Vasodilators for women undergoing fertility treatment (Review)

Gutarra-Vilchez RB, Urrúa G, Gluvovsky D, Coscia A, Bonfill Cosp X

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Vasodilators for women undergoing fertility treatment

Rosa B Gutarra-Vilchez, Gerard Urrútia, Demián Glujovsky, Andrea Coscia, Xavier Bonfill Cosp

1Vitarte Hospital, Health Ministry, Lima, Peru. 2Iberoamerican Cochrane Centre - Biomedical Research Institute Sant Pau (IIB Sant Pau), CIBER Epidemiología y Salud Pública (CIBERESP), Spain, Barcelona, Spain. 3Reproductive Medicine, CEGYR (Centro de Estudios en Genética y Reproducción), Buenos Aires, Argentina. 4Iberoamerican Cochrane Centre - Biomedical Research Institute Sant Pau (IIB Sant Pau), CIBER Epidemiología y Salud Pública (CIBERESP) - Universitat Autònoma de Barcelona, Barcelona, Spain

Contact address: Rosa B Gutarra-Vilchez, Vitarte Hospital, Health Ministry, Avenida Nicolas Ayllon, Lima, 5880 - ATE, Peru.

dragutarra2@gmail.com.

Editorial group: Cochrane Menstrual Disorders and Subfertility Group.


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ABSTRACT

Background

Since 1978, when Patrick Steptoe and Robert Edwards achieved the birth of the first test tube baby, assisted reproductive techniques have been refined and improved. However, the rate of successful pregnancies brought to term has barely increased. Therefore closer evaluation of the interventions is needed along with working towards improving uterus receptivity. Vasodilators have been proposed to increase endometrial receptivity, thicken the endometrium and favour uterine relaxation, all of which could improve uterine receptivity and enhance the chances for successful assisted pregnancies.

Objectives

To evaluate the effectiveness and safety of vasodilators in women undergoing fertility treatment.

Search methods

We searched the following electronic databases, trial registers and websites: the Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE, MEDLINE, the Menstrual Disorders and Subfertility Group (MDSG) Specialised Register of controlled trials, PsycINFO, the Cumulative Index to Nursing and Allied Health Literature (CINAHL), The Cochrane Library, Web of Knowledge, the Open System for Information on Grey Literature in Europe (OpenSIGLE), the Latin American and Caribbean Health Science Information Database (LILACS) and ClinicalTrials.gov. The search was conducted in February 2014. No language restrictions were applied.

Selection criteria

Randomised controlled trials (RCTs) of vasodilators alone or in combination with other treatments compared with placebo or with other agents in women undergoing fertility treatment.

Data collection and analysis

Two review authors independently selected the studies, assessed the risk of bias and extracted data. Risk ratios (RRs) were calculated using the numbers of events in the control and intervention groups of each study. Study data were combined using a random-effects model, and evidence quality was assessed using Grades of Recommendation, Assessment, Development and Evaluation Working Group (GRADE) methods.
Main results

Ten studies with a total of 797 women were included in this review. Most of the studies were judged as having an unclear risk of bias. Three studies reported live births, two reported vasodilator-related side effects, 10 reported clinical pregnancies (diagnosed by differing criteria) and four reported other side effects (multiple gestation, miscarriage, ectopic pregnancy).

Overall, no evidence suggested that treatment with vasodilators increased live birth rates compared with placebo or no treatment (RR 1.18, 95% confidence interval (CI) 0.82 to 1.69, P value 0.37, three RCTs, 350 women, I² = 0%, moderate-quality evidence). This indicates that among women undergoing fertility treatment who have a 24% chance of live birth without the use of vasodilators, between 19% and 40% will achieve live birth with the use of vasodilators.

No evidence was found of a difference between vasodilators and placebo or no treatment in the incidence of treatment side effects (RR 1.63, 95% CI 0.33 to 7.93, P value 0.55, two RCTs, 258 women, I² = 32%, low-quality evidence). Nor did any evidence show a difference between them in terms of multiple gestation, spontaneous abortion/miscarriage or ectopic pregnancy rates. However few relevant data were available.

Overall, treatment with vasodilators was associated with an increased clinical pregnancy rate compared with placebo or no treatment (RR 1.38, 95% CI 1.00 to 1.92, P value 0.05, eight RCTs, 717 women, I² = 0%, low-quality evidence). However, confidence intervals do not rule out no effect of the intervention, and when studies of vasodilators combined with another medication (vitamin E or oestrogen) were excluded, the effects of treatment with vasodilators alone on clinical pregnancy rates were more uncertain.

The evidence was of low or moderate quality, and the main limitations were imprecision and lack of clarity about study methods. Risk of publication bias could not be assessed because of the low number of identified studies.

Authors’ conclusions

Evidence was insufficient to show that vasodilators increased the live birth rate in women undergoing fertility treatment. However, low-quality evidence suggests that vasodilators may increase clinical pregnancy rates in comparison with placebo or no treatment. Evidence was insufficient to show whether any particular vasodilator, administered alone or in combination with other active medications, was superior, and evidence was insufficient to allow the review authors to reach any conclusions regarding adverse effects. Adequately powered studies are needed so that each treatment can be evaluated more accurately.

PLAIN LANGUAGE SUMMARY

Vasodilators in women undergoing fertility treatment

Review question: Cochrane review authors investigated the effectiveness and safety of vasodilators (drugs used to widen blood vessels) in women undergoing fertility treatment.

Background: In women undergoing fertility treatment for different causes, interventions aimed at improving the receptivity of the uterus are of utmost importance. Many different drugs have been evaluated, with the aim of increasing rates of implantation and live birth. These include vasodilating agents, which are used to dilate blood vessels to improve endometrial receptivity, thicken the endometrium and favour uterine relaxation, among other effects.

Study characteristics: Ten randomised controlled trials with a total of 797 women were included in this review. Investigators compared the use of vasodilators versus placebo or no treatment in women undergoing fertility treatment. The evidence is current to February 2014.

Key results: Only three of the included studies reported live birth. Overall, no evidence suggests that treatment with vasodilators increased live birth rates compared with placebo or no treatment. Moderate-quality evidence suggests that among women undergoing fertility treatment who have a 24% chance of live birth without the use of vasodilators, between 19% and 40% will achieve live birth with the use of vasodilators. However, low-quality evidence suggests that vasodilators may increase the chance of becoming pregnant. Evidence was insufficient to permit any conclusions regarding adverse effects, as only two studies reported this outcome.

Quality of the evidence: The evidence was of low or moderate quality, and the main limitations were imprecision and lack of clarity about study methods. Risk of publication bias could not be assessed because of the low number of included studies.
### SUMMARY OF FINDINGS FOR THE MAIN COMPARISON

**Patient or population:** women undergoing fertility treatment  
**Settings:** secondary care  
**Intervention:** vasodilator  
**Comparison:** placebo/no treatment

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Ilustrative 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>
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<td>Assumed risk</td>
<td>Corresponding risk</td>
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<td>Placebo</td>
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<td>Vasodilator</td>
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<td>Live birth</td>
<td>Medium-risk populationᵇ</td>
<td>RR 1.18 (0.82 to 1.69)</td>
<td>350 (3)</td>
<td>⊕⊕⊕ moderate ⚫</td>
<td>Most information comes from studies with low or unclear risk of bias. These studies have low precision, consistent direction of effect (directionality) and lack unexplained heterogeneity. Studies are insufficient to permit assessment of risk of publication bias</td>
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<td>236 per 1000 (193 to 398)</td>
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<tr>
<td>Vasodilator side effects</td>
<td>Medium-risk populationᵇ</td>
<td>RR 1.63 (0.33 to 7.93)</td>
<td>258 (2)</td>
<td>⊕⊕⊕ low ⚫</td>
<td>Proportion of information from studies with high risk of bias is sufficient to affect interpretation of results. In addition, these results have low precision and unexplained heterogeneity. However, they have directionality. Stud-</td>
</tr>
<tr>
<td>Clinical pregnancy</td>
<td>Medium-risk population</td>
<td>RR 1.38 (1.00 to 1.92)</td>
<td>717 (8)</td>
<td>⊕⊕⊕⊕ low</td>
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<td>Multiple gestation</td>
<td>Medium-risk population</td>
<td>RR 0.89 (0.39 to 2.03)</td>
<td>250 (2)</td>
<td>⊕⊕⊕ moderate</td>
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<tr>
<td>Spontaneous miscarriage</td>
<td>Medium-risk population</td>
<td>RR 0.84 (0.37 to 1.91)</td>
<td>350 (3)</td>
<td>⊕⊕⊕ moderate</td>
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</table>

Information from studies with low or unclear risk of bias. These studies have very low precision but have directionality and lack unexplained heterogeneity. Studies are insufficient to allow assessment of risk of publication bias.
### VasoDilators for women undergoing fertility treatment (Review)

#### Ectopic pregnancy

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<th>69 per 1000</th>
<th>58 per 1000 (26 to 132)</th>
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<tr>
<td><strong>Medium risk population</strong>&lt;sup&gt;b&lt;/sup&gt;</td>
<td><strong>RR 1.47 [0.24, 8.86]</strong></td>
<td><strong>250</strong> (2)</td>
</tr>
<tr>
<td><strong>Information from studies with low or unclear risk of bias. Studies have low precision but have directionality and lack unexplained heterogeneity. Studies are insufficient to allow assessment of risk of publication bias</strong></td>
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<td>16 per 1000</td>
<td>24 per 1000 (4 to 143)</td>
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</table>

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

<sup>a</sup>The vasoDilators considered in this review are nitric oxide donors (NTG, ISMN and NTG), PTX, sildenafil and 2 vasoDilators associated with other drugs compared with placebo or no treatment. Dose, route of administration, treatment time and frequency varied across treatments.

<sup>b</sup>All trials recruited participants with differing risk: participants with history of implantation failure who underwent ICSI/FIV (<sup>Ohl 2002</sup>); participants who underwent ICSI because of female and male infertility when both were present or for unknown reasons (<sup>Farzi 2005; Mostafa 2003</sup>); infertile women undergoing standardised controlled ovarian hyperstimulation for ICSI-ZIFT (<sup>Aleyasin 2009</sup>); participants with an antecedent of poor endometrial response and frozen embryos (<sup>Firouzabadi 2013</sup>); participants with tubal infertility who had had at least 2 unsuccessful IVF and embryo transfer attempts when transferred embryos were of high quality (<sup>Alieva 2012</sup>); participants undergoing IVF and embryo transfer (<sup>Shaker 1993</sup>) and participants with a thin endometrium undergoing IVF cycles (<sup>Kim 2010</sup>).

<sup>c</sup>The confidence interval does not rule out benefit, harm or no effect from the intervention.

<sup>d</sup>Only 2 studies report adverse effects, which are subjective variables.

<sup>e</sup>The confidence interval does not rule out no effect from the intervention; some studies did not clearly describe methods used.
**BACKGROUND**

**Description of the condition**

Between 0.2% and 4.3% of babies born in developed countries are conceived through assisted reproduction techniques (Bouillon 2013; Sunderam 2012). A total of 237,809 babies were reported to have been born worldwide in 2004 (Sullivan 2013). In the 21 European countries that report the number of assisted reproduction procedures, 399,020 assisted reproduction technique cycles were performed in a population of 373.8 million (1067 cycles per million). In these countries, the clinical pregnancy rates for in vitro fertilization (IVF) per aspiration and per transfer were 28.9% and 32.9%, respectively. Those for intracytoplasmic sperm injection (ICSI) were 28.7% and 32.0% (Ferraretti 2013). Stats are very similar in recent years (Ferraretti 2012; de Mouzon 2012).

According to the World Health Organization, medically assisted reproduction is reproduction brought about through ovulation induction, controlled ovarian stimulation, ovulation triggering, insemination and assisted reproduction techniques (ART) (Zegers-Hochschild 2009). ART refers to “all treatments or procedures that include the in vitro handling of both human oocytes and sperm or of embryos for the purpose of establishing a pregnancy. This includes, but is not limited to, in vitro fertilization and embryo transfer, gamete intrafallopian transfer, zygote intrafallopian transfer, tubal embryo transfer, gamete and embryo cryopreservation, oocyte and embryo donation, and gestational surrogacy” (Zegers-Hochschild 2009). The success of assisted reproduction varies depending on several factors, such as maternal age (Marinakis 2011; Schmidt 2012), maternal weight (Pinborg 2011), the number of embryos transferred (McLernon 2010), the use of gonadotropins (Maheshwari 2011), inadequate endometrial thickness, uterine contractions and others. A thin endometrium (measured at less than 8 mm by ultrasound scan) has a negative impact on the success of assisted reproduction (Check 2011); live births are possible despite thin endometria, but the pregnancy rate among these women is poor (Dix 2010). Investigators have expressed a marked interest in studying the role that the endometrium plays in the success of assisted reproduction (Casper 2011; Senturk 2008).

Uterine contractions influence embryo implantation, possibly through mechanical displacement of the embryo. Decreases in pregnancy rates and implantation rates were found as the frequency of uterine contractions increased. Approaches aimed at inhibiting uterine contractions could improve pregnancy rates for assisted reproduction (Aguilar 2010; Bulletti 2006; Fanchin 2001; Fanchin 2009; Lesny 1998).

