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TABLE OF CONTENTS

HEADER 1
ABSTRACT 1
PLAIN LANGUAGE SUMMARY 2
SUMMARY OF FINDINGS 3
BACKGROUND 5
OBJECTIVES 6
METHODS 6
Figure 1. 8
Figure 2. 10
Figure 3. 11
RESULTS 13
Figure 4. 15
Figure 5. 16
Figure 6. 17
DISCUSSION 18
AUTHORS' CONCLUSIONS 19
ACKNOWLEDGEMENTS 20
REFERENCES 21
CHARACTERISTICS OF STUDIES 26
DATA AND ANALYSES 48
Analysis 1.1. Comparison 1 Vasodilator vs placebo or no treatment, Outcome 1 Live birth. 50
Analysis 1.2. Comparison 1 Vasodilator vs placebo or no treatment, Outcome 2 Vasodilator side effects. 51
Analysis 1.3. Comparison 1 Vasodilator vs placebo or no treatment, Outcome 3 Specific vasodilator side effects. 51
Analysis 1.4. Comparison 1 Vasodilator vs placebo or no treatment, Outcome 4 Clinical pregnancy. 52
Analysis 1.5. Comparison 1 Vasodilator vs placebo or no treatment, Outcome 5 Thickened endometrium. 53
Analysis 1.6. Comparison 1 Vasodilator vs placebo or no treatment, Outcome 6 Other adverse effects. 54
APPENDICES 55
WHAT'S NEW 61
CONTRIBUTIONS OF AUTHORS 61
DECLARATIONS OF INTEREST 62
SOURCES OF SUPPORT 62
DIFFERENCES BETWEEN PROTOCOL AND REVIEW 62
INDEX TERMS 62

[Intervention Review]

Vasodilators for women undergoing fertility treatment

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ABSTRACT

Background

The rate of successful pregnancies brought to term has barely increased since the first assisted reproductive technology (ART) technique became available. 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 pregnancy.

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 Gynaecology and Fertility Group (CGF) Specialised Register of controlled trials, the Cochrane Central Register of of Controlled Trials, via the Cochrane Register of Studies Online (CRSO), MEDLINE, Embase, PsycINFO, the Cumulative Index to Nursing and Allied Health Literature (CINAHL), Web of Knowledge, the Open System for Information on Grey Literature in Europe (OpenSIGLE), the Latin American and Caribbean Health Science Information Database (LILACS), clinical trial registries, and the reference lists of relevant articles. We conducted the search in October 2017 and applied no language restrictions.

Selection criteria

Randomised controlled trials (RCTs) comparing vasodilators alone or in combination with other treatments versus placebo or no treatment or versus other agents in women undergoing fertility treatment.

Data collection and analysis

Four review authors independently selected studies, assessed risk of bias, extracted data, and calculated risk ratios (RRs). We combined study data using a fixed-effect model and assessed evidence quality using Grades of Recommendation, Assessment, Development and Evaluation Working Group (GRADE) methods. Our primary outcomes were live birth or ongoing pregnancy and vasodilator side effects. Secondary outcomes included clinical pregnancy, endometrial thickness, multiple pregnancy, miscarriage, and ectopic pregnancy.

Main results

We included 15 studies with a total of 1326 women. All included studies compared a vasodilator versus placebo or no treatment. We judged most of these studies as having unclear risk of bias. Overall, the quality of evidence was low to moderate for most outcomes. The main limitations were imprecision due to low numbers of events and participants and risk of bias due to unclear methods of randomisation.

Vasodilators probably make little or no difference in rates of live birth compared with placebo or no treatment (RR 1.18, 95% confidence interval (CI) 0.83 to 1.69; three RCTs; N = 350; I^2 = 0%; moderate-quality evidence) but probably increase overall rates of side effects including headache and tachycardia (RR 2.35, 95% CI 1.51 to 3.66; four RCTs; N = 418; I^2 = 0%; moderate-quality evidence). Evidence suggests that if 236 per 1000 women achieve live birth with placebo or no treatment, then between 196 and 398 per 1000 will do so with the use of vasodilators.

Compared with placebo or no treatment, vasodilators may slightly improve clinical pregnancy rates (RR 1.45, 95% CI 1.19 to 1.77; 11 RCTs; N = 1054; I^2 = 6%; low-quality evidence). Vasodilators probably make little or no difference in rates of multiple gestation (RR 1.15, 95% CI 0.55 to 2.42; three RCTs; N = 370; I^2 = 0%; low-quality evidence), miscarriage (RR 0.83, 95% CI 0.37 to 1.86; three RCTs; N = 350; I^2 = 0%; low-quality evidence), or ectopic pregnancy (RR 1.48, 95% CI 0.25 to 8.69; two RCTs; N = 250; I^2 = 5%; low-quality evidence). All studies found benefit for endometrial thickening, but reported effects varied (I^2 = 92%) and ranged from a mean difference of 0.80 higher (95% CI 0.18 to 1.42) to 3.57 higher (95% CI 3.01 to 4.13) with very low-quality evidence, so we are uncertain how to interpret these results.

Authors' conclusions

Evidence was insufficient to show whether vasodilators increase the live birth rate in women undergoing fertility treatment. However, low-quality evidence suggests that vasodilators may slightly increase clinical pregnancy rates. Moderate-quality evidence shows that vasodilators increase overall side effects in comparison with placebo or no treatment. Adequately powered studies are needed so that each treatment can be evaluated more accurately.

PLAIN LANGUAGE SUMMARY

Vasodilators for women undergoing fertility treatment

Review question

Researchers at Cochrane reviewed available evidence on the effects of vasodilators (drugs used to widen blood vessels) in women undergoing fertility treatment.

Background

For 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

We found 15 randomised controlled trials (a type of experiment in which people are randomly allocated to one or more treatment groups) that compared the use of vasodilators versus placebo or no treatment in a total of 1326 women undergoing fertility treatment. The evidence is current to October 2017.

Key results

Only three of the included studies reported live birth rates. Overall, vasodilators probably make little or no difference in rates of live birth. Moderate-quality evidence shows that vasodilators probably increase overall rates of side effects (including headache and tachycardia (faster than normal heartbeat)) in comparison with placebo or no treatment. However, low-quality evidence suggests that vasodilators may increase the chance of becoming pregnant.

Quality of the evidence

The evidence is of low to moderate quality. More research is needed (one study is ongoing and will be incorporated into this review in a subsequent update).

Summary of findings for the main comparison. Vasodilator compared to placebo or no treatment for women undergoing fertility treatment

Vasodilator compared to placebo or no treatment for women undergoing fertility treatment

Patient or population: women undergoing fertility treatment
Setting: secondary care
Intervention: vasodilator
Comparison: placebo or no treatment

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)
	Risk with placebo or no treatment	Risk with vasodilator			
Live birth	236 per 1000	278 per 1000 (196 to 398)	RR 1.18 (0.83 to 1.69)	350 (3 RCTs)	⊕⊕⊕⊖ MODERATE[a]
Vasodilator side effects	109 per 1000	256 per 1000 (164 to 398)	RR 2.35 (1.51 to 3.66)	418 (4 RCTs)	⊕⊕⊕⊖ MODERATE[b]
Clinical pregnancy	224 per 1000	325 per 1000 (267 to 397)	RR 1.45 (1.19 to1.77)	1054 (11 RCTs)	⊕⊕⊖⊖ LOW[c,d]
Thickened endometrium	Mean thickness of the endometrium was 7.6 mm.	MD 2.11 mm higher (1.16 higher to 3.07 higher)	-	477 (5 RCTs)	⊕⊖⊖⊖ VERY LOW[c,e]
Multiple gestation or birth	65 per 1000	75 per 1000 (36 to 158)	RR 1.15 (0.55 to 2.42)	370 (3 RCTs)	⊕⊕⊕⊖ LOW[a]
Spontaneous miscarriage	69 per 1000	57 per 1000 (26 to 128)	RR 0.83 (0.37 to 1.86)	350 (3 RCTs)	⊕⊕⊕⊖ LOW[a]
Ectopic pregnancy	16 per 1000	24 per 1000 (4 to 140)	RR 1.48 (0.25 to 8.69)	250 (2 RCTs)	⊕⊕⊕⊖ LOW[a]

*__The risk in the intervention group__ (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; MD: mean difference; RCT: randomised controlled trial; RR: risk ratio.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

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[a]Downgraded for Imprecision (-1) as confidence interval is wide and the confidence interval includes the line of no effect.
[b]Downgraded for risk of bias (-1) owing to unclear random generation sequencing and blinding of participants, personnel, and outcome assessor.
[c]Downgraded for risk of bias (-1) owing to some studies having unclear risk and one trial having high risk of bias because of attrition.
[d]Downgraded for publication bias (-1). The plot was asymmetrical owing to lack of small non-significant published studies.
[e]Downgraded for Inconsistency (-2) owing to high statistical heterogeneity (92%).

BACKGROUND

Description of the condition

Between 0.2% and 4.7% of babies born in developed countries are conceived through techniques of assisted reproductive technology (ART) (Bouillon 2013; Sunderam 2012; Sunderam 2017). A total of 1,144,858 babies were reported to have been born worldwide in 2008, 2009, and 2010 (Dyer 2016). Worldwide, ART practices are characterised by outcome differences between regions. By 2012-2013, fresh cycle live birth rates were highest in the United States (29%) and lowest in Japan (5%) (Kushnir 2017). In the 17 European countries that report the number of ART procedures, practitioners performed 374,177 ART cycles in a population of 310 million (1175 cycles per million). In these countries, the clinical pregnancy rates for in vitro fertilisation (IVF) per aspiration and per transfer were 29.6% and 34.5%, respectively. Those for intracytoplasmic sperm injection (ICSI) were 27.8% and 32.9% (European IVF-Monitoring Consortium (EIM) 2017). Statistics have been very similar in recent years (de Mouzon 2012; ESHIRE 2016; Ferraretti 2012; Ferraretti 2013; Sullivan 2013).

According to the World Health Organization, medically assisted reproduction is defined as reproduction brought about through ovulation induction, controlled ovarian stimulation, ovulation triggering, insemination, and ART techniques (Zegers-Hochschild 2009; Zegers-Hochschild 2017). 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; Zegers-Hochschild 2017). The success of assisted reproduction varies depending on several factors, such as maternal age (Marinakis 2011; Schmidt 2012; Yavas 2017), maternal weight (Cai 2017; Kawwass 2016; Pinborg 2011), the number of embryos transferred (Martin 2017; McLernon 2010), the use of gonadotrophins (Maheshwari 2011; Mochtar 2017; Pouwer 2015), inadequate endometrial thickness (Baradwan 2018; Oron 2018), uterine contractions (Chung 2017; Chung 2016), and others.

A thin endometrium (measured at < 8 mm by ultrasound scan) has a negative impact on the success of assisted reproduction (Check 2011; Eftekhar 2017); live births are possible despite thin endometria, but the pregnancy rate among these women is poor (Dix 2010; Kasius 2014). Investigators have expressed a marked interest in studying the role that the endometrium plays in the success of assisted reproduction (Casper 2011; Senturk 2008; Weiss 2017).

Uterine contractions influence embryo implantation, possibly through mechanical displacement of the embryo. Decreases in pregnancy rates and implantation rates were noted as the frequency of uterine contractions increased. Approaches aimed at inhibiting uterine contractions could improve pregnancy rates for assisted reproduction (Aguilar 2010; Bulletti 2006; Chung 2017; Fanchin 2001; Fanchin 2009; Lesny 1998; Ng 2014).

