random,95% CI</td>
<td></td>
<td>M-H,Random,95% CI</td>
</tr>
<tr>
<td>Alper 1986</td>
<td>15/60</td>
<td>14/46</td>
<td>16.1 %</td>
<td>0.76 [ 0.32, 1.80 ]</td>
<td></td>
</tr>
<tr>
<td>De Boer 1988</td>
<td>34/87</td>
<td>23/88</td>
<td>19.6 %</td>
<td>1.81 [ 0.95, 3.44 ]</td>
<td></td>
</tr>
<tr>
<td>Lindequist 1994</td>
<td>29/121</td>
<td>24/121</td>
<td>20.1 %</td>
<td>1.27 [ 0.69, 2.35 ]</td>
<td></td>
</tr>
<tr>
<td>Rasmussen 1991</td>
<td>30/98</td>
<td>34/300</td>
<td>21.0 %</td>
<td>3.45 [ 1.97, 6.03 ]</td>
<td></td>
</tr>
<tr>
<td>Spring 2000</td>
<td>53/273</td>
<td>54/260</td>
<td>23.2 %</td>
<td>0.92 [ 0.60, 1.40 ]</td>
<td></td>
</tr>
</tbody>
</table>

**Total (95% CI)**: 639 815 100.0 % 1.44 [ 0.84, 2.47 ]

Total events: 161 (OSCM), 149 (WSCM)

Heterogeneity: \( \tau^2 = 0.28; \chi^2 = 16.48, df = 4 (P = 0.002); I^2 = 76\%

Test for overall effect: \( Z = 1.31 \) (\( P = 0.19 \))

Test for subgroup differences: Not applicable
### Analysis 3.3. Comparison 3 OSCM versus WSCM, Outcome 3 Miscarriage per pregnancy.

**Review:** Tubal flushing for subfertility  
**Comparison:** 3 OSCM versus WSCM  
**Outcome:** 3 Miscarriage per pregnancy

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>OSCM n/N</th>
<th>WSCM n/N</th>
<th>Odds Ratio M-H,Fixed,95% CI</th>
<th>Weight</th>
<th>Odds Ratio M-H,Fixed,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spring 2000</td>
<td>19/74</td>
<td>25/84</td>
<td>0.82 [ 0.40, 1.64 ]</td>
<td>100.0%</td>
<td>0.82 [ 0.40, 1.64 ]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>74 /84</td>
<td>84 /84</td>
<td></td>
<td>100.0%</td>
<td>0.82 [ 0.40, 1.64 ]</td>
</tr>
</tbody>
</table>

Total events: 19 (OSCM), 25 (WSCM)  
Heterogeneity: not applicable  
Test for overall effect: Z = 0.57 (P = 0.57)  
Test for subgroup differences: Not applicable

---

### Analysis 3.4. Comparison 3 OSCM versus WSCM, Outcome 4 Ectopic pregnancy.

**Review:** Tubal flushing for subfertility  
**Comparison:** 3 OSCM versus WSCM  
**Outcome:** 4 Ectopic pregnancy

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>OSCM n/N</th>
<th>WSCM n/N</th>
<th>Odds Ratio M-H,Fixed,95% CI</th>
<th>Weight</th>
<th>Odds Ratio M-H,Fixed,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spring 2000</td>
<td>2/74</td>
<td>4/84</td>
<td>0.56 [ 0.10, 3.12 ]</td>
<td>100.0%</td>
<td>0.56 [ 0.10, 3.12 ]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>74 /84</td>
<td>84 /84</td>
<td></td>
<td>100.0%</td>
<td>0.56 [ 0.10, 3.12 ]</td>
</tr>
</tbody>
</table>

Total events: 2 (OSCM), 4 (WSCM)  
Heterogeneity: not applicable  
Test for overall effect: Z = 0.67 (P = 0.50)  
Test for subgroup differences: Not applicable
Analysis 3.5. Comparison 3 OSCM versus WSCM, Outcome 5 Any postprocedural pain (dichotomous variable).

Comparison: 3 OSCM versus WSCM
Outcome: 5 Any postprocedural pain (dichotomous variable)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>OSCM</th>
<th>WSCM</th>
<th>Odds Ratio</th>
<th>Weight</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rasmussen 1991</td>
<td>54/103</td>
<td>281/314</td>
<td>0.13 [ 0.08, 0.22 ]</td>
<td>100.0 %</td>
<td>0.13 [ 0.08, 0.22 ]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>103</td>
<td>314</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 54 (OSCM), 281 (WSCM)
Heterogeneity: not applicable
Test for overall effect: Z = 7.58 (P < 0.00001)
Test for subgroup differences: Not applicable

Analysis 3.6. Comparison 3 OSCM versus WSCM, Outcome 6 Procedural pain (continuous variable).