Different vasodilating agents have been proposed to thicken the endometrium and to favour uterine relaxation. Agents used in assisted reproduction include sildenafil, glyceryltrinitrate (GTN), nifedipine, nimodipine, pentoxifylline and isosorbide monohydrate. Sildenafil (Viagra) is a phosphodiesterase-5-specific inhibitor that increases the vasodilatory effects of nitric oxide on vascular smooth muscle by preventing the degradation of cyclic guanosine monophosphate (cGMP). Studies report that vaginally administered sildenafil could lead to an improvement in uterine blood flow (Sher 2002; Takasaki 2010). Nitric oxide donors such as isosorbide monohydrate and glyceryltrinitrate are used in assisted reproduction. Glyceryltrinitrate is also used medically as a vasodilator; in 2002 it was discovered that these effects occur because glyceryltrinitrate is converted in the body to nitric oxide by mitochondrial aldehyde dehydrogenase. Glyceryltrinitrate, which is available in the form of tablets, sprays and patches, is used in assisted reproduction in an effort to improve pregnancy rates (Chen 2005). Pentoxifylline plus vitamin E was used in women undergoing assisted reproduction (Acharya 2009; Letur-Konirsch 2003). Reports have described successful conception and pregnancy with nifedipine given in doses of 30 mg/d after secondary infertility (Wilson 1990).

**How the intervention might work**

Endometrial thickness varies with the vascularity of the endometrium and the subendometrium, regardless of the concentration of oestradiol or progesterone (Raine-Fenning 2004). It is well known that some vasodilators, such as vaginal sildenafil citrate, produce selective endometrial vasodilation in women with Asherman’s syndrome (a condition characterised by the presence of adhesions or fibrosis, or both, within the uterine cavity), which results in endometrial thickening (Zinger 2006). Vasodilators also increase radial artery flow, improving the quality of the endometrium in women with a thin endometrium (Takasaki 2010). It has been observed in animal studies that sildenafil plays a role in both implantation and decidualisation (cellular changes in the endometrium in preparation for implantation of the embryo caused by the effects of progesterone) by affecting β(3) integrins (which are cell membrane proteins) and vascular endothelial growth factor (VEGF) expression during the implantation period (Biyiksiz 2011). In addition, we know that markers of endometrial receptivity are reduced in stimulated cycles compared with natural cycles (Chen 2008; Evans 2012; Revel 2012), and that vasodilators have an effect on amelioration of endometrial receptivity when used in combination with an ovarian hyperstimulation protocol (Biyiksiz 2011). A limited number of studies have reported enhanced endometrial development, implantation rates and ongoing pregnancy rates after administration of vasodilators (Sher 2002; Takasaki 2010; Zinger 2006). Glyceryltrinitrate given in very low doses showed a significant inhibitory effect on human
myometrium in vitro (Orth 2011; Wetzka 2001). Pentoxifylline may be beneficial in reducing hydrogen peroxide-induced embryo damage and in improving outcomes of in vitro fertilisation (Zhang 2004). It also appears to improve the pregnancy rate in patients with a thin endometrium when combined with vitamin E (Acharya 2009; Letur-Könirsch 2002; Lédée-Bataille 2002). Nimodipine, which is a vasodilator calcium channel blocker, is currently under study, as it may prevent or delay the luteinising hormone (LH) surge during controlled ovarian stimulation cycles when clomiphene citrate is used in subfertile patients undergoing assisted reproduction by intruterine insemination (Penzias 2012).

Why it is important to do this review
Several randomised controlled trials (RCTs) have studied the efficacy of different treatments (gonadotrophin-releasing hormone (GnRH) agonist, progesterone, aspirin, steroids, human chorionic gonadotrophin (hCG), vitamin E, cytokines, and vasodilators) in endometrial preparation for women undergoing assisted reproduction (Aleyasin 2009; Glujovsky 2010; Kim 2010; Ohl 2002; Shaker 1993). However, evidence is insufficient to allow investigators to endorse a particular protocol for endometrial preparation. The effect of vasodilators on endometrial preparation in fertility treatment has been studied only partially. Their role in implantation, decidualisation and uterine relaxation, among others, has not been evaluated. A previous systematic review assessed different treatments for endometrial preparation in embryo transfer (Glujovsky 2010) but excluded the comparison of vasodilators versus other treatments. Instead, the effectiveness of these treatments remains unproven, which could potentially incrementally increase costs or side effects in assisted reproduction. Studies are needed to identify and assess the efficacy and safety of vasodilators with or without other agents, or compared with placebo or other agents, in women undergoing fertility treatment.

OBJECTIVES
To evaluate the effectiveness and safety of vasodilators in women undergoing fertility treatment.

METHODS

Criteria for considering studies for this review

Types of studies

Only RCTs were eligible for inclusion. Cross-over trials were also excluded given that their design is not valid in this context. Quasi-randomised trials were excluded.

Types of participants
Women undergoing fertility treatment were considered, regardless of the thickness of the endometrium. No restrictions on age or comorbidities were applied.

For the purposes of this review, fertility treatment means medically assisted reproduction, such as ovulation induction; controlled ovarian stimulation; ovulation triggering; assisted reproduction technique procedures; and intruterine, intracervical and intravaginal insemination with the semen of husband, partner or donor (Zegers-Hochschild 2009).

Types of interventions
Vasodilators (nifedipine, nimodipine, pentoxifylline; nitric oxide donors such as GTN and isosorbide mononitrate; and sildenafil, among others) administered via any route, with or without other agents (oestrogen or tocopherol vitamin E) compared with placebo or no treatment or any other active intervention (progesterone, oestrogen or other).

Types of outcome measures

Primary outcomes
1. Live birth or ongoing pregnancy.
2. Vasodilator side effects: hypotension, headache, tachycardia or other effects related to vasodilators, as defined by primary study authors.

Secondary outcomes
3. Clinical pregnancy.
4. Thickened endometrium.
5. Other adverse events: multiple gestation or birth, spontaneous miscarriage, ectopic pregnancy.

Definitions of terms

Live birth: the complete expulsion or extraction of a product of fertilisation from the mother, irrespective of the duration of pregnancy, which after such separation breathes or shows any other evidence of life, such as heartbeat, umbilical cord pulsation or definitive movement of voluntary muscles, irrespective of whether the umbilical cord has been cut or the placenta is attached. A minimum gestational age is not included in this definition.

Ongoing pregnancy: any pregnancy after 12 weeks. This can be combined with live birth.
Clinical pregnancy: a pregnancy diagnosed by ultrasonographic visualisation of one or more gestational sacs or definitive clinical signs of pregnancy. It includes ectopic pregnancies.

Thickened endometrium: an endometrium that measures 8 mm or greater, as determined by ultrasound scan.

Multiple gestation or birth: a pregnancy or delivery with more than one fetus or neonate.

Spontaneous abortion or miscarriage: the spontaneous loss of a clinical pregnancy before 20 completed weeks of gestational age (18 weeks after fertilisation) or, if gestational age is unknown, loss of an embryo or fetus weighing less than 400 g.

Ectopic pregnancy: a pregnancy in which implantation takes place outside the uterine cavity.

Search methods for identification of studies

We searched all published and unpublished RCTs of vasodilators in fertility treatment, without language restriction. Search strategies were designed in consultation with the Menstrual Disorders and Subfertility Group (MDSG) Trials Search Co-ordinator.

Electronic searches

We searched the following electronic databases, trial register and websites: Cochrane Central Register of Controlled Trials (CENTRAL) (Appendix 1), EMBASE (Appendix 2), MEDLINE (Appendix 3), Menstrual Disorders and Subfertility Group (MDSG) Specialised Register of controlled trials (Appendix 4), PsycINFO (Appendix 5) and Cumulative Index to Nursing and Allied Health Literature (CINAHL) (Appendix 6). All databases were date limited from inception to February 25, 2014, except for EMBASE, which was date limited from January 1, 2010 to February 25, 2014, because CENTRAL contains all EMBASE records previous to this date. Other electronic sources of trials were included.


2. The Cochrane Library: http://www.cochrane.org/index.htm
4. OpenSigle for Grey Literature from Europe: http://opensigle.inist.fr/

Searching other resources

The reference lists of articles retrieved by the aforementioned search were reviewed. We contacted experts in the field to obtain additional data. We handsearched conference abstracts of the International Federation of Gynaecology and Obstetrics (FIGO) World Congress from 1985, 1988, 1991, 1994, 1997, 2000, 2003, 2006, 2009 and 2012, and checked the references of relevant identified systematic reviews.

Data collection and analysis

Selection of studies

The pertinent statistical analysis was performed in accordance with the guidelines for statistical analysis developed by The Cochrane Collaboration.

Two review authors (RG and DG or AC) independently examined titles and abstracts retrieved through the search and determined whether studies met the inclusion criteria. For studies with potential or unclear eligibility, the full text of the article was obtained for independent assessment. If needed, study investigators were contacted to clarify study eligibility. Disagreements were resolved by discussion and consensus with a third review author (GU or XB).

The selection process was documented on a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow chart (Figure 1).
Figure 1. Flow of information through different phases of the systematic review.

347 records identified through database searching: CENTRAL, EMBASE, MDSG, MEDLINE, PsycINFO.

284 additional records identified through other sources.

631 registers before remove duplicates.

278 records screened

255 records excluded

10 articles excluded, with reasons:
- 4 non parallel RCTs
- 1 inadequate comparisons
- 4 no include participants of interest
- 1 no include outcome of interest
- 3 ongoing studies.

23 full-text articles assessed for eligibility

10 studies included in qualitative synthesis

8 studies included in quantitative synthesis (meta-analysis)
Data extraction and management
Two review authors (RG and DG or AC) independently extracted data from eligible studies using a data extraction form designed and pilot-tested by the review authors. Disagreements were solved by discussion and consensus with a third review author (GU or XB). Data extracted included study characteristics, methods and outcome data. When a study had multiple publications, the main trial report was used for reference purposes, and additional details were derived from secondary papers. The original study authors were contacted if further information was required. In multiarm studies, data from arms that do not meet eligibility criteria will be excluded.

Assessment of risk of bias in included studies
Two review authors (RG and GU) independently assessed the included studies for risk of bias using the risk of bias assessment tool of The Cochrane Collaboration (Higgins 2011). We assessed allocation (random sequence generation and allocation concealment), blinding of participants and personnel, incomplete outcome data, selective reporting and other biases. Disagreements were resolved by discussion and consensus with a third review author. We fully described all judgements and presented conclusions in the ‘Risk of bias’ table (Figure 2; Figure 3), which was incorporated into the interpretation of review findings by means of sensitivity analyses (see below).

We assessed whether evidence suggested within-trial selective reporting, including failure to report obvious outcomes or insufficient reporting of outcomes. We searched published protocols to compare outcomes versus those of the corresponding published studies. When a study failed to report live birth but did report interim outcomes such as pregnancy, an informal assessment was undertaken to determine whether interim values (e.g. clinical pregnancy) were similar to those reported in studies that also reported live birth.
Figure 2. Risk of bias summary: review authors’ judgements about each risk of bias 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>
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<td>Aleyasin 2009</td>
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</table>
Figure 3. Risk of bias graph: review authors’ judgements about each risk of bias item presented as percentages across all included studies.

<table>
<thead>
<tr>
<th>Risk of bias Category</th>
<th>Percentage Distribution</th>
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<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>75%</td>
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<tr>
<td>Allocation concealment (selection bias)</td>
<td>75%</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>75%</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>75%</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>75%</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>75%</td>
</tr>
<tr>
<td>Other bias</td>
<td>75%</td>
</tr>
</tbody>
</table>

Low risk of bias: **Green**, Unclear risk of bias: **Yellow**, High risk of bias: **Red**

**Measures of treatment effect**

For dichotomous data (e.g. live birth), we calculated risk ratios (RRs) using the numbers of events in the control and intervention groups of each study. We presented 95% confidence intervals (CIs) for all outcomes. When data were not available to calculate RRs, we used the most detailed available numerical data that can be used to complete similar analysis (e.g. test statics, P value). We compared the magnitude and direction of effect reported by studies against the way in which they are presented in the review, while taking account of legitimate differences.

**Unit of analysis issues**

All analyses were carried out per woman randomly assigned. When data did not allow valid analyses (e.g. “per cycle” data), study authors were contacted to request “per woman” data. If available data could not be analysed, we planned to summarise the data briefly in an additional table without meta-analysis. Multiple live births (e.g. twins, triplets) were counted as a single live birth event.

**Dealing with missing data**

Data were analysed on an intention-to-treat basis. Attempts were made to obtain missing data from the original trialists. Because information was not missing for any of the primary outcomes, imputation of individual values was not undertaken. It was not necessary to assume that a live birth did not occur in participants for whom no outcome was reported. For other outcomes, only available data were analysed.

**Assessment of heterogeneity**

It was determined whether clinical and methodological characteristics of included studies were sufficiently similar for meta-analysis to provide a clinically meaningful summary. Statistical heterogeneity was assessed through the $I^2$ statistical measure. An $I^2$ value greater than 50% was considered to show evidence of substantial heterogeneity (Higgins 2003). When we detected substantial heterogeneity, we explored possible explanations in the corresponding analyses. We took statistical heterogeneity into account when interpreting the results.

**Assessment of reporting biases**

If all eligible studies are not retrieved, the review may be biased. The review authors have tried to minimise the potential impact of publication and other reporting biases by ensuring a comprehensive search for eligible studies and by remaining alert to data duplication. If 10 or more studies had been included in an analysis, we would have used 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). Because the
included studies were fewer than 10, a funnel plot to explore the possibility of small-study effects was not presented.