Description of the intervention

Different vasodilating agents have been proposed to thicken the endometrium and to favour uterine relaxation. Agents used in assisted reproduction include sildenafil, glyceryl trinitrate (GTN), nifedipine, amlodipine, pentoxifylline, and isosorbide monohydrate (Abdel 2017; Aleyasin 2009; Alieva 2012; Azmy 2016; Das 2009; Dehghani Firouzabadi 2013; El-Berry 2010; Fahmy 2015; Farzi 2005; Kim 2010; Magdi Ammar 2017; Mahran 2016; Mostafa 2003; Ohl 2002; Shaker 1993). 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 improvement in uterine blood flow (Fetih 2017; Sher 2002; Takasaki 2010;). Nitric oxide donors such as isosorbide monohydrate and GTN are used in assisted reproduction. Glyceryl trinitrate is also used medically as a vasodilator; in 2002 it was discovered that these effects occur because GTN is converted inside the body to nitric oxide by mitochondrial aldehyde dehydrogenase. Glyceryl trinitrate, 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). Acharya 2009 and Letur-Konirsch 2003 used pentoxifylline plus vitamin E in women undergoing assisted reproduction. Reports have described successful conception and pregnancy with nifedipine given at doses of 30 mg/d after secondary infertility (Wilson 1990).

How the intervention might work

Endometrial thickness varies with vascularity of the endometrium and the sub-endometrium, regardless of the concentration of oestradiol or progesterone (Raine-Fenning 2004). It is well known that some vasodilators, such as vaginal sildenafil citrate, can produce selective endometrial vasodilation: this occurred in two women with Asherman's syndrome (a condition characterised by the presence of adhesions or fibrosis, or both, within the uterine cavity). "These women achieved pregnancy in the first treatment cycle with vaginal sildenafil citrate" (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 during 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 and increased implantation rates after administration of vasodilators (Sher 2002; Takasaki 2010; Zinger 2006). Glyceryl trinitrate at 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 improving outcomes of in vitro fertilisation (Zhang 2004). It also appears to improve the pregnancy rate among patients with a thin endometrium when combined with vitamin E (Acharya 2009; Lédée-Bataille 2002; Letur-Könirsch 2002). Nimodipine, which is a vasodilator calcium channel blocker, may prevent or delay the luteinising

hormone (LH) surge during controlled ovarian stimulation cycles when clomiphene citrate is used in sub-fertile patients undergoing assisted reproduction by intrauterine 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; Eftekhar 2017; Gelbaya 2005; Glujovsky 2010; Kim 2010; Lensen 2016; Ohl 2002; Shaker 1993; Torres 2005). However, evidence is insufficient to allow investigators to endorse a particular protocol for endometrial preparation.

Researchers have only partially studied the effects of vasodilators on endometrial preparation in fertility treatment. Their role in implantation, decidualisation, and uterine relaxation, among other events, has not been evaluated. A previous systematic review assessed different treatments for endometrial preparation for embryo transfer but excluded the comparison of vasodilators versus other treatments (Glujovsky 2010). Instead, the effectiveness of these treatments remains unproven, and this could potentially increase incrementally costs or side effects involved in assisted reproduction. Studies are needed to identify and assess the efficacy and safety of vasodilators used 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

We included randomised controlled trials (RCTs).

- We excluded cross-over trials, as the design is not valid in this context.

Types of participants

We considered women undergoing fertility treatment, regardless of the thickness of the endometrium. We applied no restrictions on age or comorbidities.

For the purposes of this review, fertility treatment means medically assisted reproduction, such as ovulation induction; controlled ovarian stimulation; ovulation triggering; assisted reproductive technology procedures; and intrauterine, intracervical, and intravaginal insemination with the semen of husband, partner, or donor (Zegers-Hochschild 2009; Zegers-Hochschild 2017).

Types of interventions

We planned to include 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

1. Clinical pregnancy
2. Thickened endometrium (reported as dichotomous or continuous data)
3. Other adverse events: multiple gestation or birth, spontaneous miscarriage, ectopic pregnancy

Definitions of terms

Terms were defined as follows.

1. **Live birth:** the complete expulsion or extraction from a woman of a product of fertilisation after 22 completed weeks' gestation, 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 birth weight of 500 grams or more can be used if gestational age is unknown. 'Live birth' refers to the individual newborn, for example, a twin delivery represents two live births (Zegers-Hochschild 2017).
   a. **Ongoing pregnancy** is defined as evidence of a gestational sac with foetal heart motion at 12 weeks, confirmed by ultrasound.
2. **Clinical pregnancy:** a pregnancy diagnosed by ultrasonographic visualisation of one or more gestational sacs or definitive clinical signs of pregnancy. In addition to intrauterine pregnancy, this includes a clinically documented ectopic pregnancy (Zegers-Hochschild 2017).
3. **Thickened endometrium:** an endometrium that measures 8 mm or greater, as determined by ultrasound scan.
4. **Multiple gestation or birth:** a pregnancy that involves more than one embryo or fetus (Zegers-Hochschild 2017).
5. **Spontaneous abortion or miscarriage:** the spontaneous loss of an intrauterine pregnancy before 22 completed weeks' gestation (Zegers-Hochschild 2017).
6. **Ectopic pregnancy:** a pregnancy outside the uterine cavity diagnosed by ultrasound, surgical visualisation, or histopathology (Zegers-Hochschild 2017).

Search methods for identification of studies

We searched for all published and unpublished RCTs of vasodilators in fertility treatment, without language restriction and in consultation with the Cochrane Gynaecology and Fertility Group (CGFG) Information Specialist.

Electronic searches

For this update, we searched the following databases, trial registers, and websites in October 2017.

1. Cochrane Gynaecology and Fertility Group (CGFG) Specialised Register of Controlled Trials; PROCITE platform (searched 24 October 2017) (Appendix 1).
2. Cochrane Central Register of Controlled Trials, via the Cochrane Register of Studies Online (CRSO Web platform) (searched 24 October 2017) (Appendix 2).
3. MEDLINE: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid (searched from 1946 to 24 October 2017) (Appendix 3).
4. Embase: Ovid (searched from 1980 to 24 October 2017) (Appendix 4).
5. PsycINFO: Ovid (searched from 1806 to 24 October 2017) (Appendix 5).
6. Cumulative Index to Nursing and Allied Health Literature (CINAHL) EBSCO platform (searched from 1982 to 24 October 2017) (Appendix 6).
7. Other electronic sources of trials, including:
   a. clinical trial registries for ongoing and registered trials, including:
      i. http://www.clinicaltrials.gov (a service of the US National Institutes of Health); and
      ii. http://www.who.int/trialsearch/Default.aspx (World Health Organization International Trials Registry Platform search portal).
8. Latin American Caribbean Health Sciences Literature (LILACS) and other Spanish/Portuguese language databases (searched 24 October 2017), including:
   a. those found in the Virtual Health Library Regional Portal (VHL), at http://bvsalud.org/portal/?lang=en .
9. The Cochrane Library, at http://www.cochrane.org/index.htm.
10. Conference abstracts in the Web of Knowledge, at http://wokinfo.com/.
11. OpenSigle for Grey Literature from Europe, at http://opensigle.inist.fr/.
12. PubMed and Google Scholar (for recent trials not yet indexed in the major databases).

Searching other resources

We reviewed the reference lists of articles retrieved by the aforementioned search. We contacted experts in the field to request 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, 2012, and 2015, and we checked the references of relevant identified systematic reviews.

Data collection and analysis

Selection of studies

We performed the pertinent statistical analysis in accordance with the guidelines for statistical analysis developed by Cochrane. Review authors (RG or DG and MJM or AV) independently examined titles and abstracts retrieved through the search and determined whether studies met review inclusion criteria. For studies with potential or unclear eligibility, we obtained the full text of the article for independent assessment. If needed, we contacted study investigators to clarify study eligibility. We resolved disagreements by discussion and consensus with a third review author (DG or XB). We documented the selection process in 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.

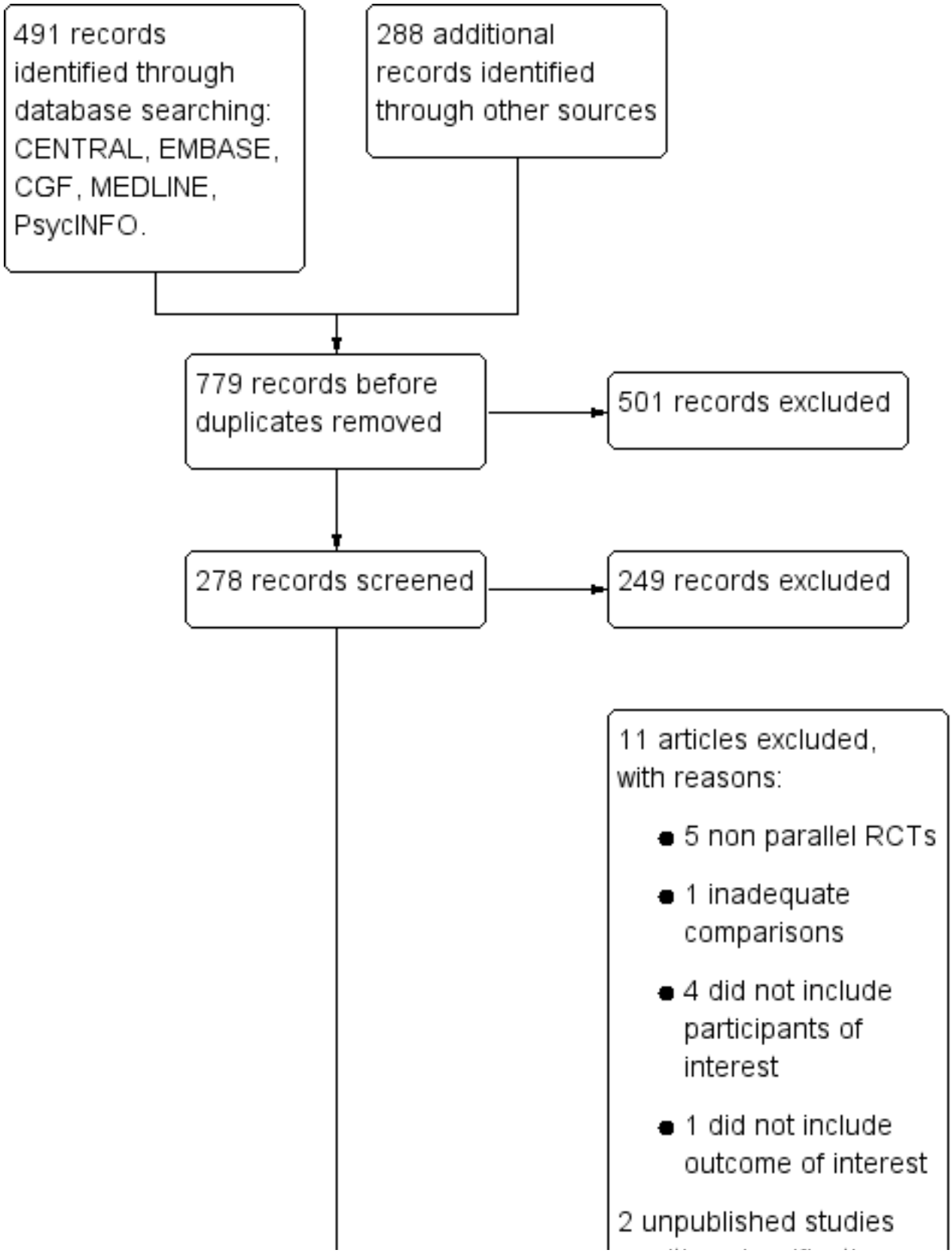
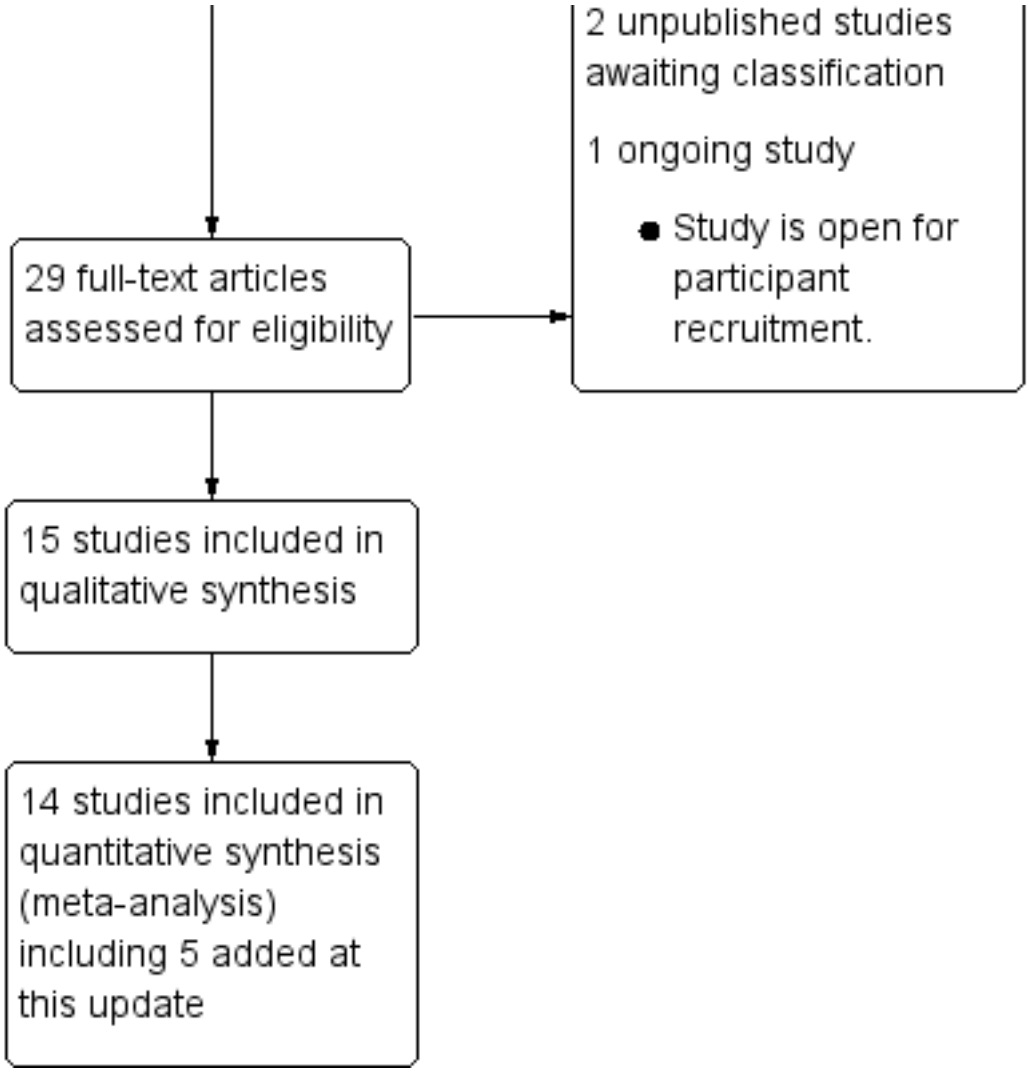