Comparison: 3 OSCM versus WSCM
Outcome: 6 Procedural pain (continuous variable)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>OSCM</th>
<th>WSCM</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alper 1986</td>
<td>46</td>
<td>60</td>
<td>-0.30 [ -0.78, 0.18 ]</td>
<td>100.0 %</td>
<td>-0.30 [ -0.78, 0.18 ]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>46</td>
<td>60</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: not applicable
Test for overall effect: Z = 1.22 (P = 0.22)
Test for subgroup differences: Not applicable
### Analysis 3.7. Comparison 3 OSCM versus WSCM, Outcome 7 Intravasation.

Review: Tubal flushing for subfertility

Comparison: 3 OSCM versus WSCM

Outcome: 7 Intravasation

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>OSCM n/N</th>
<th>WSCM n/N</th>
<th>Odds Ratio M-H,Fixed 95% CI</th>
<th>Weight</th>
<th>Odds Ratio M-H,Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alper 1986</td>
<td>6/46</td>
<td>1/60</td>
<td>13.0 % 8.85 [ 1.03, 76.34 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lindequist 1994</td>
<td>8/123</td>
<td>3/122</td>
<td>48.5 % 2.76 [ 0.71, 10.66 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>272</strong></td>
<td><strong>496</strong></td>
<td>100.0 % 5.05 [ 2.27, 11.22 ]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 24 (OSCM), 9 (WSCM)

Heterogeneity: Chi² = 1.27, df = 2 (P = 0.53); I² = 0.0%

Test for overall effect: Z = 3.97 (P = 0.000073)

Test for subgroup differences: Not applicable

---

### Analysis 3.8. Comparison 3 OSCM versus WSCM, Outcome 8 Infection.

Review: Tubal flushing for subfertility

Comparison: 3 OSCM versus WSCM

Outcome: 8 Infection

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>OSCM n/N</th>
<th>WSCM n/N</th>
<th>Odds Ratio M-H,Fixed 95% CI</th>
<th>Weight</th>
<th>Odds Ratio M-H,Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lindequist 1994</td>
<td>0/123</td>
<td>0/122</td>
<td>Not estimable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rasmussen 1991</td>
<td>1/103</td>
<td>14/314</td>
<td>100.0 % 0.21 [ 0.03, 1.62 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>226</strong></td>
<td><strong>436</strong></td>
<td>100.0 % 0.21 [ 0.03, 1.62 ]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 1 (OSCM), 14 (WSCM)

Heterogeneity: not applicable

Test for overall effect: Z = 1.50 (P = 0.13)

Test for subgroup differences: Not applicable
Analysis 3.9. Comparison 3 OSCM versus WSCM, Outcome 9 Haemorrhage.

Review: Tubal flushing for subfertility
Comparison: 3 OSCM versus WSCM
Outcome: 9 Haemorrhage

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>OSCM</th>
<th>WSCM</th>
<th>Odds Ratio</th>
<th>Weight</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lindequist 1994</td>
<td>50/123</td>
<td>63/122</td>
<td>0.64 [0.39, 1.06]</td>
<td>95.0 %</td>
<td></td>
</tr>
<tr>
<td>Rasmussen 1991</td>
<td>1/103</td>
<td>4/314</td>
<td>0.76 [0.08, 6.88]</td>
<td>5.0 %</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>226</strong></td>
<td><strong>436</strong></td>
<td>0.65 [0.40, 1.06]</td>
<td>100.0 %</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 51 (OSCM), 67 (WSCM)
Heterogeneity: Chi^2 = 0.02, df = 1 (P = 0.88); I^2 = 0.0%
Test for overall effect: Z = 1.73 (P = 0.084)
Test for subgroup differences: Not applicable
Analysis 4.1. Comparison 4 OSCM + WSCM versus WSCM, Outcome 1 Live birth.