Data synthesis
Because the studies were judged to be sufficiently similar, we combined their data using random-effects models in the following comparisons.
1. Vasodilator alone versus placebo or no treatment stratified by mode of administration (oral, vaginal and other) and by vasodilator type (sildenafil, glyceryltrinitrate (GTN) and other).
   a. Glyceryltrinitrate (GTN)
   b. Isosorbide mononitrate (ISMN)
   c. Sildenafil
2. Vasodilator alone versus alternative active therapy, stratified by alternative (oestrogens, progesterone, other) and by vasodilator type.
3. Vasodilator combined with other agent versus placebo or no treatment, stratified by agent (oestrogens, progesterone, other) and by vasodilator type.
   a. Pentoxifylline (PTX) and vitamin E.
   b. Sildenafil and oestradiol.
4. Vasodilator combined with other agent versus alternative active therapy, stratified by alternative and by vasodilator type.
Some analyses initially proposed as stratified were not conducted because no suitable studies were found.

Subgroup analysis and investigation of heterogeneity
If data had been available, we would have conducted subgroup analyses to determine separate evidence within the following subgroups.
1. Studies in women with thin endometrium (< 8 mm) undergoing fertility treatment.
Subgroup analysis was not undertaken according to type of control/other treatments. However, we have added a post hoc subgroup analysis for the secondary outcome of clinical pregnancy to evaluate studies that used only vasodilators with no co-intervention.

Sensitivity analysis
Sensitivity analyses for the primary outcomes were conducted to determine whether conclusions were robust enough to withstand arbitrary decisions regarding eligibility and analysis of included studies.
These analyses included considerations of whether the review conclusions would have differed if:
1. a fixed-effect model had been adopted.

Results of the search
The search retrieved 631 articles. A total of 23 studies were potentially eligible and were retrieved in full text. Ten studies (Aleyasin 2009; Alieva 2012; Das 2009; El-Berry 2010; Farzi 2005; Firouzabadi 2013; Kim 2010; Mostafa 2003; Ohl 2002; Shaker 1993) met the inclusion criteria of this review. Ten studies (Alborzi 2007; Balasch 1997; Check 2004; Creus 2008; Kamencic 2008; Malinova 2013; Raine-Fenning 2009; Rosen 1987; Sher 2000; Shin 2002) were excluded, and three (Ben-Meir 2014; Casper 2013; Penzias 2012) are ongoing. For further information, see the following tables: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.
See Figure 1 (PRISMA study screening and selection flow chart) for details of this process.

Included studies
See Characteristics of included studies.

Study design and setting
Ten randomised controlled trials (RCTs) with a parallel design (Aleyasin 2009; Alieva 2012; Das 2009; El-Berry 2010; Farzi 2005; Firouzabadi 2013; Kim 2010; Mostafa 2003; Ohl 2002; Shaker 1993) were included in this review. Publication dates of the included studies ranged from 1993 to 2013.

Participants
Ten studies with a total of 797 women were included in this review. The studies included 396 women in the intervention groups and 401 in the control groups. Mean participant age was 31.39 years (± 4.43). Four trials included women with a “poor prognosis” (i.e. infertile women with a thin endometrium or an antecedent...
of poor endometrial response or with a history of two or more previous implantation failures) (Das 2009; Firouzabadi 2013; Kim 2010; Ohl 2002). Six trials included women with a “good prognosis” (i.e. women without a previous history of failure of zygote intrafallopian transfer (ZIFT) or in vitro fertilisation (IVF)) (Aleyasin 2009; Alieva 2012; El-Berry 2010; Farzi 2005; Mostafa 2003; Shaker 1993). Eight of the 10 studies were performed in women undergoing assisted reproduction techniques (Aleyasin 2009; Alieva 2012; Farzi 2005; Firouzabadi 2013; Kim 2010; Mostafa 2003; Ohl 2002; Shaker 1993). One was performed in women undergoing artificial insemination (Das 2009) and one involved ovulation induction (El-Berry 2010).

**Interventions**

The vasodilators used in the studies include pentoxifylline 400 mg/BD oral dose + tocopherol vitamin E 400 mg/BD oral dose (Aleyasin 2009); nitric oxide donors (isosorbide mononitrate 20 mg vaginal) (El-Berry 2010) and glyceryl trinitrate 0.4 mg oral dose (Farzi 2005); sildenafil 50 mg oral dose (Firouzabadi 2013); sildenafil 25 mg vaginally four times a day (Das 2009); sildenafil 25 mg/d vaginally + oestradiol valerate 4 mg/d oral (Kim 2010); glyceryl trinitrate patch 5 mg (Ohl 2002); glyceryl trinitrate 400 µg/spray (Shaker 1993); sildenafil citrate (Alieva 2012) and glyceryl trinitrate skin patches 5 mg daily (Mostafa 2003).

1. Eight of 10 studies compared vasodilator alone versus placebo or no treatment (Alieva 2012; El-Berry 2010; Das 2009; Farzi 2005; Mostafa 2003; Ohl 2002; Shaker 1993; Firouzabadi 2013).
2. Two of 10 studies compared vasodilator plus other agent versus placebo or no treatment (Aleyasin 2009; Kim 2010).
3. No study used an active comparator.

**Outcomes**

2. Two of 10 studies reported side effects (Ohl 2002; Shaker 1993).
3. All 10 studies reported clinical pregnancy (Aleyasin 2009; Alieva 2012; Das 2009; El-Berry 2010; Farzi 2005; Firouzabadi 2013; Kim 2010; Mostafa 2003; Ohl 2002; Shaker 1993). However, two studies reported biochemical pregnancy (Das 2009; El-Berry 2010), and the method used to diagnose pregnancy was not reported by two studies (Alieva 2012; Shaker 1993).
4. Four of 10 studies reported other adverse events (Aleyasin 2009; Alieva 2012; Farzi 2005; Ohl 2002). In one study, the miscarriage rate in the control group looks unusually high (Alieva 2012).

No study provided data on the number of participants with thickened endometrium. Therefore, it was not possible to analyse this outcome. Only two studies (Das 2009; Kim 2010) mentioned that all women had a thin endometrium before treatment.

**Excluded studies**

Ten studies were excluded from the review for the following reasons.
1. Four of 10 were not parallel RCTs (Check 2004; Raine-Fenning 2009; Sher 2000; Shin 2002).
2. Four of 10 did not include participants of interest for this review (Alborzi 2007; Balasch 1997; Creus 2008; Kamencic 2008).
3. One of 10 did not include comparisons of interest for this review (Rosen 1987).
4. One of 10 did not include outcomes of interest for this review (Malinova 2013).

In addition, three studies are ongoing (Ben-Meir 2014; Casper 2013; Penzias 2012).

**Risk of bias in included studies**

The judgements of review authors regarding each risk of bias item for each included study are shown and summarised in Figure 2 and Figure 3.

**Allocation**

**Random sequence generation**

Two studies (Aleyasin 2009; Ohl 2002) had low risk of selection bias related to sequence generation. The other eight studies (Alieva 2012; Das 2009; El-Berry 2010; Farzi 2005; Firouzabadi 2013; Kim 2010; Mostafa 2003; Shaker 1993) did not describe the method of randomisation, and were ranked as at unclear risk of bias.

**Allocation concealment**

Two studies (Aleyasin 2009; Ohl 2002) had low risk of bias related to allocation concealment. The other eight studies (Alieva 2012; Das 2009; El-Berry 2010; Farzi 2005; Firouzabadi 2013; Kim 2010; Mostafa 2003; Shaker 1993) did not describe the method used to conceal the sequence and were ranked as having unclear risk of bias.

**Blinding**

Four of 10 studies had low risk of detection bias (Aleyasin 2009; Farzi 2005; Ohl 2002; Shaker 1993). Three of these (Farzi 2005; Ohl 2002; Shaker 1993) were double-blind and used placebo as a control, and one (Aleyasin 2009) was single-blind (surgeons who conducted the operations were blinded). Two studies did not provide a description of blinding (Alieva 2012; Mostafa 2003). Four of 10 studies (Das 2009; El-Berry 2010; Firouzabadi 2013; Kim 2010) did not mention blinding and were judged as having unclear risk of detection bias. Blinding was not considered as likely to influence the outcome of live birth or clinical pregnancy. The same was not true for adverse events, for which lack of blinding could potentially affect findings.
Incomplete outcome data

Seven of 10 studies (Aleyasin 2009; Das 2009; Farzi 2005; Firouzabadi 2013; Kim 2010; Ohl 2002; Shaker 1993) analysed all or most (> 95%) of the women randomly assigned and had low risk of attrition bias. Only one study (El-Berry 2010) used the number of cycles instead of the number of participants in analysis, and two studies did not describe attrition (Alieva 2012; Mostafa 2003). These studies had an unclear risk of attrition bias.

Selective reporting

Five of 10 studies (Aleyasin 2009; Farzi 2005; Firouzabadi 2013; Ohl 2002; Shaker 1993) reported outcomes that were clearly pre-specified in the methods section and were classified as having low risk of selective reporting bias. Primary outcomes were reported in four of these studies (Aleyasin 2009; Farzi 2005; Ohl 2002; Shaker 1993): Three studies reported live birth (Aleyasin 2009; Farzi 2005; Ohl 2002), and two studies reported adverse effects (Ohl 2002; Shaker 1993). However, the protocol was available for only one study (Firouzabadi 2013).

Other potential sources of bias

Eight of 10 studies (Aleyasin 2009; Das 2009; El-Berry 2010; Farzi 2005; Firouzabadi 2013; Kim 2010; Ohl 2002; Shaker 1993) reported baseline balance between groups in terms of age and duration of infertility. In addition, four studies reported baseline comparability regarding type of infertility, cause of infertility and body mass index. These studies were classified as having low risk of bias. No other potential sources of bias were identified. However, two studies did not report baseline features and were judged to have unclear risk of detection bias (Alieva 2012; Mostafa 2003).

Effects of interventions

See: Summary of findings for the main comparison Vasodilator compared with placebo/no treatment for women undergoing fertility treatment

Primary outcomes

1 Vasodilator (with or without an additional intervention) versus placebo or no treatment

1.1 Live birth or ongoing pregnancy

(Analysis 1.1)

Three studies reported this outcome. All reported live birth.

1. Glyceryltrinitrate (GTN) was compared with placebo (Farzi 2005; Ohl 2002).

2. Pentoxifylline + tocopherol vitamin E was compared with no treatment (Aleyasin 2009).

No evidence indicated that treatment with a vasodilator (alone or with another agent) influenced live birth rate compared with placebo or no treatment (RR 1.18, 95% CI 0.82 to 1.69, P value 0.37, three RCTs, 350 women, I^2 = 0%, moderate-quality evidence) (Analysis 1.1; Figure 4). This suggests that among women undergoing fertility treatment who have a 24% chance of live birth without use of vasodilators, between 19% and 40% will achieve live birth with use of vasodilators. No evidence showed an effect in the NTG subgroup (RR 1.08, 95% CI 0.69 to 1.71, P value 0.73, two RCTs, 238 women, I^2 = 0%, moderate-quality evidence) nor in the PTX + vitamin E subgroup (RR 1.36, 95% CI 0.76 to 2.43, P value 0.30, one RCT, 112 women, I^2 = 0%, moderate-quality evidence).
Sensitivity analyses using a fixed-effect model (RR 1.18, 95% CI 0.83 to 1.69, P value 0.35, three RCTs, 350 women, I² = 0%) or an odds ratio effect measure (OR 1.25, 95% CI 0.77 to 2.03, P value 0.36, three RCTs, 350 women, I² = 0%) did not affect the statistical significance of the main analysis for this outcome.

1.2 Vasodilator side effects
(Analysis 1.2)
Two studies reported this outcome. The most commonly reported adverse events (AEs) in the vasodilator group were nervousness, insomnia, constipation and a feeling of weakness.

Glyceryl trinitrate (GTN) was compared with placebo (Ohl 2002; Shaker 1993). No evidence suggested that treatment with vasodilators increased the rate of side effects compared with placebo or no treatment (RR 1.63, 95% CI 0.33 to 7.93, P value 0.55, two RCTs, 258 women, I² = 32%, low-quality evidence) (Analysis 1.2; Figure 5).
1.3 Clinical pregnancy

(Analysis 1.3) (Figure 6)

**Secondary outcomes**

**1.3 Clinical pregnancy**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Vasodilator</th>
<th>Placebo or no treatment</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
<th>Heterogeneity: Test for overall effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.3 Glyceryl trinitrate (GTN) vs placebo or no treatment</td>
<td>Farzi 2005 (1)</td>
<td>16</td>
<td>50</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>Mostafa 2002 (2)</td>
<td>30</td>
<td>9</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>Ch 2002 (3)</td>
<td>20</td>
<td>70</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>Shaker 1993 (4)</td>
<td>18</td>
<td>60</td>
<td>19</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>210</td>
<td>208</td>
<td>61.4%</td>
<td>1.11 (0.73, 1.68)</td>
</tr>
<tr>
<td>Total events</td>
<td>66</td>
<td>61</td>
<td>6.6%</td>
<td>1.59 (0.44, 5.74)</td>
</tr>
</tbody>
</table>

**1.3.2 Sildenafil vs no treatment**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Vasodilator</th>
<th>Placebo or no treatment</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
<th>Heterogeneity: Test for overall effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.3.3 Sildenafil + oestrogen vs no treatment</td>
<td>Aleyasin 2009 (7)</td>
<td>10</td>
<td>21</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Subtotal (95% CI)</td>
<td>21</td>
<td>27</td>
<td>7.3%</td>
</tr>
<tr>
<td>Total events</td>
<td>22</td>
<td>10</td>
<td>5.7%</td>
<td>3.56 (1.00, 1.92)</td>
</tr>
</tbody>
</table>

**1.3.4 P TX + vitamin E vs no treatment**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Vasodilator</th>
<th>Placebo or no treatment</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
<th>Heterogeneity: Test for overall effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (95% CI)</td>
<td>356</td>
<td>361</td>
<td>100.0%</td>
<td>1.38 (1.00, 1.92)</td>
</tr>
<tr>
<td>Total events</td>
<td>356</td>
<td>361</td>
<td>100.0%</td>
<td>1.38 (1.00, 1.92)</td>
</tr>
</tbody>
</table>

Ten studies reported clinical pregnancy.