Figure 1. (Continued)



Data extraction and management

Review authors (RG or FR and MJM or AV) independently extracted data from eligible studies using a data extraction form designed and pilot-tested by the review authors. We resolved disagreements by discussion and consensus with a third review author (DG or XB). Data extracted included study characteristics, methods, and outcome data. When a study had multiple publications, we used the main trial report for reference purposes and derived additional details from secondary papers. We contacted the original study authors if we needed further information. For multi-arm studies, we excluded data from arms that did not meet review eligibility criteria.

Assessment of risk of bias in included studies

Review authors (RG or FR and MJM or AV) independently assessed the included studies for risk of bias using Cochrane's 'Risk of bias' assessment tool (Higgins 2011). We assessed allocation (random sequence generation and allocation concealment), blinding of participants and personnel, incomplete outcome data, selective reporting, and other biases. We resolved disagreements 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 we incorporated into our interpretation of review findings by performing 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 births but did report interim outcomes such as pregnancy, we undertook an informal assessment to determine whether interim values (e.g. clinical pregnancy) were similar to those reported in studies that also reported live births.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

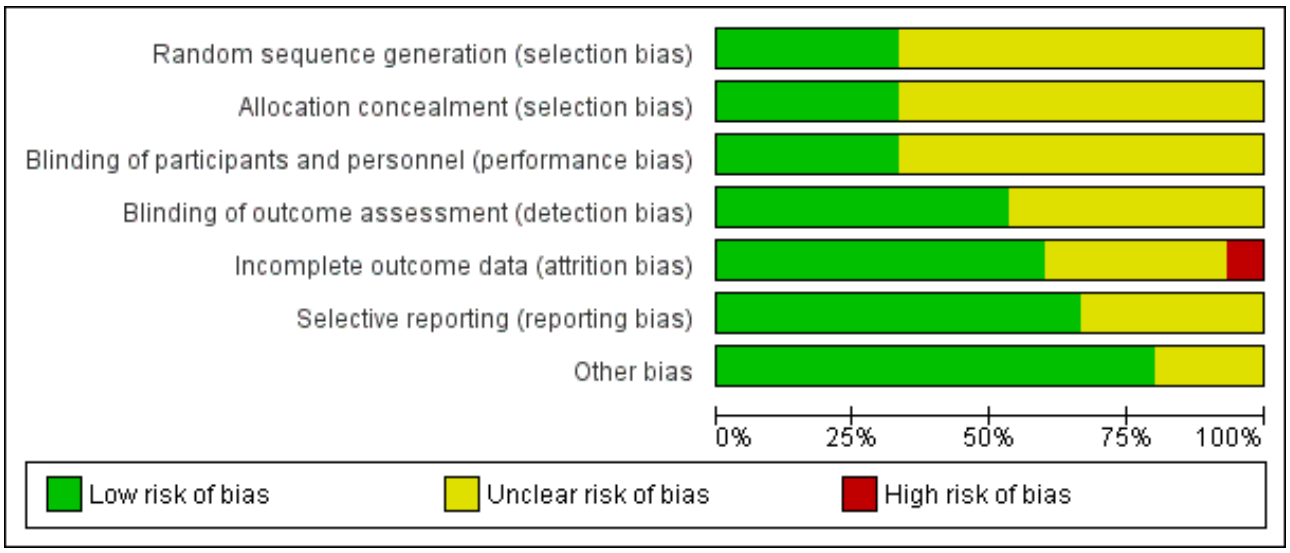


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

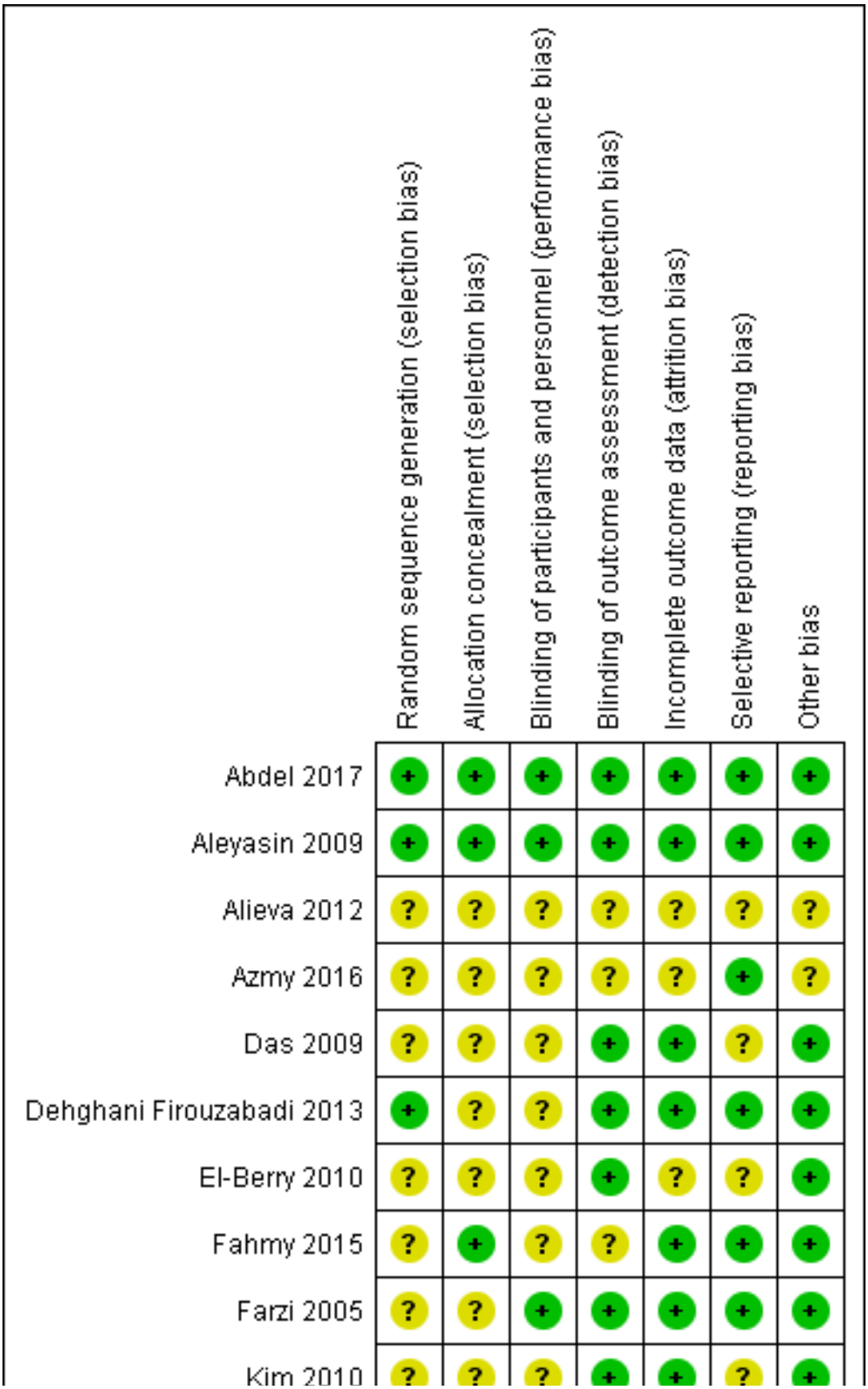
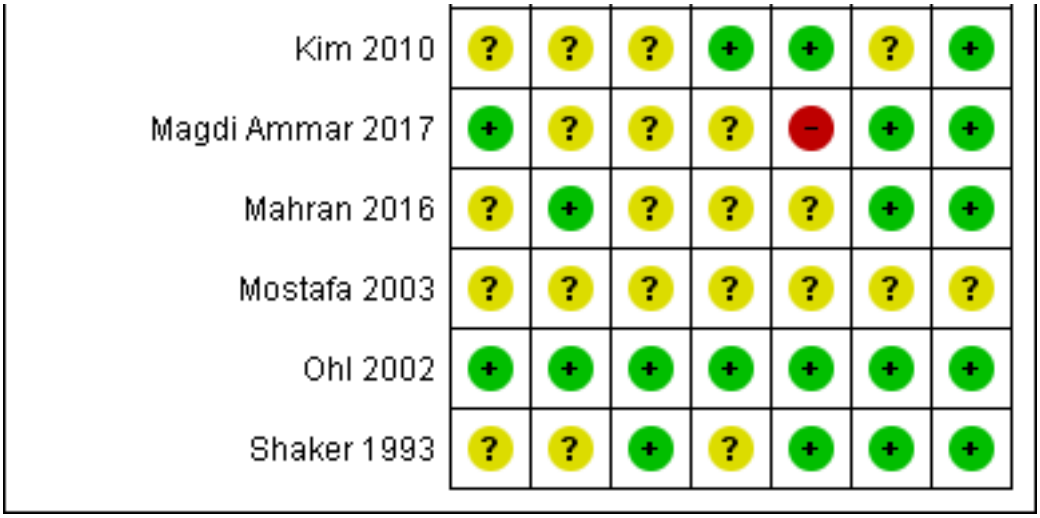


Figure 3. (Continued)



Measures of treatment effect

For dichotomous data (e.g. live births), we calculated risk ratios (RRs) using the numbers of events in 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 could be used to complete similar analyses (e.g. test statistics, 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. For continuous data, we calculated the mean difference (MD) with 95% CI.