Review: Tubal flushing for subfertility

Comparison: 4 OSCM + WSCM versus WSCM

Outcome: 1 Live birth

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>OSCM + WSCM</th>
<th>WSCM</th>
<th>Odds Ratio M-H,Fixed,95% CI</th>
<th>Weight</th>
<th>Odds Ratio M-H,Fixed,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spring 2000</td>
<td>29/133</td>
<td>54/260</td>
<td>1.06 [0.64, 1.77]</td>
<td>100.0%</td>
<td>1.06 [0.64, 1.77]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>133</td>
<td>260</td>
<td>100.0%</td>
<td>1.06 [0.64, 1.77]</td>
<td>1.06 [0.64, 1.77]</td>
</tr>
</tbody>
</table>

Total events: 29 (OSCM + WSCM), 54 (WSCM)
Heterogeneity: not applicable
Test for overall effect: Z = 0.24 (P = 0.81)
Test for subgroup differences: Not applicable

Analysis 4.2. Comparison 4 OSCM + WSCM versus WSCM, Outcome 2 Ongoing Pregnancy.

Review: Tubal flushing for subfertility

Comparison: 4 OSCM + WSCM versus WSCM

Outcome: 2 Ongoing Pregnancy

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>OSCM + WSCM</th>
<th>WSCM</th>
<th>Odds Ratio M-H,Fixed,95% CI</th>
<th>Weight</th>
<th>Odds Ratio M-H,Fixed,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Al-Fadhli 2006</td>
<td>16/39</td>
<td>12/39</td>
<td>1.57 [0.62, 3.98]</td>
<td>11.8%</td>
<td>1.57 [0.62, 3.98]</td>
</tr>
<tr>
<td>Spring 2000</td>
<td>46/133</td>
<td>84/260</td>
<td>1.11 [0.71, 1.72]</td>
<td>62.0%</td>
<td>1.11 [0.71, 1.72]</td>
</tr>
<tr>
<td>Steiner 2003</td>
<td>18/28</td>
<td>14/25</td>
<td>1.41 [0.47, 4.27]</td>
<td>8.8%</td>
<td>1.41 [0.47, 4.27]</td>
</tr>
<tr>
<td>Yang 1989</td>
<td>18/48</td>
<td>19/61</td>
<td>1.33 [0.60, 2.94]</td>
<td>17.4%</td>
<td>1.33 [0.60, 2.94]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>248</td>
<td>385</td>
<td>100.0%</td>
<td>1.23 [0.87, 1.72]</td>
<td>1.23 [0.87, 1.72]</td>
</tr>
</tbody>
</table>

Total events: 98 (OSCM + WSCM), 129 (WSCM)
Heterogeneity: Chi$^2$ = 0.57, df = 3 (P = 0.90); I$^2$ =0.0% 
Test for overall effect: Z = 1.18 (P = 0.24)
Test for subgroup differences: Not applicable

Tubal flushing for subfertility (Review)

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### Analysis 4.3. Comparison 4 OSCM + WSCM versus WSCM, Outcome 3 Miscarriage per pregnancy.

**Review:** Tubal flushing for subfertility  
**Comparison:** 4 OSCM + WSCM versus WSCM  
**Outcome:** 3 Miscarriage per pregnancy

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>OSCM + WSCM</th>
<th>WSCM</th>
<th>Odds Ratio</th>
<th>Weight</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H,Fixed,95% CI</td>
<td></td>
<td>M-H,Fixed,95% CI</td>
</tr>
<tr>
<td>Spring 2000</td>
<td>15/46</td>
<td>25/84</td>
<td>1.14 [ 0.53, 2.48 ]</td>
<td>100.0 %</td>
<td>1.14 [ 0.53, 2.48 ]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>46</strong></td>
<td><strong>84</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total events: 15 (OSCM + WSCM), 25 (WSCM)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Heterogeneity: not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Test for overall effect: Z = 0.34 (P = 0.74)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Test for subgroup differences: Not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

0.1 0.2 0.5 1 2 5 10  
Favours OSCM + WSCM  
Favours WSCM
Analysis 4.4. Comparison 4 OSCM + WSCM versus WSCM, Outcome 4 Ectopic pregnancy.

Review: Tubal flushing for subfertility

Comparison: 4 OSCM + WSCM versus WSCM

Outcome: 4 Ectopic pregnancy

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>OSCM + WSCM</th>
<th>WSCM</th>
<th>Odds Ratio</th>
<th>Weight</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H,Fixed,95% CI</td>
<td>M-H,Fixed,95% CI</td>
<td></td>
</tr>
<tr>
<td>Letterie 1990</td>
<td>0/15</td>
<td>0/14</td>
<td>Not estimable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spring 2000</td>
<td>1/133</td>
<td>4/260</td>
<td>100.0 %</td>
<td>0.48 [ 0.05, 4.38 ]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>148</strong></td>
<td><strong>274</strong></td>
<td>100.0 %</td>
<td>0.48 [ 0.05, 4.38 ]</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 1 (OSCM + WSCM), 4 (WSCM)
Heterogeneity: not applicable
Test for overall effect: Z = 0.64 (P = 0.52)
Test for subgroup differences: Not applicable

AP P E N D I C E S

Appendix 1. MDSG search strategy

Menstrual Disorders and Subfertility database search strategy for NJ212 11.01.11- limited to 2007 until present.