However, two studies reported biochemical pregnancy (El-Berry 2010; Das 2009). The method used to diagnose pregnancy was not reported by two studies (Aleyasin 2012; Shaker 1993). We included them in the analyses with this limitation stated in footnotes. We analysed eight studies (Aleyasin 2009; Alieva 2012; Farzi 2005; Firouzabadi 2013; Kim 2010; Mostafa 2003; Ohl 2002; Shaker 1993).

1. Glyceryl trinitrate (GTN) was compared with placebo (Farzi 2005; Mostafa 2003; Ohl 2002; Shaker 1993).

2. Sildenafil was compared with no treatment (Alieva 2012; Firouzabadi 2013).

3. Sildenafil plus oestrogen was compared with no treatment (Kim 2010).

4. Pentoxifylline + tocopherol vitamin E was compared with no treatment (Aleyasin 2009).

Overall, treatment with vasodilators was associated with an increased clinical pregnancy rate compared with placebo or no treatment (RR 1.38, 95% CI 1.00 to 1.92, eight RCTs, 717 women, I² = 0%, low-quality evidence). However, if studies of vasodilators associated with other medications (vitamin E, oestrogen) were excluded, treatment with vasodilators alone was not associated with an increased clinical pregnancy rate (RR 1.17, 95% CI 0.80 to
1.4 Other adverse events

(Analysis 1.4)

1.4.1 Multiple gestation or birth
Two studies reported this outcome.

1. Glyceryl trinitrate (GTN) was compared with placebo (Ohl 2002).

2. Pentoxifylline + tocopherol vitamin E was compared with no treatment (Aleyasin 2009).

No evidence showed that treatment with vasodilators influenced multiple gestation rate or birth rate compared with placebo or no treatment (RR 0.89, 95% CI 0.39 to 2.03, P value 0.79, two RCTs, 250 women, I² = 0%, moderate-quality evidence).

1.4.2 Spontaneous miscarriage
Four studies reported this outcome.

1. Glyceryl trinitrate (GTN) was compared with placebo (Farzi 2005; Ohl 2002).

2. Pentoxifylline + tocopherol vitamin E was compared with no treatment (Aleyasin 2009).

3. Sildenafil (NTG) was compared with no treatment (Alieva 2012).

In one study, the miscarriage rate in the control group looked unusually high (Alieva 2012). So, we analysed only three studies (Aleyasin 2009; Farzi 2005; Ohl 2002). No evidence suggested that treatment with vasodilators influenced spontaneous abortion/miscarriage rate compared with placebo or no treatment (RR 0.84, 95% CI 0.37 to 1.91, P value 0.99, three RCTs, 350 women, I² = 0%, moderate-quality evidence).

1.4.3 Ectopic pregnancy
Two studies reported this outcome.

1. Glyceryl trinitrate (GTN) was compared with placebo (Ohl 2002).

2. Pentoxifylline + tocopherol vitamin E was compared with no treatment (Aleyasin 2009).

No evidence indicated that treatment with vasodilators influenced the ectopic pregnancy rate compared with placebo or no treatment (RR 1.47, 95% CI 0.24 to 8.86, P value 0.67, two RCTs, 250 women, I² = 0%, moderate-quality evidence).

Subgroup analyses
As the included studies did not provide data on the number of women with endometrium measured as greater or less than 8 mm, planned subgroup analyses could not be performed. Only two studies (Das 2009; Kim 2010) mentioned that all women had a thin endometrium before interventions were provided. In these studies, treatment with a vasodilator with an influence on clinical pregnancy rate was compared with placebo or no treatment (RR 1.17, 95% CI 0.80 to 1.72, P value 0.41, six RCTs, 557 women, I² = 0%, low-quality evidence).

D I S C U S S I O N

Summary of main results
The results of this systematic review suggest that evidence is insufficient to show that vasodilators influence the live birth rate in women undergoing fertility treatment (Aleyasin 2009; Farzi 2005; Ohl 2002).

Evidence was insufficient to permit any conclusions regarding adverse effects, as only two studies reported this outcome (Ohl 2002; Shaker 1993).

Low-quality evidence showed that vasodilators alone or in combination with other treatments (vitamin E, oestradiol) increased clinical pregnancy rate compared with placebo or no treatment (Aleyasin 2009; Farzi 2005; Firouzabadi 2013; Kim 2010; Mostafa 2003; Ohl 2002). Evidence was insufficient to show whether any particular vasodilator, alone or administered in combination with other active medications, was superior. Adequately powered studies are needed to evaluate each treatment more accurately.

Last, no evidence was found to suggest differences between groups for other adverse effects such as multiple gestation or birth (Aleyasin 2009; Ohl 2002), spontaneous abortion/miscarriage (Aleyasin 2009; Farzi 2005; Ohl 2002) and ectopic pregnancy (Aleyasin 2009; Ohl 2002); few relevant data were available.

No evidence showed statistical heterogeneity in this review, suggesting that factors that may have differed between studies had little effect on the overall findings. However, confidence intervals overlapped in individual trials and easily changed in the sensitivity analysis. Therefore, the results of this review should be interpreted with caution.

Overall completeness and applicability of evidence
All studies reported pregnancy as an outcome (Aleyasin 2009; Alieva 2012; Das 2009; El-Berry 2010; Farzi 2005; Firouzabadi 2013; Kim 2010; Mostafa 2003; Ohl 2002; Shaker 1993). However, for women and for clinicians, live birth rate and side effects are the most important outcomes of fertility treatment. As these outcomes were reported in only three studies (Aleyasin 2009; Farzi 2005; Ohl 2002) and in two studies (Ohl 2002; Shaker 1993),
respectively, this review might not address the main concerns surrounding fertility treatment. This, in turn, serves as evidence that more studies should assess these important outcomes.

Age restrictions for women in the inclusion and exclusion criteria of studies were similar across eight included studies. However, some trials included women with a “bad prognosis” (i.e. infertile women with a thin endometrium or with a history of two or more previous implantation failures), while other trials included women with a “good prognosis” (i.e. women without a previous history of failure of ZIFT or IVF). Even though no evidence of statistical heterogeneity among trials was found, the effects of clinical heterogeneity on results could not be ruled out.

Quality of the evidence

Evidence for live birth, clinical pregnancy, multiple gestation, miscarriage and ectopic pregnancy was rated as moderate quality, with the main limitation of low precision. Evidence for vasodilator side effects was of low quality, as it showed low precision and unexplained heterogeneity. Risk of publication bias could not be assessed because of the small number of identified studies (see Summary of findings for the main comparison).

Allocation (selection bias) was unclear in six studies. Among the 10 studies included, one trial used computer-generated randomisation (Aleyasin 2009), in another allocation was randomly performed by four blocks and stratified by centre (Ohl 2002) and one used randomised tables (Firouzabadi 2013). Concealment of allocation was adequate and was explicitly described in two trials (Aleyasin 2009; Ohl 2002).

Three studies (Farzi 2005; Ohl 2002; Shaker 1993) were placebo-controlled but did not specify the use of blinding. Other studies were not blinded or failed to mention blinding. However, as most assessed outcomes were not subjective (live birth, clinical pregnancy, multiple gestation, ectopic pregnancy, miscarriage), lack of blinding did not imply an increase in risk of bias.

Seven studies (Aleyasin 2009; Das 2009; Farzi 2005; Firouzabadi 2013; Kim 2010; Ohl 2002; Shaker 1993) had low risk of attrition bias. These studies were analysed with intention to treat. Three studies (Alieva 2012; El-Berry 2010; Mostafa 2003) had unclear risk of attrition bias. One study (El-Berry 2010) used cycle numbers in the analysis.

Risk of selective reporting was unclear. Live birth rate was reported in a minority of cases, and only two studies reported adverse events as an outcome (El-Berry 2010; Kim 2010). However, four studies reported clinical pregnancy rates (Aleyasin 2009; Farzi 2005; Kim 2010; Ohl 2002), two studies reported implantation rates and six studies reported pregnancy.

Baseline equality between groups was acceptable in eight studies. Two studies (Alieva 2012; Mostafa 2003) had an unclear risk of bias. No other potential sources of bias were identified. Therefore, clinically significant differences in treatment effects might be hidden. Additional RCTs with adequate power are required if investigators are to determine whether any of the vasodilators assessed in our review do enhance the live birth rate among women undergoing fertility treatment.

Potential biases in the review process

The process of identifying all potentially eligible studies was thorough and meticulous, even yielding three studies published only in abstract form. The authors of these works were contacted, but only one of them replied (Das 2009). Regarding all other procedures related to this review, we used the updated version of the Cochrane Handbook for Systematic Reviews of Interventions, and, as far as possible, protocol methodology was adhered to, so potential biases could be limited. Also, it was not possible to evaluate potential biases in all studies for lack of data. These studies were considered to have unclear risk of bias. We contacted authors of these studies, but only two of them replied (Farzi 2005; Kim 2010).

Agreements and disagreements with other studies or reviews

Other reviews in women undergoing assisted fertility treatment with vasodilators have not been identified. However, other relevant observational studies were identified (Sher 2000; Sher 2002; Takasaki 2010). One of the most important was a cohort study of the effect of vaginal sildenafil on the outcome of in vitro fertilisation after multiple IVF failures attributed to poor endometrial development found high ongoing pregnancy rates (Sher 2002).

Authors’ Conclusions

Implications for practice

Evidence was insufficient to show that vasodilators increased the live birth rate in women undergoing fertility treatment. However, low-quality evidence suggests that vasodilators increase clinical pregnancy rates in comparison with placebo or no treatment. Evidence is insufficient to show whether any particular vasodilator, administered alone or in combination with other active medications, is superior. Evidence is insufficient to permit any conclusions regarding adverse effects.

Implications for research

Although this review suggests that vasodilators increase clinical pregnancy rates compared with placebo or no treatment, further studies on vasodilators should report live birth rates, side effects and other important outcomes to enable consumers and healthcare providers to make well-informed decisions on the best treatment options. Based on the results of this review, the following recommendations are made.
1. RCTs with larger sample sizes are needed to evaluate whether any vasodilator is associated with an increase in live birth rate or pregnancy rate.

2. Future research should help to determine the optimal route of administration and dosage of different vasodilators.

3. Future research probably should focus mainly on sildenafil and should include assessment of the optimal route of administration and dosage.

4. Future research should evaluate relevant outcomes such as live birth, taking baby home and side effects.

5. Future research should investigate whether women with a thin endometrium may benefit from this medication.

6. Improved description of methods and adherence to CONSORT (Consolidated Standards of Reporting Trials) recommendations are needed for all RCTs.

ACKNOWLEDGEMENTS

To MDSG, especially Marian Showell, who devised the search strategy and contributed to identification of some studies. To Daniel Comande, librarian, who contributed to the search identifying some studies. To Marta Roque, who advised and supervised the methods and the analysis. To Hector Pardo for help in editing the final version of the manuscript.

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RG is a PhD candidate at the Paediatrics, Obstetrics and Gynaecology, Preventive Medicine and Public Health Department at the Universitat Autònoma de Barcelona, Spain.

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Das 2009 [published data only]

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Kim 2010 [published data only]

Mostafa 2003 [published and unpublished data]

Ohl 2002 [published data only]


Shaker 1993 [published data only]

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Acharya 2009

Aguilar 2010

Biyikziz 2011

Bouillon 2013
Bouillon C, Fauque P. [Follow-up of children conceived by assisted reproductive technologies] [Devenir des enfants issus des techniques d’assistance medicale a la procreation]. Archives de Pediatrie (Organe Officiel de la Societe Francaise de Pediatrie) 2013; 20(5):575–9. [PUBMED: 23545282]

Bulletti 2006
Vasodilators for women undergoing fertility treatment (Review)

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Casper 2011
Casper RF. It’s time to pay attention to the endometrium. *Fertility and Sterility* 2011;96(3):519–21. [PUBMED: 21880272]

Check 2011

Chen 2005

Chen 2008

de Mouzon 2012

Dix 2010

Evans 2012

Fanchin 2001

Fanchin 2009

Ferraretti 2012

Ferraretti 2013

Glu lovsky 2010

Higgins 2003

Higgins 2011

Lesny 1998

Letur-Konirsch 2003
Letur-Konirsch H, Delanian S. Successful pregnancies after combined pentoxifylline-tocopherol treatment in women with premature ovarian failure who are resistant to hormone replacement therapy. *Fertility and Sterility* 2003;89:439–41.