Unit of analysis issues

We conducted all analyses per woman randomly assigned. When data did not allow valid analyses (e.g. "per cycle" data), we contacted study authors 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. We counted multiple live births (e.g. twins, triplets) as a single live birth event.

Dealing with missing data

We analysed data on an intention-to-treat basis. We attempted to obtain missing data from the original researchers. We asked trial authors via email or telephone to provide further details. We planned to impute individual values for missing data for any of the primary outcomes, but no study with data for primary outcomes presented important attrition bias.

Assessment of heterogeneity

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

Assessment of reporting biases

If all eligible studies were 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 more studies had been included in an analysis, we would have used a funnel plot to explore the possibility of small-study effects (i.e. the tendency for estimates of the intervention effect to be more beneficial in smaller studies).

Data synthesis

When we judged studies to be sufficiently similar, we combined data using a fixed-effect model for the following comparisons.

1. Vasodilator (with or without an additional intervention) versus placebo or no treatment.
   a. Glyceryl trinitrate (GTN).
   b. Isosorbide mononitrate (ISMN or IMN).
   c. Sildenafil.
   d. Amlodipine.
   e. Tadalafil.
   f. Pentoxifylline (PTX) and vitamin E.
   g. Sildenafil and oestradiol.
2. Vasodilator (with or without an additional intervention) versus active intervention.
   a. Stratified by type of vasodilator.

Subgroup analysis and investigation of heterogeneity

If data had been available, we would have conducted subgroup analyses to examine separate evidence within the following subgroups.

1. Studies in women with thin endometrium (< 8 mm) undergoing fertility treatment.
2. Studies in women with normal endometrial thickness undergoing fertility treatment.
3. Studies including different routes of administration.
4. Studies with and without co-interventions.

We also performed a post hoc subgroup analysis to evaluate studies that used only vasodilators versus no co-intervention (vitamin E, oestrogen).

Sensitivity analysis

We conducted sensitivity analyses for the primary outcomes to determine whether conclusions were robust enough to withstand arbitrary decisions regarding eligibility and analysis of included studies.

These analyses required consideration of whether the review conclusions would have differed if we had adopted a random-effects model.

Overall quality of the body of evidence - 'Summary of findings' table

We prepared a 'Summary of findings' table using GRADEpro and Cochrane methods (GRADEpro GDT 2014; Higgins 2011). This table presents overall quality of the body of evidence for the review outcomes live birth or ongoing pregnancy, vasodilator side effects, clinical pregnancy, thickened endometrium, multiple gestation, spontaneous miscarriage, and ectopic pregnancy for the main review comparison (vasodilator vs placebo or no treatment). We assessed the quality of evidence using GRADE criteria: risk of bias, consistency of effect, imprecision, indirectness, and publication bias. Two review authors (MJM and AV) working independently judged evidence quality (high, moderate, low, or very low) and resolved disagreements by discussion. We justified, documented, and incorporated judgements into reporting of results for each outcome.

RESULTS

Description of studies

Results of the search

Through the search, we retrieved 779 articles. A total of 29 studies were potentially eligible, and we retrieved those full texts. Fifteen studies met the inclusion criteria of this review (Abdel 2017; Aleyasin 2009; Alieva 2012; Azmy 2016; Das 2009; Dehghani Firouzabadi 2013; El-Berry 2010; Fahmy 2015; Farzi 2005; Kim 2010; Magdi Ammar 2017; Mahran 2016; Mostafa 2003; Ohl 2002; Shaker 1993). We excluded 11 studies (Alborzi 2007; Ataalla 2016; Balasch 1997; Check 2004; Creus 2008; Kamencic 2008; Malinova 2013; Raine-Fenning 2009; Rosen 1987; Sher 2000; Shin 2002); two studies are awaiting classification (Casper 2013; Penzias 2012); and one study is ongoing (NCT02072291).

For further information, see the following tables: Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification; and Characteristics of ongoing studies.

See Figure 1 (PRISMA study screening and selection flow chart) for details of this process.

Included studies

Study design and setting

We included in this review 15 randomised controlled trials (RCTs) with a parallel design (Abdel 2017; Aleyasin 2009; Alieva 2012; Azmy 2016; Das 2009; Dehghani Firouzabadi 2013; El-Berry 2010; Fahmy 2015; Farzi 2005; Kim 2010; Magdi Ammar 2017; Mahran 2016; Mostafa 2003; Ohl 2002; Shaker 1993). Publication dates for the included studies ranged from 1993 to 2017. Most studies were conducted at hospital clinics for infertility.

Participants

We included in this review 15 studies with a total of 1326 women.

The studies included 690 women in the intervention groups and 636 in the control groups. Mean participant age was 31.50 (± 4.92) years. 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; Dehghani Firouzabadi 2013; Kim 2010; Ohl 2002). Eleven 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), or women with unexplained infertility, or women with infertility and with regular menstrual cycles, or women who had received a diagnosis of polycystic ovarian syndrome) (Abdel 2017; Aleyasin 2009; Alieva 2012; Azmy 2016; El-Berry 2010; Fahmy 2015; Farzi 2005; Magdi Ammar 2017; Mahran 2016; Mostafa 2003; Shaker 1993). Eight of the 15 studies were performed in women undergoing ART (Aleyasin 2009; Alieva 2012; Dehghani Firouzabadi 2013; Farzi 2005; Kim 2010; Mostafa 2003; Ohl 2002; Shaker 1993), one was performed in women undergoing artificial insemination (Das 2009), and six involved ovulation induction (Abdel 2017; Azmy 2016; El-Berry 2010; Fahmy 2015; Magdi Ammar 2017; Mahran 2016).

Interventions

Vasodilators used in these studies included pentoxifylline 400 mg twice daily + tocopherol vitamin E 400 mg twice daily 2 cycles before starting ZIFT cycle until the β-hCG became positive or the cycle was cancelled (Aleyasin 2009); nitric oxide donors (isosorbide mononitrate (ISMN)) 20 mg vaginally until diagnosis of ovulation and pregnancy (El-Berry 2010); isosorbide mononitrate (IMN) 10 mg vaginal tablets from cycle day 5 to 9 (Abdel 2017); 10 mg isosorbide mononitrate (ISMN) tablets applied vaginally from day 2 to day 15 of the cycle or 20 mg ISMN tablets applied vaginally from day 2 to day 15 of the cycle (Mahran 2016); glyceryl trinitrate (GTN) 0.4 mg oral dose 15 minutes before fresh ET (Farzi 2005); sildenafil citrate tablets (50 mg) daily (from first day of cycle until day progesterone was started) (Dehghani Firouzabadi 2013); sildenafil 25 mg vaginally 4 times a day from day 5 of cycle until day of hCG administration (Das 2009); sildenafil citrate 25 mg orally 3 times/d from seventh to 11th day of cycle (Fahmy 2015); amlodipine (Azmy 2016); tadalafil oral 5 mg/d for 7 days (from fourth day until 10th day of the cycle) (Magdi Ammar 2017); vaginal sildenafil 25 mg/d + oral oestradiol valerate 4 mg/d from day of embryo transfer until pregnancy test (11 days) (Kim 2010); 5 mg glyceryl trinitrate (GTN) patch applied once daily, beginning the morning of the day before transfer, just after transvaginal ultrasonography and colour doppler were performed (Ohl 2002); 2 sublingual spray emissions of GTN 400 µg/spray (Shaker 1993); sildenafil citrate in the IVF cycle (Alieva 2012); and glyceryl trinitrate skin patches 5 mg daily for 2 weeks (Mostafa 2003).

1. Thirteen of 15 studies compared vasodilator alone versus placebo or no treatment (Abdel 2017; Alieva 2012; Azmy 2016; Das 2009; Dehghani Firouzabadi 2013; El-Berry 2010; Fahmy 2015; Farzi 2005; Magdi Ammar 2017; Mahran 2016; Mostafa 2003; Ohl 2002; Shaker 1993).

2. Two of 15 studies compared vasodilator plus another agent versus placebo or no treatment (Aleyasin 2009; Kim 2010).

Outcomes

Researchers reported the following outcomes.

1. Three of 15 studies reported live births (Aleyasin 2009; Farzi 2005; Ohl 2002).
2. Four of 15 studies reported side effects (Fahmy 2015; Mahran 2016; Ohl 2002; Shaker 1993).
3. Eight of 15 studies reported clinical pregnancy (Aleyasin 2009; Dehghani Firouzabadi 2013; Fahmy 2015; Farzi 2005; Kim 2010; Magdi Ammar 2017; Mostafa 2003; Ohl 2002). However, four studies reported biochemical pregnancy (Abdel 2017; Das 2009; El-Berry 2010; Mahran 2016), and three studies did not report the method used to diagnose pregnancy (Alieva 2012; Azmy 2016; Shaker 1993). We did not include in analyses studies reporting biochemical pregnancy.
4. Four of 15 studies reported other adverse events (Aleyasin 2009; Alieva 2012; Farzi 2005; Ohl 2002). In one study, reproductive loss in the control group looks unusually high (20%), but the adverse event was not defined (Alieva 2012).

No study provided data on the number of participants with thickened endometrium. Only two studies mentioned that all women had a thin endometrium before treatment (Das 2009; Kim 2010). However, five studies reported a mean difference in thickened endometrium (Abdel 2017; Azmy 2016; Das 2009; Magdi Ammar 2017; Mahran 2016).

Excluded studies

We excluded 11 studies from the review for the following reasons.

1. Five of 11 studies were not parallel RCTs (Ataalla 2016; Check 2004; Raine-Fenning 2009; Sher 2000; Shin 2002).
2. Four of 11 studies did not include participants of interest for this review (Alborzi 2007; Balasch 1997; Creus 2008; Kamencic 2008).
3. One of 11 studies did not include comparisons of interest for this review (Rosen 1987).
4. One of 11 studies did not include outcomes of interest for this review (Malinova 2013).

In addition, two studies are awaiting classification (Casper 2013; Penzias 2012), and one study is ongoing (NCT02072291).

Risk of bias in included studies

In Figure 2 and Figure 3, we have shown and summarised the judgements of review authors regarding each risk of bias item for each included study.

Allocation

Random sequence generation

Five studies had low risk of selection bias related to sequence generation (Abdel 2017; Aleyasin 2009; Dehghani Firouzabadi 2013; Magdi Ammar 2017; Ohl 2002). The other 10 studies did not describe the method of randomisation, and we ranked them as having unclear risk of bias (Alieva 2012; Azmy 2016; Das 2009; El-Berry 2010; Fahmy 2015; Farzi 2005; Kim 2010; Mahran 2016; Mostafa 2003; Shaker 1993).

Allocation concealment

Five studies had low risk of bias related to allocation concealment (Abdel 2017; Aleyasin 2009; Fahmy 2015; Mahran 2016; Ohl 2002). The other 10 studies did not describe the method used to conceal the sequence, and we ranked them as having unclear risk of bias (Alieva 2012; Azmy 2016; Das 2009; Dehghani Firouzabadi 2013; El-Berry 2010; Farzi 2005; Kim 2010; Magdi Ammar 2017; Mostafa 2003; Shaker 1993).