Keywords CONTAINS “fertility” or “subfertility” or “infertility” or “hysterosalpingogram” or “hysterosalpingography” or “laparoscopic chromopertubation” or “laparoscopy” or “Fallopian-Tube-Patency-Tests” or “tubal flushing” or “tubal patency” or “flushing media” or Title CONTAINS “fertility” or “subfertility” or “infertility” or “hysterosalpingogram” or “hysterosalpingography” or “laparoscopic chromopertubation” or “laparoscopy” or “Fallopian-Tube-Patency-Tests” or “tubal flushing” or “tubal patency” or “flushing media” AND

Keywords CONTAINS “oil” or “oil-soluble contrast” or “Water-Soluble Contrast” or “Aqueous” or “lipiodol” or “lipiodol flushing” or “lipiodol-pingyangmycin emulsion” or “Contrast-Media” or “Flushing” or Title CONTAINS “oil” or “oil-soluble contrast” or “Water-Soluble Contrast” or “Aqueous” or “lipiodol” or “lipiodol flushing” or “lipiodol-pingyangmycin emulsion” or “Contrast-Media” or “Flushing”
Appendix 2. MEDLINE search strategy

1 HYSTEROSALPINGOGRAPHY/ or hysterosalpingog$.tw. (4547)
2 salpingog$.tw. (181)
3 HSG.tw. (1046)
4 laparoscop$.tw. (82655)
5 LAPAROSCOPY/ (59726)
6 Fallopian Tube Patency Tests/ (601)
7 (tubal adj flush$).tw. (23)
8 (tub$ adj patency).tw. (833)
9 chromopertub$.tw. (99)
10 fertili$.tw. (105699)
11 or/1-10 (199539)
12 OILS/ (9645)
13 oil$.tw. (97949)
14 Ethiodized Oil/ (529)
15 ethiodol.tw. (119)
16 iotrolan.tw. (199)
17 poppy.tw. (766)
18 Iodized Oil/ (2894)
19 IODIPAMIDE/ (620)
20 WATER/ (111567)
21 Contrast Media/ (65942)
22 contrast medi$.tw. (20603)
23 (water adj soluble).tw. (31267)
24 (oil adj soluble).tw. (339)
25 aqueous.tw. (131938)
26 lipiodol.tw. (2225)
27 OSCM.tw. (12)
28 WSCM.tw. (15)
29 or/12-28 (419392)
30 11 and 29 (3180)
31 randomized controlled trial.pt. (376220)
32 controlled clinical trial.pt. (88548)
33 randomized.ab. (296250)
34 placebo.tw. (159087)
35 clinical trials as topic.sh. (170403)
36 randomly.ab. (214362)
37 trial.ti. (127538)
38 (crossover or cross-over or cross over).tw. (60957)
39 or/31-38 (929229)
40 exp animals/ not humans.sh. (3951224)
41 39 not 40 (3951224)
42 30 11 and 29 (3180)
43 randomized controlled trial.pt. (376220)
44 controlled clinical trial.pt. (88548)
45 randomized.ab. (296250)
46 placebo.tw. (159087)
47 (crossover or cross-over or cross over).tw. (60957)
48 or/31-38 (929229)
49 exp animals/ not humans.sh. (3951224)
50 39 not 40 (3951224)
51 30 11 and 29 (3180)
52 randomized controlled trial.pt. (376220)
53 controlled clinical trial.pt. (88548)
54 randomized.ab. (296250)
55 placebo.tw. (159087)
56 (crossover or cross-over or cross over).tw. (60957)
57 or/31-38 (929229)
58 exp animals/ not humans.sh. (3951224)
59 39 not 40 (3951224)
60 30 11 and 29 (3180)
61 randomized controlled trial.pt. (376220)
62 controlled clinical trial.pt. (88548)
63 randomized.ab. (296250)
64 placebo.tw. (159087)
65 (crossover or cross-over or cross over).tw. (60957)
66 or/31-38 (929229)
67 exp animals/ not humans.sh. (3951224)
68 39 not 40 (3951224)
69 30 11 and 29 (3180)
70 randomized controlled trial.pt. (376220)
71 controlled clinical trial.pt. (88548)
72 randomized.ab. (296250)
73 placebo.tw. (159087)
74 (crossover or cross-over or cross over).tw. (60957)
75 or/31-38 (929229)
76 exp animals/ not humans.sh. (3951224)
77 39 not 40 (3951224)
78 30 11 and 29 (3180)
Appendix 3. EMBASE search strategy