Letur-Könirsch 2002

Lédée-Bataille 2002

Maheshwari 2011

Marinakis 2011
Marinakis G, Nikolaou D. What is the role of assisted reproduction technology in the management of age-related

McLernon 2010

Orth 2011

Pinborg 2011

Raine-Fenning 2004

Revel 2012

Schmidt 2012

Senturk 2008

Sher 2002

Sullivan 2013

Sunderam 2012

Takasaki 2010

Wetzka 2001

Wilson 1990

Zegers-Hochschild 2009

Zhang 2004

Zinger 2006

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

### Aleyasin 2009

<table>
<thead>
<tr>
<th>Methods</th>
<th>Randomised clinical trial. Not blinded</th>
</tr>
</thead>
</table>
| Participants   | 112 infertile women (56 intervention, 56 control) planned for ZIFT (zygote intrafallopian transfer)  
They were younger than 39 years of age without a previous history of ZIFT or IVF failure  
Exclusion criteria were hypothalamic amenorrhoea, drug reactions or complications, endometriosis and fibroids |
| Interventions  | **Intervention:** pentoxifylline 400 mg/BD + tocopherol vitamin E 400 mg/BD 2 cycles before starting ZIFT cycle until the $\beta$-hCG became positive or the cycle was cancelled  
**Control:** Participants did not receive the aforementioned drugs |
| Outcomes       | **Primary outcome:** clinical pregnancy  
**Other outcomes:** term delivery (equivalent "live birth"), multiple gestation or birth, spontaneous abortion/miscarriage, ectopic pregnancy and preterm labor |
| Notes          | **Both groups** received gonadotrophin-releasing hormone (GnRH) agonist 500 mg SC started at day 22 of previous cycle + hMG (human menopausal gonadotrophins) 150-225 IU/d commenced on day 3 of the next cycle (dose determined for each participant on the basis of age and response to previous treatments) + hCG (human chorionic gonadotrophin) 10,000 IU IM (when < 2 follicles with diameter 17 mm observed) + ICSI and ZIFT (laparoscopic). Luteal phase support was started the day of ovum pick-up via administration of a progesterone suppository of 800 mg/d, and 25 mg progesterone in oil a week later (until fetal heart rate detection) |

### 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>Study authors described the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups: Computer-generated random number table was used for randomisation</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>Study authors described the method used to conceal the allocation sequence in sufficient detail to reveal whether intervention allocations could have been determined in advance of, or during, enrolment: Group assignments were placed in sealed, opaque, sequentially numbered envelopes</td>
</tr>
</tbody>
</table>
**Aleyasin 2009**  
(Continued)

<table>
<thead>
<tr>
<th>Blinding of participants and personnel (performance bias)</th>
<th>Low risk</th>
<th>The intervention was not blinded, but surgeons who performed the operations were blinded to participant groups. However, this does not seem to have affected study results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Low risk</td>
<td>No blinding of outcome assessment was described, but the review authors judge that outcome measurement is not likely to be influenced by lack of blinding</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Low risk</td>
<td>No participant dropout was reported (all participants were followed up)</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>Study protocol not available, but it is clear that published reports include all expected outcomes, including those that were prespecified</td>
</tr>
<tr>
<td>Other bias</td>
<td>Low risk</td>
<td>Groups were comparable for the variables described (age, duration of infertility, type of infertility, cause of infertility, endometrial thickness, retrieved oocytes, metaphase II oocytes)</td>
</tr>
</tbody>
</table>

**Alieva 2012**

<table>
<thead>
<tr>
<th>Methods</th>
<th>Randomised controlled trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>91 participants with tubal infertility, who had undergone at least 2 unsuccessful IVF and embryo transfer attempts when transferred embryos were of high quality and disturbances in uterine haemodynamics were present</td>
</tr>
</tbody>
</table>

| Interventions | **Intervention**  
**Group I:** 32 women for whom impact on rates of blood flow and endometrial condition was assessed using intense low-frequency magnetic therapy in the cycle previous to IVF  
**Group II:** 29 women treated by sildenafil citrate in the IVF cycle  
**Control:** Group III (control): 30 women not given additional treatment |
|---------------|-------------------------------------------------------------|
| Outcomes      | **Primary:** evidence of increasing end-diastolic flow velocity, decrease in vascular resistance and increased blood flow to uterine vessels  
**Secondary:** thickness of the endometrium after intervention and pregnancy rate (we do not know the method used to establish pregnancy)  
**Other:** spontaneous abortion/miscarriage |
| Notes         | Published currently only as an abstract |

**Risk of bias**

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
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</tr>
</thead>
</table>
**Alieva 2012**  (Continued)

<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>Methods were not adequately described</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Methods were not adequately described</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>Unclear risk</td>
<td>Methods were not adequately described</td>
</tr>
<tr>
<td>All outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Unclear risk</td>
<td>Methods were not adequately described</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>Methods were not adequately described</td>
</tr>
<tr>
<td>All outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>Methods were not adequately described</td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>Methods were not adequately described</td>
</tr>
</tbody>
</table>

**Das 2009**

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods</td>
<td>Randomised controlled trial</td>
<td></td>
</tr>
<tr>
<td>Participants</td>
<td>50 infertile women (25 intervention, 25 control) with a thin endometrium (&lt; 9 mm) undergoing Intrauterine Insemination on 2 occasions</td>
<td></td>
</tr>
</tbody>
</table>
| Interventions | **Intervention**: sildenafil 25 mg vaginally 4 times a day from day 5 of cycle until day of hCG administration  
**Control**: no sildenafil |                |
| Outcomes | **Primary outcome**: pregnancy or conception rates (positive urine pregnancy test)  
**Other outcome**: endometrial thickness and uterine artery PI on day of hCG administration |                |
| Notes | **Both groups**: Ovulation induction was achieved with clomiphene citrate 100 mg from days 2 through 6. Follicular monitoring was conducted until the follicle reached 18-20 mm, at which time 5000 IU hCG injection was given and IUI was done on 2 occasions: after 24 hours and after 48 hours. Before IUI, couples were advised abstinence for 3-4 days. 200 mg micronised progesterone was given orally as luteal phase support twice daily for 14 days after 2nd IUI |                |

**Risk of bias**
### Das 2009

(Continued)

<table>
<thead>
<tr>
<th>Risk of bias</th>
<th>Unclear risk</th>
<th>Low risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Methods were not adequately described (alternate participants were taken as case and control. Cases received sildenafil 25 mg vaginal suppositories; controls received no treatment)</td>
<td></td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Methods were not adequately described (all cases were given tab sildenafil 25 mg vaginally 4 times a day from day 5 of cycle until day of hCG administration)</td>
<td></td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
<td>Study did not use placebo</td>
<td></td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) All outcomes</td>
<td>No blinding of outcome assessment was described, but review authors judged that measurement of pregnancy outcome is not likely to be influenced by lack of blinding</td>
<td></td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>Investigators evaluated all randomly assigned women</td>
<td></td>
</tr>
<tr>
<td>Selective reporting (reporting bias) Unclear risk</td>
<td>Study protocol not available, and published reports do not include all expected outcomes-only those that were prespecified</td>
<td></td>
</tr>
<tr>
<td>Other bias Low risk</td>
<td>No statistically significant differences in age or BMI were noted between the 2 groups</td>
<td></td>
</tr>
</tbody>
</table>

### El-Berry 2010

<table>
<thead>
<tr>
<th>Methods</th>
<th>Randomised controlled study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants 30 polycystic ovary infertile women diagnosed according to American Society of Reproductive Medicine and European Society of Human Reproductive and Embryology (15 women in intervention group, 15 women in control group) underwent ovulation induction</td>
<td></td>
</tr>
</tbody>
</table>
| Interventions | **Intervention**: nitric oxide donors (isosorbide mononitrate (ISMN)) 20 mg vaginally until diagnosis of ovulation and pregnancy  
**Control**: did not receive this drug | |
| Outcomes | **Primary outcome**: ovulation and pregnancy rates (diagnosed by serum β-hCG)  
**Other outcome**: number of mature follicles, cervical mucus score and endometrial thickness | |
| Notes | **Both groups** received 100 mg clomiphene citrate on fifth, sixth, seventh, eighth and ninth CD. Treatment in both groups continued for 3 cycles | |

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Vasodilators for women undergoing fertility treatment (Review)

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## Authors' judgement

<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>Insufficient information about the sequence generation process to allow judgement</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Method of concealment not described to allow a definitive judgement</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>Unclear risk</td>
<td>Methods used in this study not adequately described</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Low risk</td>
<td>No blinding of outcome assessment, but review authors judge that measurement of pregnancy outcome is not likely to be influenced by lack of blinding</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Unclear risk</td>
<td>No losses of participants, but unclear how many cycles each participant received and reasons for interrupting treatment. 37 cycles in the intervention group and 40 in the control group, but we used number of women (15 in each group)</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>Study protocol is not available, and published reports do not include all expected outcomes-only those that were prespecified</td>
</tr>
<tr>
<td>Other bias</td>
<td>Low risk</td>
<td>Groups were comparable for variables described (age, body mass index, FSH, LH)</td>
</tr>
</tbody>
</table>

## Farzi 2005

### Methods

Prospective randomised double-blinded placebo-controlled clinical trial

### Participants

100 participants in fresh ICSI-ET (50 participants in the intervention group, 50 in the control group)

Participants underwent ICSI regardless of male or female infertility when both were present or when causes were unknown

### Interventions

**Intervention:** glyceryltrinitrate (GTN) 0.4 mg oral dose 15 minutes before fresh ET

**Control:** placebo

### Outcomes

**Primary outcome:** implantation rate and clinical pregnancy rate

**Other outcome:** taking baby home (equivalent “live birth”), spontaneous abortion/miscarriage and biochemical pregnancy

### Notes

Both groups were initially stimulated with a long protocol. Then, on the third day of of the next menstrual cycle, hMG 150-225 IU was injected and was adjusted with follicular...
**Farzi 2005**  (Continued)

Development monitoring by vaginal ultrasound. In addition, 10,000 IU hCG was given IM when at least 3 follicular diameters of 18 mm 38 hours later led to ovarian puncture.

**Additional information from study authors:** 100 participants entered and completed this study; 1 cycle was performed for each participant.

<table>
<thead>
<tr>
<th>Risk of 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>Information about the sequence generation process was insufficient to allow judgement</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Method of concealment not described</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
<td>Low risk</td>
<td>Double-blinded with use of placebo</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) All outcomes</td>
<td>Low risk</td>
<td>Not described, but main outcome not subjective. Outcome measurement not likely to be influenced by lack of blinding</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>Low risk</td>
<td>Study described 100 randomly assigned cycles</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>Study protocol is not available, but it is clear that published reports include all expected outcomes, including those that were pre-specified</td>
</tr>
</tbody>
</table>

**Firouzabadi 2013**

**Methods**

Randomised clinical controlled trial, not blinded

**Participants**

Total of 80 participants with an antecedent of poor endometrial response and frozen embryos were included in this study. Inclusion criteria required participants to be younger than 40 years of age and to have high-quality frozen embryos. Exclusion criteria included...
Firouzabadi 2013  (Continued)

<table>
<thead>
<tr>
<th>History of endocrine disease; history of hysteroscopic surgery; cardiovascular, renal and liver disease; hypotension (blood pressure &lt; 90/50 mmHg) and history of stroke or myocardial infarction</th>
</tr>
</thead>
</table>

### Interventions

**Intervention:** sildenafil citrate tablets (50 mg) daily (from first day of cycle until day progesterone was started)

**Control:** no sildenafil

### Outcomes

**Primary outcome:** endometrial thickness

**Other outcome:** implantation rate and chemical pregnancy rate (we used implantation rate as clinical pregnancy rate)

### Notes

Both groups

On 13th day of menstrual cycle, endometrial thickness was measured by transvaginal ultrasonography. If endometrial thickness > 8 mm, 100 mg progesterone was injected IM

Oral oestradiol valerate (first to fourth days of menstrual cycle, 2 mg oestradiol valerate tablets; fifth to eighth day of menstrual cycle, 4 mg oestradiol valerate tablets; ninth to 12th day of menstrual cycle, 6 mg oestradiol valerate tablets) was given daily

Administering oestradiol valerate and progesterone continued until 2 weeks after embryos were transferred

### 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>Participants were divided into 2 groups on the basis of randomised tables</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Information was insufficient to permit judgement of ‘low risk’ or ‘high risk’: Allocation was not described</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
<td>Unclear risk</td>
<td>Study did not use placebo</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) All outcomes</td>
<td>Low risk</td>
<td>No blinding of outcome assessment, but review authors judge that measurement of pregnancy outcome is not likely to be influenced by lack of blinding</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>Low risk</td>
<td>Investigators evaluated all randomly assigned women</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>Study protocol is available, and published reports include those that were prespecified. Investigators do not include all expected outcomes</td>
</tr>
</tbody>
</table>
Groups were comparable for the variables described (duration of infertility, age, basal FSH, basal LH, basal oestrogen, basal progesterone, basal FSH/LH)