Blinding

Five of 15 studies had low risk of performance bias (Abdel 2017; Aleyasin 2009; Farzi 2005; Ohl 2002; Shaker 1993). Four of these were double-blind and used placebo as a control (Abdel 2017; Farzi 2005; Ohl 2002; Shaker 1993), and one was single-blind (surgeons who conducted the operations were blinded) (Aleyasin 2009). Three studies did not provide a description of blinding (Alieva 2012; Magdi Ammar 2017; Mostafa 2003).

Eight of 15 studies had low risk of detection bias (Abdel 2017; Aleyasin 2009; Das 2009; Dehghani Firouzabadi 2013; El-Berry 2010; Farzi 2005; Kim 2010; Ohl 2002). Seven of 15 studies did not mention blinding, and we judged them as having unclear risk of detection bias (Alieva 2012; Azmy 2016; Fahmy 2015; Magdi Ammar 2017; Mahran 2016; Mostafa 2003; Shaker 1993). 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

Nine of 15 studies analysed all or most (> 95%) of the women randomly assigned and had low risk of attrition bias (Abdel 2017; Aleyasin 2009; Das 2009; Dehghani Firouzabadi 2013; Fahmy 2015; Farzi 2005; Kim 2010; Ohl 2002; Shaker 1993). Only one study used the number of cycles instead of the number of participants in analysis (El-Berry 2010), and four studies did not describe attrition (Alieva 2012; Azmy 2016; Mahran 2016; Mostafa 2003). These studies had unclear risk of attrition bias. One of 15 studies was at high risk of attrition bias (Magdi Ammar 2017).

Selective reporting

Ten of 15 studies reported outcomes that were clearly prespecified in the methods section, and we classified them as having low risk of selective reporting bias (Abdel 2017; Aleyasin 2009; Azmy 2016; Dehghani Firouzabadi 2013; Fahmy 2015; Farzi 2005; Kim 2010; Magdi Ammar 2017; Ohl 2002; Shaker 1993). Four of these studies reported primary outcomes (Aleyasin 2009; Farzi 2005; Ohl 2002; Shaker 1993): three studies reported live birth (Aleyasin 2009; Farzi 2005; Ohl 2002), and four reported adverse effects (Fahmy 2015; Mahran 2016; Ohl 2002; Shaker 1993). However, the protocol was available for only one study (Dehghani Firouzabadi 2013).

Other potential sources of bias

Twelve of 15 studies reported baseline balance between groups in terms of age and duration of infertility (Abdel 2017; Aleyasin 2009; Das 2009; Dehghani Firouzabadi 2013; El-Berry 2010; Fahmy 2015; Farzi 2005; Kim 2010; Magdi Ammar 2017; Mahran 2016; Ohl 2002; Shaker 1993). In addition, four studies reported baseline comparability regarding type of infertility, cause of infertility, and body mass index. We classified these studies as having low risk of bias. We identified no other potential sources of bias. However,

three studies did not report baseline features, and we judged them to have unclear risk of detection bias (Alieva 2012; Azmy 2016; Mostafa 2003).

Effects of interventions

See: **Summary of findings for the main comparison** Vasodilator compared to placebo or no treatment for women undergoing fertility treatment

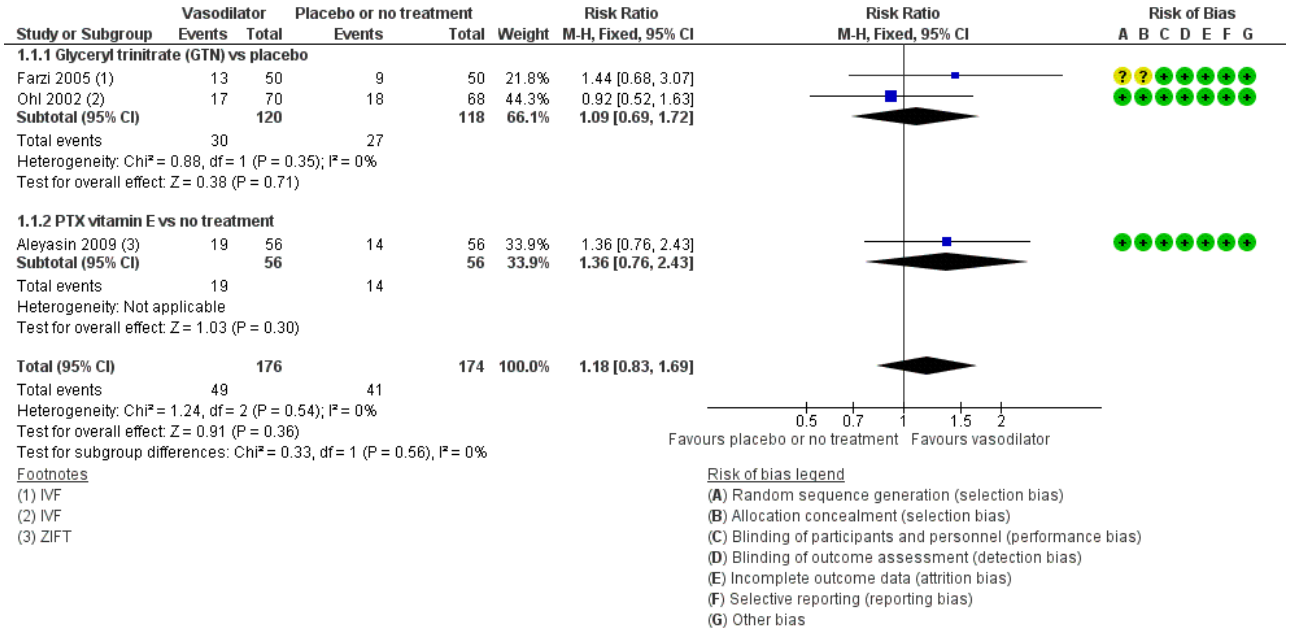
1. Vasodilator (with or without an additional intervention) versus placebo or no treatment

Primary outcomes

1.1. Live birth or ongoing pregnancy

(Analysis 1.1; Figure 4)

Figure 4. Forest plot of comparison: 1 Vasodilator vs placebo or no treatment, outcome: 1.1 Live birth.



Three studies reported this outcome. All reported live births.

1. Comparison of glyceryl trinitrate (GTN) versus placebo (Farzi 2005; Ohl 2002).
2. Comparison of pentoxifylline + tocopherol vitamin E versus no treatment (Aleyasin 2009).

Vasodilators (given alone or with another agent) probably make little or no difference in rates of "live birth or ongoing pregnancy" compared with placebo or no treatment (RR 1.18, 95% CI 0.83 to 1.69; three RCTs; N = 350; I^2 = 0%; moderate-quality evidence; Analysis 1.1; Figure 4; Summary of findings for the main comparison). Limiting the analysis to studies of vasodilators given without a co-intervention did not substantially change the main finding (RR 1.09, 95% CI 0.69 to 1.72; two RCTs; N = 238; I^2 = 0%; moderate-quality evidence).

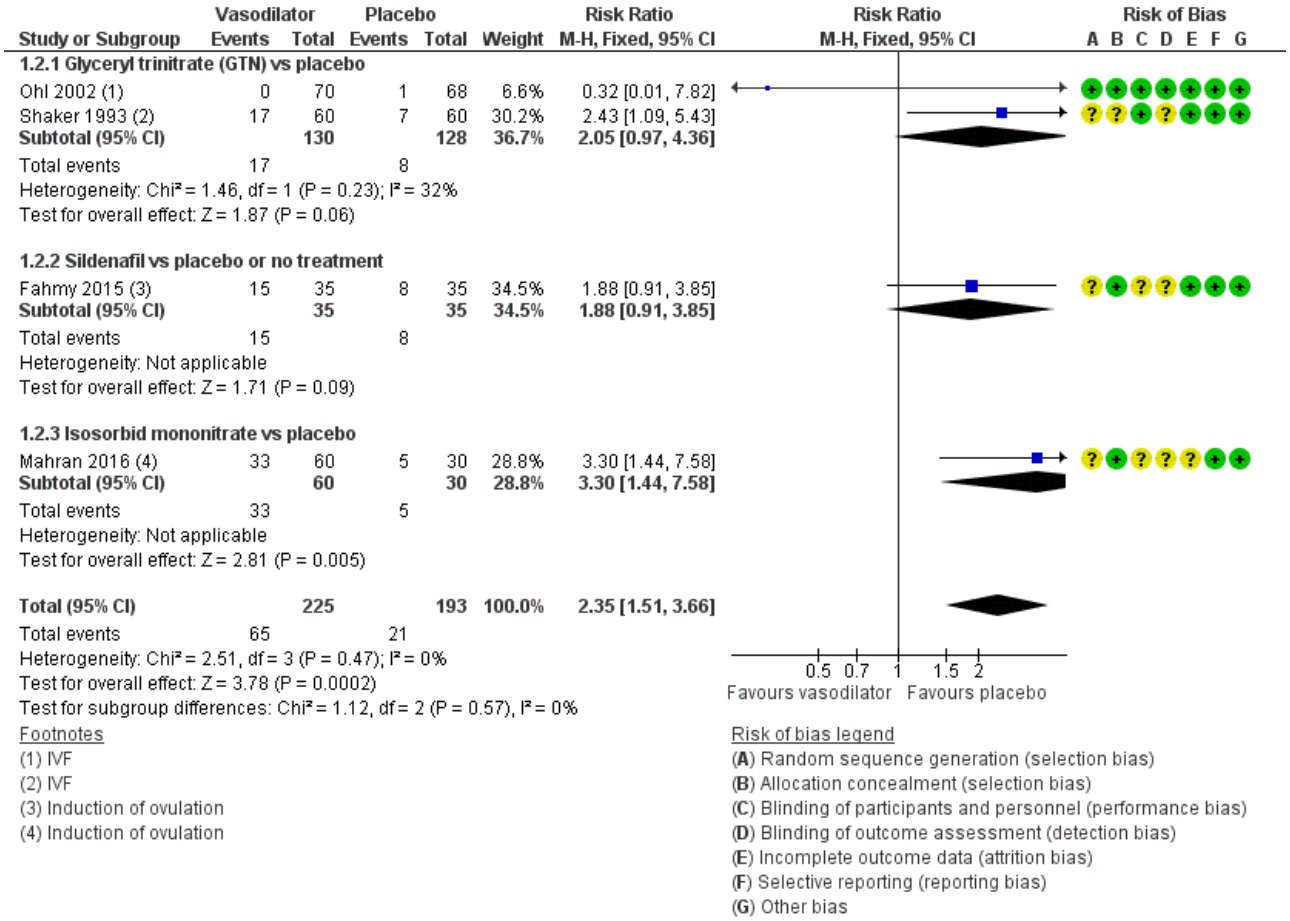
We stratified the analysis by type of vasodilator. The test for subgroup differences shows no evidence of differences between subgroups for this outcome (Chi^2 = 0.33, df = 1 (P = 0.56), I^2 = 0%).

Sensitivity analyses based on a random-effects model did not change the evidence (RR 1.18, 95% CI 0.83 to 1.69; three RCTs; N = 350; I^2 = 0%; moderate-quality evidence).

1.2. Vasodilator side effects

(Analysis 1.2: Figure 5)

Figure 5. Forest plot of comparison: 1 Vasodilator vs placebo or no treatment, outcome: 1.2 Vasodilator side effects.



Four studies reported the number of vasodilator side effects by group. Two assessed glyceryl trinitrate (GTN) versus placebo (Ohl 2002; Shaker 1993), one sildenafil versus placebo (Fahmy 2015), and another isosorbide mononitrate (ISMN) versus no treatment (Mahran 2016).

The vasodilator group most commonly reported the following adverse events (AEs): hypotension, headache, tachycardia, dizziness, hot flushes, nervousness, insomnia, constipation, and a feeling of weakness.