1 exp HYSTEROSALPINGOGRAPHY/ (4376)
2 hysterosalpingog$.tw. (2694)
3 salpingog$.tw. (227)
4 HSG.tw. (1452)
5 laparoscop$.tw. (117162)
6 exp LAPAROSCOPY/ (99372)
7 (tubal adj flush$).tw. (27)
8 (tub$ adj patency).tw. (994)
9 chromopertub$.tw. (130)
10 fertili$.tw. (119535)
11 or/1-10 (258375)
12 exp oil/ (14298)
13 oil$.tw. (124170)
14 exp ethiodized oil/ (577)
15 ethiodol.tw. (242)
16 iotrolan.tw. (222)
17 poppy.tw. (908)
18 exp ethiodized oil/ (577)
19 exp adipiodone/ (591)
20 exp WATER/ (277044)
21 IODIPAMIDE.tw. (134)
22 water.tw. (576375)
23 exp contrast medium/ (117267)
24 contrast medi$.tw. (22787)
25 (water adj soluble).tw. (35678)
26 (oil adj soluble).tw. (386)
27 aqueous.tw. (155448)
28 lipiodol.tw. (3652)
29 OSCM.tw. (16)
30 WSCM.tw. (16)
31 or/12-30 (987131)
32 11 and 31 (10395)
33 Clinical Trial/ (831601)
34 Randomized Controlled Trial/ (343448)
35 exp randomization/ (62313)
36 Single Blind Procedure/ (18367)
37 Double Blind Procedure/ (113645)
38 Crossover Procedure/ (39147)
39 Placebo/ (240637)
40 Randomi?ed controlled trial$.tw. (98971)
41 Ret.tw. (13930)
42 random allocation.tw. (1308)
43 randomly allocated.tw. (20183)
44 allocated randomly.tw. (1921)
45 (allocated adj2 random).tw. (712)
46 Single blind$.tw. (14252)
47 Double blind$.tw. (140404)
48 ((treble or triple) adj blind$).tw. (370)
49 placebo$.tw. (197255)
50 prospective study/ (252453)
51 or/33-50 (1358985)
Appendix 4. CENTRAL search strategy

1 Hysterosalpingography/ or hysterosalpingog$.tw. (171)
2 Salpingog$.tw. (7)
3 HSG.tw. (75)
4 Laparoscopy$.tw. (5936)
5 Laparoscopy/ (2714)
6 Fallopian Tube Patency Tests/ (28)
7 (tubal adj flush$).tw. (4)
8 (tub$ adj patency).tw. (60)
9 Chromopertub$.tw. (11)
10 Fertilization$.tw. (2691)
11 or/1-10 (8766)
12 Oils/ (107)
13 Oil$.tw. (4703)
14 Ethiodized Oil/ (24)
15 Ethiodol.tw. (2)
16 Iotrolan.tw. (37)
17 Poppy.tw. (18)
18 Iodized Oil/ (115)
19 Iodipamide/ (18)
20 Water/ (1487)
21 Contrast Media/ (2127)
22 Contrast medi$.tw. (1449)
23 (water adj soluble).tw. (467)
24 (oil adj soluble).tw. (20)
25 Aqueous.tw. (2238)
26 Lipiodol.tw. (155)
27 OS CM.tw. (4)
28 WSCM.tw. (4)
29 or/12-28 (11564)
30 11 and 29 (106)
31 Limit 30 to yr="2013 -Current" (5)
Appendix 5. PsycINFO search strategy

1 exp Fertility Enhancement/ or exp Infertility/ (1731)
2 hysterosalpingog$.tw. (3)
3 HSG.tw. (22)
4 laparoscopy$.tw. (299)
5 (tubal adj flush$).tw. (0)
6 (tub$ adj patency).tw. (2)
7 chromopertub$.tw. (0)
8 fertil$.tw. (7390)
9 or/1-8 (8828)
10 oil$.tw. (3378)
11 Ethiodized Oil.tw. (0)
12 ethiodol.tw. (0)
13 iotrolan.tw. (0)
14 poppy.tw. (81)
15 Iodized Oil.tw. (3)
16 IODIPAMIDE.tw. (0)
17 WATER.tw. (27085)
18 Contrast Media.tw. (95)
19 aqueous.tw. (503)
20 lipiodol.tw. (8)
21 OSCM.tw. (1)
22 WSCM.tw. (0)
23 or/10-22 (30736)
24 9 and 23 (90)
25 limit 24 to yr="2013 -Current" (10)