### Kim 2010

<table>
<thead>
<tr>
<th>Methods</th>
<th>Randomised</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>48 women (21 intervention, 27 control) among 170 patients with a thin endometrium (&lt; 8 mm: range, 5-7.9 mm) at the time of ET undergoing IVF</td>
</tr>
</tbody>
</table>
| Interventions | **Intervention**: vaginal sildenafil 25 mg/d + oral oestradiol valerate 4 mg/d from day of embryo transfer until pregnancy test (11 days)  
**Control**: did not receive the above drugs |
| Outcomes | **Primary outcome**: clinical pregnancy  
**Other outcome**: fertilisation rate |
| Notes | **Both groups** received recombinant FSH beginning on 3 CD + multiple-dose protocol of GnRH antagonist + 250 µg recombinant hCG (when dominant follicles averaged 19 mm in diameter to trigger ovulation)  
In all participants, luteal phase was supported by vaginal micronised progesterone 600 mg/d, starting on the day of oocyte retrieval and continued for another 6-8 weeks in cases in which pregnancy was achieved |

### Risk of bias

<table>
<thead>
<tr>
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<th>Authors' judgement</th>
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<tr>
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</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Method of concealment not described to allow a definitive judgement</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
<td>Unclear risk</td>
<td>Study did not use placebo</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) All outcomes</td>
<td>Low risk</td>
<td>Not described, but outcome measurement is not likely to be influenced by lack of blinding</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>Low risk</td>
<td>Investigators evaluated all randomly assigned women</td>
</tr>
</tbody>
</table>
Kim 2010  (Continued)

<table>
<thead>
<tr>
<th>Selective reporting (reporting bias)</th>
<th>Unclear risk</th>
<th>Study protocol is not available, and no published reports describe all expected outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other bias</td>
<td>Low risk</td>
<td>Groups were comparable for the variables described (female age, duration of infertility, cause of infertility, total dose of gonadotrophin, day of triggering, endometrial thickness at triggering, number of ICSI cycles, number of embryos transferred)</td>
</tr>
</tbody>
</table>

**Mostafa 2003**

**Methods**
Randomised controlled trial

**Participants**
Women who underwent IVF/ICSI indicated for infertility associated with a male factor. Ages ranged from 25 to 35 years

**Interventions**
- **Intervention:** glyceryl trinitrate skin patches 5 mg daily for 2 weeks
- **Control:** Participants did not receive the aforementioned drug

**Outcomes**
- **Primary outcome:** Pregnancy (we do not know the method used to establish pregnancy) and implantation rate (number of implantations and pregnancies is equal, so we used this as clinical pregnancy rate)
- **Secondary outcome:** pulsatility index

**Notes**
Published currently only as an abstract

**Risk of bias**

<table>
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<tr>
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<td>Unclear risk</td>
<td>Methods not adequately described</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>Methods not adequately described</td>
</tr>
</tbody>
</table>
### Ohl 2002

<table>
<thead>
<tr>
<th><strong>Methods</strong></th>
<th>Randomised multi-centre double-blinded placebo-controlled trial</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Participants</strong></td>
<td>138 participants (70 in intervention group, 68 in control group) with a history of 2 or more previous implantation failures. Exclusion criteria were hypersensitivity to nitric oxide donors, heart failure, severe anaemia, high intracranial blood pressure and high intraocular blood pressure</td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td><strong>Intervention:</strong> 5 mg glyceryltrinitrate (GTN) patch applied once daily, beginning the morning of the day before transfer, just after transvaginal ultrasonography and colour doppler were performed  <strong>Control:</strong> placebo</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td><strong>Primary outcome:</strong> clinical pregnancy  <strong>Secondary outcomes:</strong> newborn (equivalent “live birth”), multiple gestation or birth, spontaneous abortion/miscarriage, ectopic pregnancy, vasodilator side effects</td>
</tr>
<tr>
<td><strong>Notes</strong></td>
<td>Both groups received GnRH agonist long protocol daily SC (continued up to the day when hCG was administered) + recombinant FSH + 5000 IU hCG + ICSI or conventional in vitro fertilisation + embryo transfer (embryos were transferred 2 or 3 days after oocyte retrieval)</td>
</tr>
</tbody>
</table>

### Risk of bias

<table>
<thead>
<tr>
<th><strong>Bias</strong></th>
<th><strong>Authors’ judgement</strong></th>
<th><strong>Support for judgement</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Investigators describe a random component in the sequence generation process. Randomisation was performed by using 4 randomly permuted blocks and was stratified by centre</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>Participants and investigators enrolling participants could not foresee assignment because central allocation was used to conceal allocation</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
<td>Low risk</td>
<td>Double-blinded with the use of placebo.</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) All outcomes</td>
<td>Low risk</td>
<td>Not described, but main outcome measurement is not likely to be influenced by lack of blinding</td>
</tr>
<tr>
<td>Bias</td>
<td>Authors’ judgement</td>
<td>Support for judgement</td>
</tr>
<tr>
<td>------------------------------------------</td>
<td>--------------------</td>
<td>---------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Low risk</td>
<td>Intention-to-treat analysis was performed in this study, but study authors report losses for transvaginal ultrasonography</td>
</tr>
<tr>
<td>All outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>Study protocol is not available, but it is clear that published reports include all expected outcomes, including those that were pre-specified</td>
</tr>
<tr>
<td>Other bias</td>
<td>Low risk</td>
<td>Groups were comparable for the variables described (age, body mass index, years of infertility, causes of infertility, number of previous pregnancy failures, basal FSH level, number of ICSI cycles, duration of stimulation, oestradiol level on day of hCG, endometrial thickness, secretory change between day before and day of embryo transfer, pulsatility index)</td>
</tr>
</tbody>
</table>

**Shaker 1993**

<table>
<thead>
<tr>
<th>Methods</th>
<th>Double-blind study with random allocation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>120 participants on embryo transfer (intervention 60, placebo 60)</td>
</tr>
<tr>
<td>Interventions</td>
<td><strong>Intervention</strong>: 2 sublingual spray emissions of GTN 400 µg/spray or placebo spray <strong>Control</strong>: placebo</td>
</tr>
<tr>
<td>Outcomes</td>
<td><strong>Primary outcome</strong>: pregnancy rate (outcome definition is not clear) <strong>Secondary outcome</strong>: side effect</td>
</tr>
<tr>
<td>Notes</td>
<td>All participants received in vitro fertilisation after combined long-course gonadotrophin-releasing hormone analogue and human menopausal gonadotrophin therapy Study authors did not define pregnancy</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>Unclear risk</td>
<td>Insufficient information about sequence generation process to permit judgement of ‘low risk’ or ‘high risk’</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Insufficient information to permit judgement of ‘low risk’ or ‘high risk’: allocation not described</td>
</tr>
<tr>
<td><strong>Shaker 1993 (Continued)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
<td>Low risk</td>
<td>Double-blinded with use of placebo</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) All outcomes</td>
<td>Unclear risk</td>
<td>No blinding of outcome assessment, but review authors judge that measurement of pregnancy outcome is not likely to be influenced by lack of blinding</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>Low risk</td>
<td>Investigators evaluated women randomly assigned</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>Study protocol is not available, but it is clear that published reports include all pre-specified outcomes and some expected outcomes</td>
</tr>
<tr>
<td>Other bias</td>
<td>Low risk</td>
<td>2 participant groups were comparable with respect to age, duration of infertility and parity</td>
</tr>
</tbody>
</table>

Abbreviations:
- BD: twice daily or bi-daily
- CD: cycle day
- FSH: follicle-stimulating hormone
- GnRH: gonadotrophin-releasing hormone
- GTN: glyceryltrinitrate
- hCG: human chorionic gonadotrophin
- hMG: human menopausal gonadotrophin
- ICSI: intracytoplasmic sperm injection
- ICSI-ET: intracytoplasmic sperm injection - embryo transfer
- IM: intramuscular
- ISMN: isosorbide mononitrate
- IUI: intrauterine insemination
- IVF: in vitro fertilisation
- LH: luteinising hormone
- PI: pulsatility index
- SC: subcutaneous
- ZIFT: zygote intrafallopian transfer
## Characteristics of excluded studies  [ordered by study ID]

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alborzi 2007</td>
<td>Study used pentoxifylline as an immunomodulator for controlling endometriosis. As participants did not undergo AR, they were not of interest for this review</td>
</tr>
<tr>
<td>Balasch 1997</td>
<td>This study did not report participants of interest for this review. Not all underwent AR (the study description is that only 13/29 corrected additional infertility factors in PTX group and 11/27 corrected additional infertility factors in placebo group) and used pentoxifylline as an immunomodulator for controlling endometriosis</td>
</tr>
<tr>
<td>Check 2004</td>
<td>Eliminated because it is not a parallel randomised controlled trial. In this study some participants do cross over. Nine women were randomly assigned to vaginal sildenafil vs protocol in their first cycle, and seven to vaginal oestradiol. Only 3 women in the vaginal sildenafil group completed both study arms</td>
</tr>
<tr>
<td>Creus 2008</td>
<td>This study did not report participants of interest for this review. Only some participants underwent insemination or ovulation induction, and investigators used pentoxifylline as an immunomodulator to control endometriosis</td>
</tr>
<tr>
<td>Kamencic 2008</td>
<td>Study did not report participants or outcomes of interest for this review</td>
</tr>
<tr>
<td>Malinova 2013</td>
<td>Study did not report outcomes of interest for this review. Time frame was too short for investigator to evaluate them</td>
</tr>
<tr>
<td>Raine-Fenning 2009</td>
<td>Eliminated because it is not a parallel randomised controlled trial, but rather is a cross-over study</td>
</tr>
<tr>
<td>Rosen 1987</td>
<td>Study reported no comparisons of interest for this review. Study compared 0.7% isoflurane + nitrous oxide vs 1.4% isoflurane + nitrous oxide</td>
</tr>
<tr>
<td>Sher 2000</td>
<td>Eliminated because this is not a parallel randomised controlled trial, but rather is an observational study in 4 participants</td>
</tr>
<tr>
<td>Shin 2002</td>
<td>Eliminated because this is not a parallel randomised controlled trial, but rather is a controlled clinical trial</td>
</tr>
</tbody>
</table>

AR: assisted reproduction  
PTX: pentoxifylline

## Characteristics of ongoing studies  [ordered by study ID]
### Ben-Meir 2014

<table>
<thead>
<tr>
<th>Trial name or title</th>
<th>Nifedipine treatment on uterine contractility in in vitro fertilisation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods</td>
<td>Randomised parallel double blind controlled trial</td>
</tr>
<tr>
<td>Participants</td>
<td>Women 18-45 years of age undergoing frozen embryo transfer</td>
</tr>
<tr>
<td>Interventions</td>
<td><strong>Experimental group</strong>: nifedipine 5 mg single dose &lt;br&gt;<strong>Control group</strong>: placebo</td>
</tr>
<tr>
<td>Outcomes</td>
<td><strong>Primary outcome measures</strong>: uterine contractility after treatment (time frame 30 minutes after treatment) (designated as safety issue: no)&lt;br&gt;<strong>Secondary outcome measures</strong>: implantation and pregnancy rates (time frame 4 weeks) (designated as safety issue: no)</td>
</tr>
<tr>
<td>Starting date</td>
<td>February 24, 2014</td>
</tr>
<tr>
<td>Contact information</td>
<td>Assaf Ben-Meir, MD; 972-2-6776425; <a href="mailto:assaf.benmeir@gmail.com">assaf.benmeir@gmail.com</a></td>
</tr>
<tr>
<td>Notes</td>
<td>Study is not yet open for participant recruitment</td>
</tr>
</tbody>
</table>

### Casper 2013

<table>
<thead>
<tr>
<th>Trial name or title</th>
<th>Use of a calcium channel blocker to prevent premature luteinizing hormone surges in infertility patients (nimodipine)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods</td>
<td>Randomised parallel double-blind controlled trial</td>
</tr>
<tr>
<td>Participants</td>
<td>Women 25-40 years of age with intact normal ovaries, early follicular phase (day 2-4), serum follicle-stimulating hormone (FSH) level &lt; 20 mIU/mL and diagnosis of infertility, with recommended treatment of ovarian stimulation and intrauterine insemination (IUI)</td>
</tr>
<tr>
<td>Interventions</td>
<td><strong>Experimental group</strong>: Nimodipine 30 mg tablets will be self-administered by participants every 6 hours, starting on the day that the ultrasound criterion for hCG triggering is met. Tablets will be taken for 2 days or until an LH surge is detected, whichever comes first. If no LH surge occurs by 2 days, the hCG trigger (250 micrograms recombinant hCG) will be given, followed by IUI in 40 hours. If luteinising hormone (LH) surge is detected, human chorionic gonadotrophin (hCG) will be given immediately and 2 IUIs will be performed 24 hours apart&lt;br&gt;<strong>Control group</strong>: same as for nimodipine but an identical placebo will be self-administered</td>
</tr>
<tr>
<td>Outcomes</td>
<td><strong>Primary outcome measures</strong>: delay in LH surge by at least 2 days&lt;br&gt;<strong>Secondary outcome measures</strong>: side effect profile of nimodipine or placebo</td>
</tr>
<tr>
<td>Starting date</td>
<td>July 2012</td>
</tr>
<tr>
<td>Contact information</td>
<td>Robert F Casper; 416-972-0777; <a href="mailto:casper@lunenfeld.ca">casper@lunenfeld.ca</a></td>
</tr>
</tbody>
</table>
### Penzias 2012