Vasodilators (alone or with another agent) probably increase side effects compared with placebo or no treatment (RR 2.35, 95% CI 1.51 to 3.66; four RCTs; N = 418; I^2 = 0%; moderate-quality evidence).

We stratified the analysis by type of vasodilator. The test for subgroup differences shows no evidence of differences between subgroups for this outcome (Chi^2 = 1.12, df = 2 (P = 0.57), I^2 = 0%).

1.3. Specific vasodilator side effects

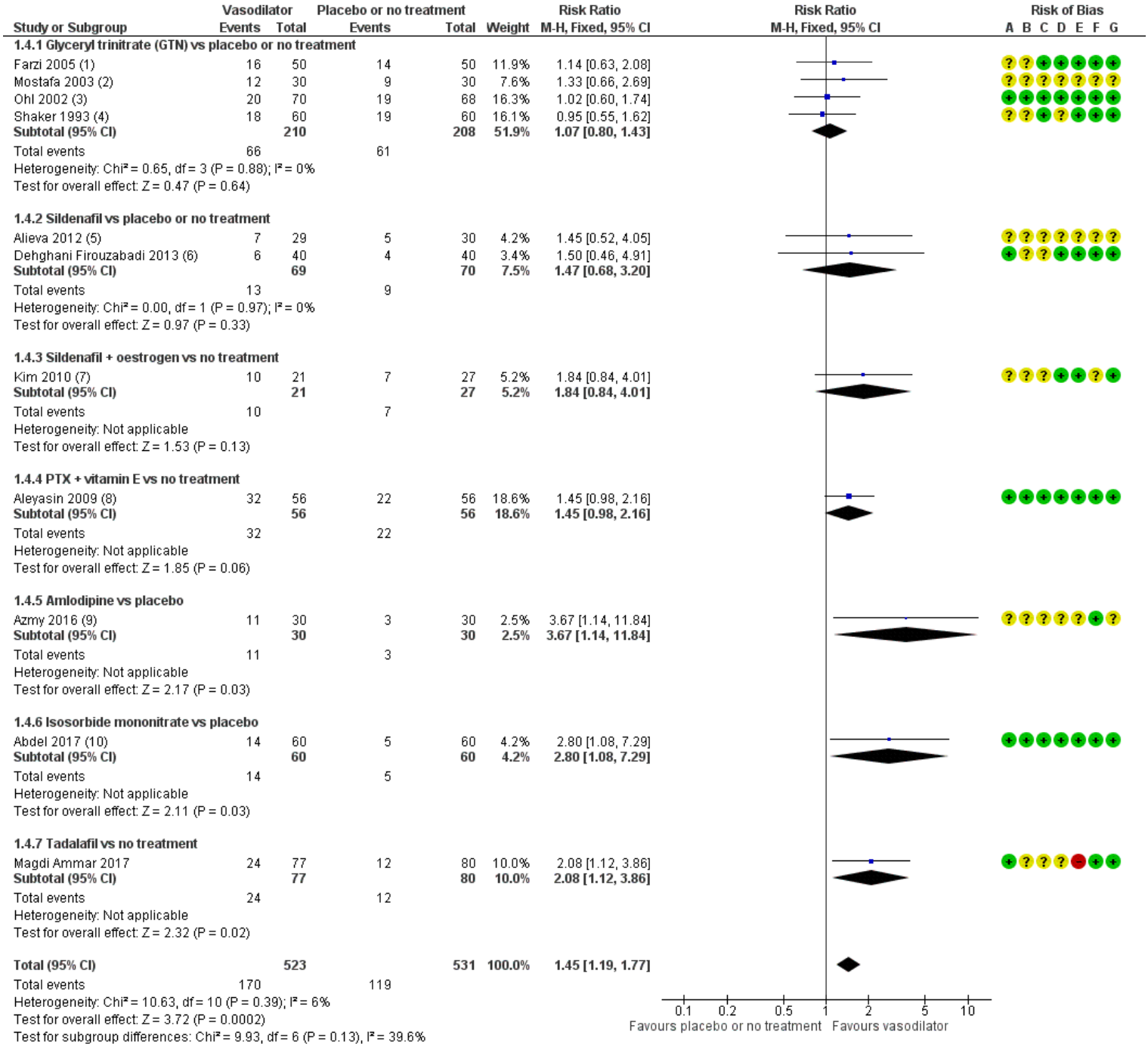
Two studies reported specific vasodilator side effects. One compared sildenafil versus placebo (Fahmy 2015), and another isosorbide mononitrate (ISMN) versus no treatment (Mahran 2016). Vasodilators may increase headache (RR 4.12, 95% CI 1.87 to 9.06; two RCTs; N = 160; I^2 = 7%; low-quality evidence) and tachycardia (RR 3.83, 95% CI 1.25 to 11.75; one RCT; N = 90; low-quality evidence). Evidence was insufficient to show whether groups had differences in hypotension (RR 1.11, 95% CI 0.58 to 2.14; one RCT; N = 90; low-quality evidence), dizziness (RR 1.57, 95% CI 0.76 to 3.26; one RCT; N = 90; low-quality evidence), or hot flushes (RR 2.40, 95% CI 0.96 to 5.99; two RCTs; N = 160; I^2 = 7%; low-quality evidence).

Secondary outcomes

1.4. Clinical pregnancy

(Analysis 1.4; Figure 6)

Figure 6. Forest plot of comparison: 1 Vasodilator vs placebo or no treatment, outcome: 1.4 Clinical pregnancy.



Footnotes
(1) IVF
(2) ICSI
(3) IVF
(4) IVF; method of establishing pregnancy not described
(5) IVF; method of establishing pregnancy not described
(6) IVF
(7) IVF
(8) ZIFT
(9) Induction of ovulation
(10) Intrauterune insemination

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Fifteen studies reported clinical pregnancy. However, four studies reported biochemical pregnancy, and we did not include them in the analysis (Das 2009; El-Berry 2010; Fahmy 2015; Mahran 2016). Two studies did not report the method used to diagnose pregnancy (Alieva 2012; Shaker 1993). We included them in the analyses and noted this limitation in the footnotes. We analysed 11 studies (Abdel 2017; Aleyasin 2009; Alieva 2012; Azmy 2016; Dehghani Firouzabadi 2013; Farzi 2005; Kim 2010; Magdi Ammar 2017; Mostafa 2003; Ohl 2002; Shaker 1993).

1. Farzi 2005,Mostafa 2003,Ohl 2002, and Shaker 1993 compared glyceryl trinitrate (GTN) versus placebo or no treatment.
2. Alieva 2012 and Dehghani Firouzabadi 2013 compared sildenafil versus no treatment or placebo.
3. Kim 2010 compared sildenafil plus oestrogen versus no treatment.
4. Aleyasin 2009 compared pentoxifylline (PTX) + tocopherol vitamin E versus no treatment.
5. Abdel 2017 compared isosorbide mononitrate (IMN or ISMN) versus placebo or no treatment.
6. Azmy 2016 compared amlodipine versus placebo.
7. Magdi Ammar 2017 compared tadalafil versus placebo.

Vasodilators (alone or with another agent) may slightly improve clinical pregnancy compared with placebo or no treatment (RR 1.45, 95% CI 1.19 to 1.77; 11 RCTs; N = 1054; I^2 = 6%; low-quality evidence; Analysis 1.4; Figure 6; Summary of findings for the main comparison). Limiting the analysis to studies of vasodilators without a co-intervention (vitamin E, oestrogen) did not substantially change the main findings (RR 1.43, 95% CI 1.13 to 2.20; 11 RCTs; N = 1054; I^2 = 21%; moderate-quality evidence).

We stratified the analysis by type of vasodilator. The test for subgroup differences did not clearly suggest any differences between subgroups for this outcome (Chi^2 = 9.93, df = 6 (P = 0.13), I^2 = 39%).

1.5. Thickened endometrium

Five studies reported thickened endometrium. Two assessed isosorbide mononitrate (IMN or ISMN) (Abdel 2017; Mahran 2016), one amlodipine (Azmy 2016), one sildenafil (Das 2009), and one tadalafil (Magdi Ammar 2017); researchers compared these agents versus placebo or no treatment. The effects shown in each study varied (I^2 = 92%) and ranged from a mean difference of 0.80 higher (95% CI 0.18 to 1.42) to 3.57 higher (95% CI 3.01 to 4.13). We are uncertain whether vasodilators improved thickened endometrium, as we have assessed the quality of the evidence as very low. We downgraded the quality of evidence because of high risk of bias and inconsistency (Analysis 1.5; Summary of findings for the main comparison).

1.6. Other adverse events

1.6.1. Multiple gestation or birth

Three studies reported this outcome.

1. Ohl 2002 compared glyceryl trinitrate (GTN) versus placebo.
2. Aleyasin 2009 compared pentoxifylline + tocopherol vitamin E versus no treatment.
3. Abdel 2017 compared isosorbide mononitrate (IMN) versus placebo.

Vasodilators probably make little or no difference in rates of multiple gestation or birth compared with placebo or no treatment (RR 1.15, 95% CI 0.55 to 2.42; three RCTs; N = 370; I^2 = 0%; moderate-quality evidence) (Analysis 1.6; Summary of findings for the main comparison).

1.6.2. Spontaneous miscarriage

Four studies reported this outcome.

1. Farzi 2005 and Ohl 2002 compared glyceryl trinitrate (GTN) versus placebo.
2. Aleyasin 2009 compared pentoxifylline + tocopherol vitamin E versus no treatment.
3. Alieva 2012 compared sildenafil versus no treatment.

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). Vasodilators probably make little or no difference in spontaneous abortion/miscarriage rates compared with placebo or no treatment (RR 0.83, 95% CI 0.37 to 1.86; three RCTs; N = 350; I^2 = 0%; moderate-quality evidence).

1.6.3. Ectopic pregnancy

Two studies reported this outcome.

1. Ohl 2002 compared glyceryl trinitrate (GTN) versus placebo.
2. Aleyasin 2009 compared pentoxifylline + tocopherol vitamin E versus no treatment.

Vasodilators probably make little or no difference in ectopic pregnancy rates compared with placebo or no treatment (RR 1.48, 95% CI 0.25 to 8.69; two RCTs; N = 250; I^2 = 5%; moderate-quality evidence; Analysis 1.6; Summary of findings for the main comparison).

Subgroup analyses

We did not conduct some analyses initially proposed as stratified because we found no suitable studies.

As none of the included studies provided data on the number of women with endometrium measured as greater or less than 8 mm, we could not perform planned subgroup analyses. Only two studies mentioned that all women had a thin endometrium before interventions were provided (Das 2009; Kim 2010).

Sensitivity analysis

Results of analysis did not change substantially when we excluded studies of vasodilators combined with another drug (vitamin E, oestrogen), or when we applied a random-effects model.

DISCUSSION

Summary of main results

Results of this systematic review suggest that moderate-quality evidence is insufficient to show that vasodilators improve the live birth rate among women undergoing fertility treatment. However, treatment with vasodilators was associated with an increased overall rate of side effects compared with placebo or no treatment. Analysis of specific side effects revealed that headache and tachycardia were increased.

Low-quality evidence suggests that vasodilators alone or in combination with other treatments (vitamin E, oestradiol) increased clinical pregnancy rates compared with placebo or no treatment. When we excluded studies of vasodilators combined with other medications, we noted that vasodilators alone had similar effects on clinical pregnancy rates.

Last, we found no clear evidence to suggest differences between groups for other adverse effects such as multiple gestation or birth, spontaneous abortion/miscarriage, and ectopic pregnancy; few relevant data were available.

Overall completeness and applicability of evidence

All studies reported pregnancy as an outcome. However, for women and for clinicians, live birth rate and side effects are the most important outcomes of fertility treatment. As only three studies and four studies reported these outcomes, respectively, this review might not address the main concerns surrounding fertility treatment. This, in turn, serves as evidence that more studies are needed to assess these important outcomes. No studies compared active interventions.