Appendix 6. Biological abstracts

1. Hysterosalpingography/ or hysterosalpingography.mp. or hysterosalpingog$.tw.
2. salpingog$.tw.
3. HSG.tw.
4. laparoscopy adj3 dye).tw.
5. LAPAROSCOPY/
6. Fallopian Tube Patency Tests/
7. tubal adj flush$).mp. [mp=ti, kw, ab, bc, bt, bo, sh, hw, tn, or, dm,mf, rw]
8. tub$ adj patency).tw.
9. or/1-8
10. OILS/
11. Ethiodized Oil/
12. Iodized Oil/
13. IODIPAMIDE/
14. WATER/
15. Contrast Media/
17. oil adj soluble).tw.
18. lipiodol.tw.
19. OSCM.tw.
20. WSCM.tw.
21. Or/10-20
22. 9 and 21
23. exp clinical trials/
24. exp research design/
25. clinical trial.pt.
26. randomised controlled trial.pt.
27. (singl$ or doubl$ or trebl$ or tripl$).tw.
28. (mask$ or Blind$.tw.
29. 27 and 28
30. placebos/ or placebo.tw.
31. 23 or 24 or 25 or 26 or 29 or 30
32. 22 and 31

WHAT'S NEW

Last assessed as up-to-date: 17 June 2014.

<table>
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<tr>
<th>Date</th>
<th>Event</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>16 April 2015</td>
<td>New citation required but conclusions have not changed</td>
<td>Our conclusions have not changed with the addition of one new study</td>
</tr>
<tr>
<td>16 April 2015</td>
<td>New search has been performed</td>
<td>One study added (Lindborg 2009); contact details updated; one new comparison added (water-soluble contrast media versus no treatment); risk of bias tables updated; tables of characteristics of included studies updated; review adapted to new format; summary of findings table added</td>
</tr>
</tbody>
</table>

HISTORY

Protocol first published: Issue 2, 1996
Review first published: Issue 2, 1996

<table>
<thead>
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<th>Date</th>
<th>Event</th>
<th>Description</th>
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<tbody>
<tr>
<td>13 June 2008</td>
<td>Amended</td>
<td>Converted to new review format.</td>
</tr>
<tr>
<td>16 April 2007</td>
<td>New citation required and conclusions have changed</td>
<td>Substantive amendment</td>
</tr>
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CONTRIBUTIONS OF AUTHORS
Lamiya Mohiyiddeen, Anne Hardiman, Cheryl Fitzgerald and Andrew Watson carried out this update in 2015. Andrew Watson was also an author of the original review, was involved in trial selection and data extraction of trials for the updated review and critically appraised previous updates. Neil Johnson conceptualised and carried out the updates of the former review: 'Oil-soluble versus water-soluble media for assessing tubal patency with hysterosalpingography or laparoscopy in subfertile women' (including trial selection and data extraction of trials for the updated reviews), and approved the 2015 update. Ed Hughes was author of the original review, commented on the updated review in 2007, and approved the 2015 update. Ben Mol joined the author group and commented on the 2007 update, and commented on and approved the 2015 update.

DECLARATIONS OF INTEREST
Neil Johnson and Andrew Watson were investigators in separate RCTs included in this review. Ben Mol is an investigator on ongoing trial Dreyer 2014 investigating oil-based versus water-based contrast media.

SOURCES OF SUPPORT
Internal sources
• None, Other.

External sources
• None, Other.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW
We have added one new comparison (water-soluble contrast media versus no treatment).

NOTES
This review was previously known as 'Oil-soluble versus water-soluble media for assessing tubal patency with hysterosalpingography or laparoscopy in subfertile women'.

INDEX TERMS
Medical Subject Headings (MeSH)
*Fallopian Tubes; Contrast Media [chemistry; *therapeutic use]; Infertility, Female [*therapy]; Live Birth [epidemiology]; Oils; Pregnancy Rate; Randomized Controlled Trials as Topic; Solubility; Therapeutic Irrigation [*methods]; Water
MeSH check words
Female; Humans; Pregnancy