<table>
<thead>
<tr>
<th>Trial name or title</th>
<th>Using nimodipine, a calcium channel blocker, to prevent LH surge in women undergoing controlled ovarian stimulation and intrauterine insemination: a double-blinded, randomized controlled study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods</td>
<td>Randomised parallel assignment, double-blind controlled trial</td>
</tr>
<tr>
<td>Participants</td>
<td>Women 25-40 years of age at time of enrolment, with both ovaries intact by history and ultrasound assessment, early follicular phase (day 2-4) serum FSH level &lt; 20 mIU/mL, diagnosis of subfertility with recommended treatment of controlled ovarian hyperstimulation (COH) and IUI. Women with unexplained infertility, polycystic ovarian syndrome and ovulatory dysfunction (absence of or irregular ovulation with unknown cause)</td>
</tr>
<tr>
<td>Interventions</td>
<td>Nimodipine 30 mg liquid orally 4 times a day for 8 total doses in pre-filled syringes</td>
</tr>
</tbody>
</table>
| Outcomes            | **Primary outcome measure:** LH surge  
**Secondary outcome measure:** side effect profile  
**Other outcome measures:** gonadotrophin levels and clinical pregnancy (positive pregnancy test and ultrasound evidence of fetal heart rate) |
| Starting date       | September 2012 |
| Contact information | Khanh-Ha D Nguyen, MD, MPH; knguyen@bostonivf.com  
Alan S Penzias, MD; apenzias@bostonivf.com |
| Notes               | This study is currently recruiting participants |
### Data and analyses

**Comparison 1. Vasodilator vs placebo or no treatment**

<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></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.1 Glyceryltriminitrate (GTN) vs placebo</td>
<td>2</td>
<td>238</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>1.08 [0.69, 1.71]</td>
</tr>
<tr>
<td>1.2 PTX + vitamin E vs no treatment</td>
<td>1</td>
<td>112</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>1.36 [0.76, 2.43]</td>
</tr>
<tr>
<td>2 Vasodilator side effects</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.1 Glyceryltriminitrate (GTN) vs placebo</td>
<td>2</td>
<td>258</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>1.63 [0.33, 7.93]</td>
</tr>
<tr>
<td>3 Clinical pregnancy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.1 Glyceryltriminitrate (GTN) vs placebo or no treatment</td>
<td>4</td>
<td>418</td>
<td>Odds Ratio (M-H, Random, 95% CI)</td>
<td>1.11 [0.73, 1.68]</td>
</tr>
<tr>
<td>3.2 Sildenafil vs no treatment</td>
<td>2</td>
<td>139</td>
<td>Odds Ratio (M-H, Random, 95% CI)</td>
<td>1.59 [0.63, 4.03]</td>
</tr>
<tr>
<td>3.3 Sildenafil + oestrogen vs no treatment</td>
<td>1</td>
<td>48</td>
<td>Odds Ratio (M-H, Random, 95% CI)</td>
<td>2.60 [0.77, 8.75]</td>
</tr>
<tr>
<td>3.4 PTX + vitamin E vs no treatment</td>
<td>1</td>
<td>112</td>
<td>Odds Ratio (M-H, Random, 95% CI)</td>
<td>2.06 [0.97, 4.38]</td>
</tr>
<tr>
<td>4 Other adverse effects</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.1 Multiple gestation or birth: NTG vs placebo and PTX + tocoherol vs no treatment</td>
<td>2</td>
<td>250</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>0.89 [0.39, 2.03]</td>
</tr>
<tr>
<td>4.2 Spontaneous abortion/miscarriage NTG vs placebo and PTX + tocoherol vs no treatment</td>
<td>3</td>
<td>350</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>0.84 [0.37, 1.91]</td>
</tr>
<tr>
<td>4.3 Ectopic pregnancy: NTG vs placebo and PTX + tocoherol vs no treatment</td>
<td>2</td>
<td>250</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>1.47 [0.24, 8.86]</td>
</tr>
</tbody>
</table>
## Analysis 1.1. Comparison 1 Vasodilator vs placebo or no treatment, Outcome 1 Live birth.

### Review
Vasodilators for women undergoing fertility treatment

### Comparison: 1 Vasodilator vs placebo or no treatment

### Outcome: 1 Live birth

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Vasodilator</th>
<th>Placebo or no treatment</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>H Random 95% CI</td>
<td></td>
<td>H Random 95% CI</td>
</tr>
<tr>
<td><strong>1 Glyceroltrinitrate (GTN) vs placebo</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Farzi 2005 (1)</td>
<td>13/50</td>
<td>9/50</td>
<td>22.7 %</td>
<td>0.68, 3.07</td>
<td>1.44 [0.68, 3.07]</td>
</tr>
<tr>
<td>OH 2002 (2)</td>
<td>17/70</td>
<td>18/68</td>
<td>39.3 %</td>
<td>0.52, 1.63</td>
<td>0.92 [0.52, 1.63]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>120</td>
<td>118</td>
<td>62.0 %</td>
<td>1.08 [0.69, 1.71]</td>
<td></td>
</tr>
<tr>
<td><strong>Total events: 30 (Vasodilator), 27 (Placebo or no treatment)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.0; Chi² = 1.24, df = 1 (P = 0.54); I² = 0.0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.70 (P = 0.48)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| **2 PTX vitamin E vs no treatment** | | | | | |
| Aleyasin 2009 (3) | 19/56 | 14/56 | 38.0 % | 1.36 [0.76, 2.43] |
| **Subtotal (95% CI)** | 56 | 56 | 38.0 % | 1.36 [0.76, 2.43] |
| **Total (95% CI)** | 176 | 174 | 100.0 % | 1.18 [0.82, 1.69] |
| **Total events: 49 (Vasodilator), 41 (Placebo or no treatment)** | | | | |
| Heterogeneity: Tau² = 0.0; Chi² = 1.24, df = 1 (P = 0.54); I² = 0.0% | | | | |
| Test for overall effect: Z = 0.70 (P = 0.48) | | | | |
| Test for subgroup differences: Chi² = 0.36, df = 1 (P = 0.55); I² = 0.0% | | | | |

---

(1) IVF

(2) IVF

(3) ZIFT
**Analysis 1.2. Comparison 1 Vasodilator vs placebo or no treatment, Outcome 2 Vasodilator side effects.**

Review: Vasodilators for women undergoing fertility treatment

Comparison: 1 Vasodilator vs placebo or no treatment

Outcome: 2 Vasodilator side effects

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Vasodilator</th>
<th>Placebo</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oh 2002 (1)</td>
<td>0/70</td>
<td>1/68</td>
<td>19.9% 0.32 [0.01, 7.82]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shaker 1993 (2)</td>
<td>17/60</td>
<td>7/60</td>
<td>80.1% 2.43 [1.09, 5.43]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>130</strong></td>
<td><strong>128</strong></td>
<td><strong>100.0% 1.63 [0.33, 7.93]</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 17 (Vasodilator), 8 (Placebo)

Heterogeneity: Tau^2 = 0.65; Chi^2 = 1.46, df = 1 (P = 0.23); I^2 = 32%

Test for overall effect: Z = 0.60 (P = 0.55)

Test for subgroup differences: Not applicable

(1) IVF

(2) IVF
### Analysis 1.3. Comparison 1 Vasodilator vs placebo or no treatment, Outcome 3 Clinical pregnancy.

**Review:** Vasodilators for women undergoing fertility treatment

**Comparison:** Vasodilator vs placebo or no treatment

**Outcome:** Clinical pregnancy

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Vasodilator</th>
<th>Placebo or no treatment</th>
<th>Odds Ratio M-H,Random,95% CI</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Glyceryltrimirate (GTN) vs placebo or no treatment</td>
<td>16/50</td>
<td>14/50</td>
<td>1.21 [0.51, 2.85]</td>
<td>14.6 %</td>
</tr>
<tr>
<td>Mostafa 2003 (2)</td>
<td>12/30</td>
<td>9/30</td>
<td>1.56 [0.53, 4.53]</td>
<td>9.4 %</td>
</tr>
<tr>
<td>OH 2002 (3)</td>
<td>20/70</td>
<td>19/68</td>
<td>1.03 [0.49, 2.16]</td>
<td>19.5 %</td>
</tr>
<tr>
<td>Shaker 1993 (4)</td>
<td>18/60</td>
<td>19/60</td>
<td>0.92 [0.43, 2.01]</td>
<td>17.9 %</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>210</td>
<td>208</td>
<td>1.11 [0.73, 1.68]</td>
<td>61.4 %</td>
</tr>
</tbody>
</table>

Total events: 66 (Vasodilator), 61 (Placebo or no treatment)
Heterogeneity: $\tau^2 = 0.0$; $\chi^2 = 0.67$, df = 3 ($P = 0.88$); $I^2 = 0.0$
Test for overall effect: $Z = 0.47$ ($P = 0.64$)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Vasodilator</th>
<th>Placebo or no treatment</th>
<th>Odds Ratio M-H,Random,95% CI</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 Sildenafil vs no treatment</td>
<td>7/29</td>
<td>5/30</td>
<td>1.59 [0.44, 5.74]</td>
<td>6.5 %</td>
</tr>
<tr>
<td>Firouzabadi 2013 (6)</td>
<td>6/40</td>
<td>4/40</td>
<td>1.59 [0.41, 6.12]</td>
<td>5.9 %</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>69</td>
<td>70</td>
<td>1.59 [0.63, 4.03]</td>
<td>12.4 %</td>
</tr>
</tbody>
</table>

Total events: 13 (Vasodilator), 9 (Placebo or no treatment)
Heterogeneity: $\tau^2 = 0.0$; $\chi^2 = 0.00$, df = 1 ($P = 1.00$); $I^2 = 0.0$
Test for overall effect: $Z = 0.98$ ($P = 0.33$)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Vasodilator</th>
<th>Placebo or no treatment</th>
<th>Odds Ratio M-H,Random,95% CI</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 Sildenafil + oestrogen vs no treatment</td>
<td>10/21</td>
<td>7/27</td>
<td>2.60 [0.77, 8.75]</td>
<td>7.3 %</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>21</td>
<td>27</td>
<td>2.60 [0.77, 8.75]</td>
<td>7.3 %</td>
</tr>
</tbody>
</table>

Total events: 10 (Vasodilator), 7 (Placebo or no treatment)
Heterogeneity: not applicable
Test for overall effect: $Z = 1.54$ ($P = 0.12$)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Vasodilator</th>
<th>Placebo or no treatment</th>
<th>Odds Ratio M-H,Random,95% CI</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 PTX + vitamin E vs no treatment</td>
<td>32/56</td>
<td>22/56</td>
<td>2.06 [0.97, 4.38]</td>
<td>18.9 %</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>56</td>
<td>56</td>
<td>2.06 [0.97, 4.38]</td>
<td>18.9 %</td>
</tr>
</tbody>
</table>

Total events: 32 (Vasodilator), 22 (Placebo or no treatment)
Heterogeneity: not applicable
Test for overall effect: $Z = 1.88$ ($P = 0.060$)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Vasodilator</th>
<th>Placebo or no treatment</th>
<th>Odds Ratio M-H,Random,95% CI</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>356</td>
<td>361</td>
<td>1.38 [1.00, 1.92]</td>
<td>100.0 %</td>
</tr>
</tbody>
</table>

Total events: 121 (Vasodilator), 99 (Placebo or no treatment)
Heterogeneity: $\tau^2 = 0.0$; $\chi^2 = 3.97$, df = 7 ($P = 0.78$); $I^2 = 0.0$
Test for overall effect: $Z = 1.95$ ($P = 0.052$)
Test for subgroup differences: $\chi^2 = 3.30$, df = 3 ($P = 0.35$); $I^2 = 9$

---

**Vasodilators for women undergoing fertility treatment (Review)**

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Analysis 1.4. Comparison 1 Vasodilator vs placebo or no treatment, Outcome 4 Other adverse effects.

Review: Vasodilators for women undergoing fertility treatment

Comparison: 1 Vasodilator vs placebo or no treatment

Outcome: 4 Other adverse effects

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Vasodilator</th>
<th>Placebo or no treatment</th>
<th>Risk Ratio M-H Random, 95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H Random, 95% CI</th>
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<tr>
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<td>n/N</td>
<td>n/N</td>
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<tr>
<td>1 Multiple gestation or birth: NTG vs placebo and PTX + tocopherol vs no treatment</td>
<td></td>
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<tr>
<td>Aleyasin 2009 (1)</td>
<td>4/56</td>
<td>5/56</td>
<td>-</td>
<td>42.4 %</td>
<td>0.80 [ 0.23, 2.82 ]</td>
</tr>
<tr>
<td>OH 2002 (2)</td>
<td>6/70</td>
<td>6/68</td>
<td>-</td>
<td>57.6 %</td>
<td>0.97 [ 0.33, 2.86 ]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>126</td>
<td>124</td>
<td><strong>100.0 %</strong></td>
<td>0.89 [ 0.39, 2.03 ]</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>Total events: 10 (Vasodilator), 11 (Placebo or no treatment)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.05, df = 1 (P = 0.82); I^2 =0.0%</td>
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<tr>
<td></td>
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<td></td>
<td>Test for overall effect: Z = 0.27 (P = 0.79)</td>
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<td></td>
</tr>
<tr>
<td>2 Spontaneous abortion/miscarriage NTG vs placebo and PTX + tocopherol vs no treatment</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Aleyasin 2009 (3)</td>
<td>6/56</td>
<td>5/56</td>
<td>-</td>
<td>52.7 %</td>
<td>1.20 [ 0.39, 3.71 ]</td>
</tr>
<tr>
<td>Farzi 2005 (4)</td>
<td>3/50</td>
<td>5/50</td>
<td>-</td>
<td>35.4 %</td>
<td>0.60 [ 0.15, 2.38 ]</td>
</tr>
<tr>
<td>OH 2002 (5)</td>
<td>1/70</td>
<td>2/68</td>
<td>-</td>
<td>11.9 %</td>
<td>0.49 [ 0.05, 5.23 ]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>176</td>
<td>174</td>
<td><strong>100.0 %</strong></td>
<td>0.84 [ 0.37, 1.91 ]</td>
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</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>Total events: 10 (Vasodilator), 12 (Placebo or no treatment)</strong></td>
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<tr>
<td></td>
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<td></td>
<td>Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.82, df = 2 (P = 0.66); I^2 =0.0%</td>
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<tr>
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<td></td>
<td>Test for overall effect: Z = 0.41 (P = 0.68)</td>
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<td></td>
</tr>
</tbody>
</table>

(Continued ...)