Age restrictions for women specified in the inclusion and exclusion criteria of studies were similar across 11 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), and other 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)). Even though we found no evidence of statistical heterogeneity in main outcomes among trials, we could not rule out the effects of clinical heterogeneity on study results.

All studies compared the intervention versus placebo or no treatment, so a limitation of this review is that we found no head-to-head studies comparing two different vasodilators.

Quality of the evidence

Overall, the quality of evidence was low to moderate for most comparisons. The main limitations were imprecision due to low numbers of events and participants, and risk of bias due to unclear methods of randomisation and concealment of allocation, blinding, incomplete outcome data, and selective reporting. We could not assess risk of publication bias because of the small number of identified studies.

We rated evidence for live birth and vasodilator side effects as moderate quality, with imprecision as the main limitation. Evidence for clinical pregnancy, multiple gestation, miscarriage and ectopic pregnancy, and vasodilator side effects was of low quality, with low precision and unexplained heterogeneity. Evidence for the thickened endometrium was of very low quality, and low precision and high heterogeneity are evident (Summary of findings for the main comparison).

Risk of selection bias was unclear in 10 studies. Concealment of allocation was adequate, and five trials explicitly described this. Five studies 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, lack of blinding did not imply an increase in risk of bias. Nine studies were analysed via intention-to-treat, five studies had unclear risk of attrition bias, and one study had high risk of attrition bias. Risk of selective reporting was unclear in some studies. Live birth rate was reported in a minority of cases, and only four studies reported adverse events as an outcome.

Potential biases in the review process

The process of identifying all potentially eligible studies for inclusion in this review was thorough and meticulous, even yielding three studies published only in abstract form. We contacted the authors of these works, 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, we adhered to methods specified in the protocol, so potential biases could be limited. Also, it was not possible to evaluate potential biases in all studies for lack of data. We considered these studies to have unclear risk of bias. We contacted the authors of these studies, but only two of them replied (Farzi 2005; Kim 2010).

Agreements and disagreements with other studies or reviews

We have not reviewed other reviews in women undergoing assisted fertility treatment with vasodilators. However, we identified relevant studies in women undergoing assisted fertility treatment (Fetih 2017; Sher 2000; Sher 2002; Takasaki 2010). In a self-controlled clinical trial, clinical pregnancy rate increased with sildenafil vaginal gel, but the numbers were small (Fetih 2017). Likewise, one of the most important observational studies was a cohort study examining the effect of vaginal sildenafil on the outcome of in vitro fertilisation after multiple IVF failures attributed to poor endometrial development; this study reported high ongoing pregnancy rates (Sher 2002).

AUTHORS' CONCLUSIONS

Implications for practice

Evidence was insufficient to show whether vasodilators increase the live birth rate in women undergoing fertility treatment. However, low-quality evidence suggests that vasodilators may slightly increase clinical pregnancy rates. Moderate-quality evidence shows that vasodilators increase some side effects, such as headache and tachycardia, in comparison with placebo or no treatment. Adequately powered studies are needed, so that researchers can evaluate each treatment more accurately.

Implications for research

Although this review suggests that vasodilators increase clinical pregnancy rates compared with placebo or no treatment, future 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, we provide the following recommendations.

1. Randomised controlled trials 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 tadalafil or amlodipine or "isosorbide mononitrate" and should include assessment of the optimal route of administration and the optimal dosage.
4. Future research should evaluate relevant outcomes such as live births and side effects.
5. Future research should investigate whether women with a thin endometrium may benefit from medication.
6. Improved descriptions of methods and adherence to CONSORT (Consolidated Standards of Reporting Trials) recommendations are needed for all randomised controlled trials.
7. Future researchers should perform comparisons of one active treatment versus another.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Abdel 2017

Methods	Blinded randomised controlled clinical trial
Participants	**Number of centres:** 1 **Setting:** hospital **Country:** Egypt **Length of follow-up:** not stated (at least 1 cycle) **Number of randomised participants:** 120 (60 per group) **Age (mean and SD):** 28.24 ± 6.82 years in experimental group, 26.80 ± 4.11 years in control group **Inclusion criteria:** housewives and non-smokers; diagnosis of Idiopathic or unexplained infertility due to failure to achieve pregnancy after 12 months of unprotected regular intercourse; investigations revealed (1) normal semen analysis according to WHO reference values, (2) normal regular ovulation with a mid-cycle serum progesterone level of 410 ng/mL, (3) patent fallopian tubes and normal pelvic cavity on ultrasound examination, hysterosalpingography, and hysteroscopy/laparoscopy when indicated **Exclusion criteria:** women given hypertension drug treatment; refusal of intrauterine insemination
Interventions	• **Experimental group:** CC 100 mg daily from cycle day 5 to 9 plus isosorbide mononitrate (IMN) 10 mg vaginal tablets • **Control group:** oral CC 100 mg daily from cycle day 5 to 9 plus placebo vaginal tablets **Length of treatment:** placebo and IMN were given until diagnosis of pregnancy or occurrence of menstruation
Outcomes	**Primaries:** endometrial thickness, uterine artery blood flow indices, endometrial blood flow indices **Secondaries:** pregnancy (diagnosed by serum β-hCG and vaginal ultrasound), twins

Abdel 2017 *(Continued)*

Notes	**Funding:** not reported **Conflict of interest:** study authors declare no conflict of interest **Protocol registry:** ACTRN 12613001124729 **Sample size calculation:** yes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote:** "120 patients were randomly allocated by computer-generated table in 1:1 ratio to a control group (60 cases)"
Allocation concealment (selection bias)	Low risk	**Quote:** "120 patients were randomly allocated by computer-generated table in 1:1 ratio to a control group (60 cases)" **Comment:** "however there is a sentence that makes confusion about allocation concealment" The allocated treatment was put inside a sealed opaque envelope and was chosen by the participant while all investigators were blind.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	**Quote:** "placebo vaginal tablets" and "... all investigators were blind" **Comment:** placebo vaginal tablets were used to blind the interventions
Blinding of outcome assessment (detection bias) All outcomes	Low risk	**Quote:** "... all investigators were blind" **Comment:** placebo vaginal tablets were used to blind the interventions. Study authors report that pregnancy was diagnosed by serum β-hCG and vaginal ultrasound.
Incomplete outcome data (attrition bias) All outcomes	Low risk	**Comment:** no participant dropout was reported. Study authors mention that all participants who were randomised were analysed.
Selective reporting (reporting bias)	Low risk	**Comment:** study authors did report all outcomes that they proposed to measure in the methods
Other bias	Low risk	**Comment:** Table 1 shows no significant differences between groups with regard to participant age, body mass index, duration of infertility, endometrial thickness, uterine artery resistance index and pulsation index and endometrial vascular index, and flow index and vascular flow index

Aleyasin 2009

Methods	Randomised clinical trial; not blinded
Participants	**Number of centres:** 1 **Setting:** Hospital Infertility Department **Country:** Iran

Aleyasin 2009 *(Continued)*

	Length of follow-up: not stated (at least 1 cycle) **Number of randomised participants:** 112 infertile women (56 intervention, 56 control) **Age (mean and SD):** 29.96 ± 4.62 experimental group, 29.41 ± 4.59 control group **Inclusion criteria:** infertile women planned for ZIFT (zygote intrafallopian transfer); younger than 39 years of age without a previous history of ZIFT or IVF failure **Exclusion criteria:** hypothalamic amenorrhoea, drug reactions or complications, endometriosis and fibroids
Interventions	• **Intervention:** pentoxifylline 400 mg twice daily + tocopherol vitamin E 400 mg twice daily 2 cycles before starting ZIFT cycle until the β-hCG became positive or the cycle was cancelled • **Control:** participants did not receive the experimental drugs **Length of treatment:** not reported **Co-interventions:** both groups received gonadotrophin-releasing hormone (GnRH) agonist 500 mg SC started at day 22 of the previous cycle + hMG (human menopausal gonadotrophins) 150 to 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 of 17 mm were observed) + ICSI and ZIFT (laparoscopic). Luteal phase support was started the day of ovum pickup via administration of a progesterone suppository of 800 mg/d and 25 mg progesterone in oil a week later (until foetal heart rate was detected).
Outcomes	**Primary:** clinical pregnancy **Secondaries:** term delivery (equivalent "live birth"), multiple gestation or birth, spontaneous abortion/miscarriage, ectopic pregnancy, preterm labour
Notes	**Funding:** Infertility Department of Shariati Hospital **Conflict of interest:** study authors declare no conflict of interest **Protocol registry:** not reported **Sample size calculation:** not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Comment:** 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.
Allocation concealment (selection bias)	Low risk	**Comment:** 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.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	**Comment:** the intervention was not blinded, but surgeons who performed the operations were blind to participant groups. However, this does not seem to have affected study results.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	**Comment:** 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

Aleyasin 2009 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	**Comment:** no participant dropout was reported (all participants were followed up)
Selective reporting (reporting bias)	Low risk	**Comment:** study protocol not available, but it is clear that published reports include all expected outcomes, including those that were prespecified
Other bias	Low risk	**Comment:** groups were comparable for the variables described (age, duration of infertility, type of infertility, cause of infertility, endometrial thickness, retrieved oocytes, metaphase II oocytes)

Alieva 2012

Methods	Randomised controlled trial
Participants	**Number of centres:** 1 **Setting:** Research Centre for Obstetrics Gynecology and Perinatology **Country:** Russia **Length of follow-up:** not reported **Number of randomised participants:** 91 (32 in experimental group I, 29 in experimental group II, and 30 in control or group III) **Age (mean and SD):** not reported **Inclusion criteria:** women 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 **Exclusion criteria:** not reported
Interventions	**Intervention** • **Group I:** magnetic therapy using intense low frequency in the cycle previous to IVF • **Group II:** sildenafil citrate in the IVF cycle • **Control/Group III:** no additional treatment
Outcomes	**Primaries:** evidence of increasing end-diastolic flow velocity, decreased vascular resistance, increased blood flow to uterine vessels **Secondaries:** thickness of the endometrium after intervention, pregnancy rate and reproductive loss that were not defined
Notes	**Funding:** not reported **Conflict of interest:** not reported **Protocol registry:** not reported **Sample size calculation:** not reported Published currently only as an abstract We did not include this study in the meta-analysis owing to lack of definitions for pregnancy and reproductive loss.