Vasodilators for women undergoing fertility treatment (Review)

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
3 Ectopic pregnancy: NTG vs placebo and PTX + tocopherol vs no treatment

Aleyasin 2009 (6) 2/56 1/56 57.4 % 2.00 [ 0.19, 21.43 ]
Ohl 2002 (7) 1/70 1/68 42.6 % 0.97 [ 0.06, 15.22 ]

Subtotal (95% CI) 126 124 100.0 % 1.47 [ 0.24, 8.86 ]

Total events: 3 (Vasodilator), 2 (Placebo or no treatment)
Heterogeneity: Tau² = 0.0; Chi² = 0.15, df = 1 (P = 0.70); I² =0.0%
Test for overall effect: Z = 0.42 (P = 0.67)
Test for subgroup differences: Chi² = 0.31, df = 2 (P = 0.86), I² =0.0%

A P P E N D I C E S

Appendix 1. CENTRAL search strategy

Database: EBM Reviews-Cochrane CENTRAL <August 2012>
Search strategy:
--------------------------------------------------------------------------------
1 exp embryo transfer/ or exp fertilization in vitro/ or exp sperm injections, intracytoplasmic/ (1573)
2 embryo transfer$.tw . (878)
3 vitro fertilization.tw . (1312)
4 ivf-et.tw . (253)
5 ivf.tw . (1872)
6 icsi.tw . (647)
7 intracytoplasmic sperm injection$.tw . (405)
8 (blastocyst adj2 transfer$).tw . (64)
9 exp reproductive techniques, assisted/ or exp insemination, artificial/ or exp ovulation induction/ (2194)
10 assisted reproduction$.tw . (386)

(1) IVF
(2) IVF
(3) IVF
(4) IVF
(5) IVF
(6) IVF
(7) IVF

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Appendix 2. EMBASE search strategy

Database: Embase <1980 to 2012 Week 34>
Search Strategy:
--------------------------------------------------------------------------------
1 exp embryo transfer/ or exp fertilization in vitro/ or exp intracytoplasmic sperm injection/ (46666)
2 embryo$.tw. (10692)
3 in vitro fertili?ation.tw. (18597)
4 icsi.tw. (7785)
5 intracytoplasmic sperm injection$.tw. (5539)
6 (blastocyst adj2 transfer$).tw. (794)
7 ivf.tw. (20546)
8 exp infertility therapy/ or exp artificial insemination/ or exp intrauterine insemination/ or exp ovulation induction/ (69349)
9 assisted reproduct$.tw. (10901)
10 artificial insemination.tw. (4395)
11 iui.tw. (1570)
12 intrauterine insemination$.tw. (2139)
13 ovulation induc$.tw. (4013)
14 (ovari$ adj2 stimulat$).tw. (5917)
15 superovulat$.tw. (2837)
16 ovarian hyperstimulation.tw. (4563)
17 COH.tw. (1213)
18 infertil$.tw. (47649)
19 subfertil$.tw. (3855)
20 (ovari$ adj2 induction).tw. (250)
21 or/1-20 (115602)
22 exp vasodilator agent/ (366977)
23 exp nifedipine/ (42598)
24 exp glyceryl trinitrate/ (31270)
25 nitroglycerin.tw. (10514)
26 exp nitric oxide/ (103890)
27 exp endothelium derived relaxing factor/ (3759)
28 vasodilator$.tw. (34821)
29 nifedipine.tw. (21434)
30 glyceryl trinitrate.tw. (2384)
31 nitric oxide.tw. (119671)
32 sildenafil.tw. (5694)
33 Viagra.tw. (3741)
34 exp sildenafil/ (13110)
35 or/22-34 (511916)
36 21 and 35 (1295)
37 Clinical Trial/ (870370)
38 Randomized Controlled Trial/ (327721)
39 exp randomization/ (59164)
40 Single Blind Procedure/ (16301)
41 Double Blind Procedure/ (110472)
42 Crossover Procedure/ (34756)
43 Placebo/ (203536)
44 Randomized controlled trial$.tw. (77962)
45 Rct.tw. (9835)
46 random allocation.tw. (1171)
47 randomly allocated.tw. (17528)
48 allocated randomly.tw. (1826)
49 (allocated adj2 random).tw. (710)
50 Single blind$.tw. (12457)
51 Double blind$.tw. (129919)
52 ((treble or triple) adj blind$).tw. (277)
53 placebo$.tw. (178186)
54 prospective study/ (211853)
55 or/37-54 (1268861)
56 case study/ (16724)
57 case report.tw. (229488)
58 abstract report/ or letter/ (841849)
59 or/56-58 (1083375)
60 55 nor 59 (1233599)
61 36 and 60 (236)
62 (2010$ or 2011$ or 2012$).em. (2835423)
63 61 and 62 (40)
Appendix 3. MEDLINE search strategy

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

Search Strategy:

1 exp embryo transfer/ or exp fertilization in vitro/ or exp sperm injections, intracytoplasmic/ (30226)
2 embryo transfer$.tw. (7452)
3 vitro fertilization.tw. (15444)
4 ivf-et.tw. (1722)
5 ivf.tw. (14578)
6 icsi.tw. (4836)
7 intracytoplasmic sperm injection$.tw. (4455)
8 (blastocyst adj2 transfer$).tw. (470)
9 exp reproductive techniques, assisted/ or exp insemination, artificial/ or exp ovulation induction/ (48822)
10 assisted reproduct$.tw. (7780)
11 artificial insemination.tw. (4543)
12 iui.tw. (1055)
13 intrauterine insemination$.tw. (1642)
14 ovulation induc$.tw. (3185)
15 (ovari$ adj2 stimulate$).tw. (4372)
16 superovulate$.tw. (2781)
17 ovarian hyperstimulation.tw. (3423)
18 COH.tw. (950)
19 infertil$.tw. (38594)
20 subfertil$.tw. (3181)
21 (ovari$ adj2 induction).tw. (210)
22 endometrium.tw. (20658)
23 endometrial.tw. (38491)
24 or/1-23 (134563)
25 exp vasodilator agents/ or exp nifedipine/ or exp nitroglycerin/ or exp endothelium-dependent relaxing factors/ or exp nitric oxide/ (343609)
26 vasodilator$.tw. (29687)
27 nifedipine.tw. (17611)
28 glyceryl trinitrate.tw. (1992)
29 nitroglycerin.tw. (8836)
30 nitric oxide.tw. (101850)
31 sildenafil.tw. (4111)
32 Viagra.tw. (917)
33 or/25-32 (405820)
34 24 and 33 (935)
35 randomized controlled trial.pt. (335409)
36 controlled clinical trial.pt. (84960)
37 randomized.ab. (250530)
38 placebo.tw. (142828)
39 clinical trials as topic.sh. (162041)
40 randomly.ab. (183445)
41 trial.ti. (107769)
42 (crossover or cross-over or cross over).tw. (54459)
43 or/35-42 (821588)
44 exp animals/ not humans.sh. (3773404)
45 43 not 44 (757928)
46 34 and 45 (73)
Appendix 4. Menstrual Disorders and Subfertility Group database search strategy

Menstrual disorders and subfertility database (MDSG) search for RGB1760 02.04.12

Keywords CONTAINS “ART” or “assisted reproduction” or “assisted reproduction techniques” or “IVF” or “ICSI” or “in vitro fertilisation” or “in-vitro fertilisation techniques” or “in vitro fertilization” or “in vitro maturation” or “intracytoplasmic sperm injection” or “subfertility” or “Infertility” or “IUI” or “Intrauterine Insemination” or “Embryo Transfer” or “ET” or Title CONTAINS “ART” or “assisted reproduction” or “assisted reproduction techniques” or “IVF” or “ICSI” or “in vitro fertilisation” or “in-vitro fertilisation techniques” or “in vitro fertilization” or “in vitro maturation” or “intracytoplasmic sperm injection” or “subfertility” or “Infertility” or “IUI” or “Intrauterine Insemination” or “Embryo Transfer” or “ET”

AND

Keywords CONTAINS “vasodilation” or “Vasodilator Agents” or “Nifedipine” or “Nitric Oxide” or “nitroglycerin” or “nitro oxide” or “glycerine trinitrate” or “glyceryl trinitrate” or “Sildenafil” or “Viagra” or Title CONTAINS “vasodilation” or “Vasodilator Agents” or “Nifedipine” or “Nitric Oxide” or “nitroglycerin” or “nitro oxide” or “glycerine trinitrate” or “glyceryl trinitrate” or “Sildenafil” or “Viagra”

Appendix 5. PsycINFO search strategy

Database: PsycINFO <1806 to August Week 3 2012>

Search Strategy:

1 exp reproductive technology/ (1164)
2 in vitro fertilization.tw. (466)
3 ivf-et.tw. (16)
4 (ivf or et).tw. (84558)
5 icsi.tw. (38)
6 intracytoplasmic sperm injection$.tw. (33)
7 (blastocyst adj2 transfer$).tw. (2)
8 assisted reproduct$.tw. (432)
9 artificial insemination.tw. (214)
10 iui.tw. (19)
11 intrauterine insemination$.tw. (13)
12 ovulation induc$.tw. (16)
13 (ovari$ adj2 stimulat$).tw. (44)
14 ovarian hyperstimulation.tw. (8)
15 COH.tw. (54)
16 superovulat$.tw. (5)
17 infertil$.tw. (2267)
18 subfertil$.tw. (54)
19 (ovari$ adj2 induction).tw. (4)
20 or/1-19 (87609)
21 exp vasodilator drugs/ (469)
22 nifedipine.tw. (327)
23 nitroglycerin.tw. (123)
24 exp Nitric Oxide/ (2039)
25 nitric oxide.tw. (3305)
26 vasodilator$.tw. (404)
27 glyceryl trinitrate.tw. (65)
28 exp Sildenafil/ (227)
29 sildenafil.tw. (426)
30 Viagra.tw. (198)
31 or/21-30 (4954)
32 20 and 31 (157)
33 random.tw. (35907)
Appendix 6. CINAHL search strategy

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<th>#</th>
<th>Query</th>
<th>Results</th>
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<td>S40 AND S54</td>
<td>28</td>
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<td>S54</td>
<td>S41 OR S42 or S43 or S44 OR S45 OR S46 OR S47 OR S48 OR S49 OR S50 OR S51 OR S52 OR S53</td>
<td>881,657</td>
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<td>S53</td>
<td>TX allocat* random*</td>
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<tr>
<td>S52</td>
<td>(MH &quot;Quantitative Studies&quot;)</td>
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<tr>
<td>S51</td>
<td>(MH &quot;Placebos&quot;)</td>
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<td>S50</td>
<td>TX placebo*</td>
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<tr>
<td>S49</td>
<td>TX random* allocat*</td>
<td>3,855</td>
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<td>S48</td>
<td>(MH &quot;Random Assignment&quot;)</td>
<td>36,961</td>
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<tr>
<td>S47</td>
<td>TX random* control* trial*</td>
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</tr>
<tr>
<td>S46</td>
<td>TX ( (singl* n1 blind*) or (singl* n1 mask*) ) or TX ( (doubl* n1 blind*) or (doubl* n1 mask*) ) or TX ( (tripl* n1 blind*) or (tripl* n1 mask*) ) or TX ( (trebl* n1 blind*) or (trebl* n1 mask*) )</td>
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<td>S43</td>
<td>TX clinic* n1 trial*</td>
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<td>S38</td>
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<td>S29</td>
<td>(MM “Nifedipine”)</td>
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<td>S28</td>
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CONTRIBUTIONS OF AUTHORS

RG conceived of and designed the study; co-ordinated the whole review process; and participated in the search and in selection and assessment of studies. She completed data extraction activities; conducted the analysis; wrote the review; and approved the final version of the review.

GU provided general advice on study design and other related aspects of the review; participated in the assessment of potentially eligible studies; solved discrepancies; supervised data analysis; collaborated in the writing process of the review; and approved the final version of the review.

DG provided general advice on study design; coordinated the search to identify potentially eligible studies; participated in selection, assessment and extraction of data; and approved the final version of the review.

AC participated in selection, assessment and extraction of data; and approved the final version of the review.
XB conceived of the study; co-ordinated the whole review process; provided general advice on all processes; solved discrepancies; and approved of the final version of the review.

DECLARATIONS OF INTEREST

The review authors declare that they have no conflicts of interest to report.

SOURCES OF SUPPORT

Internal sources

- None, Not specified.

External sources

- Ford Foundation International Fellowships Program, USA.
  RBG received a fellowship from the Ford Foundation International Fellowships Program

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The word "safety" was added to the objectives, and the sentence was edited for brevity.

We have added a post hoc subgroup analysis for the secondary outcome of clinical pregnancy to evaluate studies that used only vasodilators.