Alieva 2012 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Comment:** methods were not adequately described
Allocation concealment (selection bias)	Unclear risk	**Comment:** methods were not adequately described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	**Comment:** methods were not adequately described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	**Comment:** methods were not adequately described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	**Comment:** methods were not adequately described
Selective reporting (reporting bias)	Unclear risk	**Comment:** methods were not adequately described
Other bias	Unclear risk	**Comment:** methods were not adequately described

Azmy 2016

Methods	Randomised controlled clinical trial
Participants	**Clinical trial design:** randomised controlled trial **Number of participant centres:** 1 **Setting:** not reported **Country:** Egypt **Length of follow-up:** 2 cycles (56 days) **Number of randomised participants:** 65; 30 in the experimental group, 35 in the control group **Age (mean and SD):** not reported **Inclusion criteria:** infertile women with diagnosis of polycystic ovarian syndrome **Exclusion criteria:** not reported
Interventions	• **Experimental intervention:** clomiphene citrate (CC) + amlodipine • **Control intervention:** clomiphene citrate (CC) + placebo **Length of treatment:** 2 cycles (56 days)
Outcomes	**Primary:** pregnancy rate

Azmy 2016 *(Continued)*

	Secondaries: endometrial thickness, pulsatility index of uterine artery, pulsatility index of ovarian artery, ultrasound indices, sonographically detectable mature follicle by cycle
Notes	**Funding:** not reported **Conflict of interest:** not reported **Sample size calculation:** not reported Published currently only as an abstract

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Comment:** methods were not described
Allocation concealment (selection bias)	Unclear risk	**Comment:** methods were not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	**Comment:** methods were not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	**Comment:** methods were not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	**Comment:** methods were not described
Selective reporting (reporting bias)	Low risk	**Comment:** less than 20% of losses. Study authors describe that 65 women were recruited but describe only 60 in the text.
Other bias	Unclear risk	**Comment:** we did not know the original outcomes to be measured; therefore we cannot know if all of them were reported

Das 2009

Methods	Randomised controlled trial
Participants	**Number of centres:** 1 **Setting:** tertiary care hospital **Country:** India **Length of follow-up:** not reported **Number of randomised participants:** 50 (25 per group) **Age (mean and SD):** 26.96 ± 2.92 years in experimental group, 26.08 ± 3.83 years in control group **Inclusion criteria:** infertile women with a thin endometrium (< 9 mm) undergoing intrauterine insemination on 2 occasions

Das 2009 *(Continued)*

	Exclusion criteria: tubal block or severe tubal damage; ovarian failure; very poor egg quality and quantity; severe male factor infertility; known hypersensitivity to sildenafil; coronary heart disease and taking nitrates; liver or kidney disease; peptic ulcer; bleeding disorder; migraine; receiving erythromycin, ketoconazole, verapamil, or cimetidine treatment
Interventions	• **Intervention:** sildenafil 25 mg vaginally 4 times a day from day 5 of cycle until day of hCG administration • **Control:** no sildenafil **Co-interventions:** 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 to 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 to 4 days. 200 mg micronised progesterone was given orally as luteal phase support twice daily for 14 days after second IUI. **Length of treatment:** not reported
Outcomes	**Primary:** pregnancy or conception rates (positive urine pregnancy test) **Secondaries:** endometrial thickness, uterine artery PI on day of hCG administration
Notes	**Funding:** Research Cell CSMMU, Lucknow, India **Conflict of interest:** not reported **Protocol registry:** not reported **Sample size calculation:** not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Comment:** methods were not adequately described (alternate participants were taken as case and control). Patients received sildenafil 25 mg vaginal suppositories, and controls received no treatment.
Allocation concealment (selection bias)	Unclear risk	**Comment:** methods were not adequately described (all cases were given tab sildenafil 25 mg vaginally 4 times a day from day 5 of the cycle until day of hCG administration)
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	**Comment:** study did not use placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	**Comment:** 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
Incomplete outcome data (attrition bias) All outcomes	Low risk	**Comment:** investigators evaluated all randomly assigned women
Selective reporting (reporting bias)	Unclear risk	**Comment:** study protocol was not available, and published reports do not include all expected outcomes - only those that were prespecified
Other bias	Low risk	**Comment:** no statistically significant differences in age or BMI were noted between the 2 groups

Dehghani Firouzabadi 2013

Methods	Randomised clinical controlled trial, not blinded
Participants	**Number of centres:** 1 **Setting:** Centre for Infertility – University Hospital **Country:** Iran **Length of follow-up:** not reported **Number of randomised participants:** 80 (40 per group) **Age (mean and SD):** 29 years in experimental group, 28 years in control group **Inclusion criteria:** women 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:** history of endocrine disease; hysteroscopic surgery; cardiovascular, renal, and liver disease; hypotension (blood pressure < 90/50 mmHg); history of stroke or myocardial infarction
Interventions	• **Intervention:** sildenafil citrate tablets (50 mg) daily (from first day of cycle until day progesterone was started) • **Control:** no sildenafil **Co-interventions:** in both groups on the 13th day of the menstrual cycle, endometrial thickness was measured by transvaginal ultrasonography. If endometrial thickness was > 8 mm, 100 mg progesterone was injected IM Oral oestradiol valerate (first to fourth day 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.
Outcomes	**Primary outcome:** endometrial thickness **Other outcome:** implantation rate, chemical pregnancy rate (we used implantation rate as the clinical pregnancy rate)
Notes	**Funding:** Shahid Sadoughi University of Medical Sciences and Health Services, Yazd, Iran **Conflict of interest:** study authors reported no conflicts of interest **Protocol registry:** no registry reported **Sample size calculation:** not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Comment:** participants were divided into 2 groups on the basis of randomised tables
Allocation concealment (selection bias)	Unclear risk	**Comment:** information was insufficient to permit judgement of 'low risk' or 'high risk'. Allocation was not described.

Dehghani Firouzabadi 2013 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	**Comment:** study did not use placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	**Comment:** no blinding of outcome assessment, but review authors judge that measurement of pregnancy outcome is not likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	**Comment:** investigators evaluated all randomly assigned women
Selective reporting (reporting bias)	Low risk	**Comment:** study protocol is available, and published reports include those that were prespecified. Investigators did not include all expected outcomes.
Other bias	Low risk	**Comment:** groups were comparable for the variables described (duration of infertility, age, basal FSH, basal LH, basal oestrogen, basal progesterone, basal FSH/LH)

El-Berry 2010

Methods	Randomised controlled study
Participants	**Number of centres:** 1 **Setting:** University Hospital **Country:** Egypt **Length of follow-up:** not reported **Number of randomised participants:** 30 (15 per group) **Age (mean and SD):** 27.13 ± 4.32 years in experimental group, 28.40 ± 3.62 years in control group **Inclusion criteria:** polycystic ovary infertile women diagnosed according to American Society of Reproductive Medicine and European Society of Human Reproductive and Embryology who underwent ovulation induction **Exclusion criteria:** not reported
Interventions	• **Intervention:** nitric oxide donors (isosorbide mononitrate (ISMN)) 20 mg vaginally until diagnosis of ovulation and pregnancy • **Control:** did not receive experimental drug **Co-intervention:** both groups received 100 mg clomiphene citrate (CC) for 5 days from fifth day of cycle **Length of treatment:** 3 cycles
Outcomes	**Primaries:** ovulation and pregnancy rates (diagnosed by serum β-hCG) **Secondaries:** number of mature follicles, cervical mucus score, endometrial thickness
Notes	**Funding:** not reported **Conflict of interest:** not reported **Protocol registry:** not reported

El-Berry 2010 *(Continued)*

Sample size calculation: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Comment:** insufficient information about the sequence generation process to allow judgement
Allocation concealment (selection bias)	Unclear risk	**Comment:** method of concealment not described to allow a definitive judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	**Comment:** methods used in this study not adequately described
Blinding of outcome assessment (detection bias) All outcomes	Low risk	**Comment:** no blinding of outcome assessment, but review authors judge that measurement of pregnancy outcome is not likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	**Comment:** no loss 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)
Selective reporting (reporting bias)	Unclear risk	**Comment:** study protocol is not available, and published reports do not include all expected outcomes - only those that were prespecified
Other bias	Low risk	**Comment:** groups were comparable for variables described (age, body mass index, FSH, LH)

Fahmy 2015

Methods	Prospective randomised clinical trial
Participants	**Number of centres:** 1 **Setting:** clinic at a University Hospital **Country:** Egypt **Length of follow-up:** not stated (at least 1 cycle) **Number of randomised participants:** 70 (35 women per group) **Age (mean and SD):** 28.34 ± 4.13 years in experimental group, 28.40 ± 3.15 years in control group **Inclusion criteria:** infertile women between 18 and 40 years of age with primary or secondary infertility and with regular menstrual cycles **Exclusion criteria:** ovarian cysts; abnormal hormonal profile (e.g. hyperprolactinaemia); significant cardiovascular liver or renal disease; history of any pelvic pathology
Interventions	• **Experimental group:** sildenafil citrate 25 mg (Viagra, Pfizer) orally 3 times/d from seventh to 11th day of cycle • **Control group:** placebo (not described)

Fahmy 2015 *(Continued)*

	Co-interventions: induction of ovulation in both groups with clomiphene citrate (CC) 50 mg (clomid, Glopa) orally 3 times/d from third to seventh day of the cycle along with intramuscular injection of 5000 IU of human chorionic gonadotrophin (hCG), which was used to trigger ovulation **Length of treatment:** not reported
Outcomes	**Primary:** pregnancy rate (chemical (β-hCG positive)) **Secondaries:** endometrial thickness, total follicles, side effects of vasodilator (headache, flushing, blurring of vision)
Notes	**Funding:** not reported **Conflict of interest:** study authors declare no conflict of interest **Protocol registry:** not reported **Sample size calculation:** not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Quote:** "The patients in this study were divided into two groups by random allocation using sealed envelope: the treatment group (Sildenafil group) and the control group (placebo group) with 35 patients in each group" **Comment:** the method used to generate the random sequence was not specified
Allocation concealment (selection bias)	Low risk	**Quote:** "The patients in this study were divided into two groups by random allocation using sealed envelope: the treatment group (Sildenafil group) and the control group (placebo group) with 35 patients in each group"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	**Comment:** methods were not adequately described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	**Comment:** methods were not adequately described
Incomplete outcome data (attrition bias) All outcomes	Low risk	**Comment:** no participant dropout was reported (all participants were followed up). Study flow chart shows that all randomised participants were analysed.
Selective reporting (reporting bias)	Low risk	**Comment:** we defined a PICO question for the article from the abstract and the methods section; study authors did report all outcomes that they proposed to measure
Other bias	Low risk	**Comment:** differences in demographic characteristics of participants between treatment and control groups were non-significant, except for endometrial thickness

Farzi 2005

Methods	Prospective randomised double-blinded placebo-controlled clinical trial

Farzi 2005 *(Continued)*

Participants	**Number of centres:** 1 **Setting:** clinic of infertility **Country:** Iran **Length of follow-up:** not reported **Number of randomised participants:** 100 (50 per group) **Age (mean and SD):** 31 ± 5.5 years in experimental group, 30.1 ± 5.1 in control group **Inclusion criteria:** participants underwent ICSI regardless of male or female infertility when both were present, or when causes were unknown **Exclusion criteria:** not reported
Interventions	• **Intervention:** glyceryl trinitrate (GTN) 0.4 mg oral dose 15 minutes before fresh ET • **Control:** placebo (not described) **Co-interventions:** both groups were initially stimulated with a long protocol. Then, on the third day of of the next menstrual cycle, hMG 150 to 225 IU was injected and was adjusted with follicular 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 **Length of treatment:** 1 cycle was performed for each participant
Outcomes	**Primaries:** implantation rate, clinical pregnancy rate **Secondaries:** taking baby home (equivalent "live birth"), spontaneous abortion/miscarriage, biochemical pregnancy
Notes	**Funding:** not reported **Conflict of interest:** not reported **Protocol registry:** not reported **Sample size calculation:** not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Comment:** information about the sequence generation process was insufficient to allow judgement
Allocation concealment (selection bias)	Unclear risk	**Comment:** method of concealment not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	**Comment:** double-blinded with use of placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	**Comment:** not described, but main outcome not subjective. Outcome measurement is not likely to be influenced by lack of blinding.
Incomplete outcome data (attrition bias)	Low risk	**Comment:** study described 100 randomly assigned cycles

Farzi 2005 *(Continued)*

All outcomes		***Additional information from study authors:*** 100 participants entered and completed this randomisation study; 1 cycle was performed for each participant
Selective reporting (reporting bias)	Low risk	**Comment:** study protocol is not available, but it is clear that published reports include all expected outcomes, including those that were prespecified
Other bias	Low risk	**Comment:** groups were comparable for variables described: age of the father and age of the mother, duration of infertility, oocyte retrieved, oocyte injected, 2 pronuclei, cleaved embryos, embryos transferred, causes of infertility, embryo quality

Kim 2010

Methods	Pilot randomised clinical trial
Participants	**Number of centres:** 1 **Setting:** MizMedi Hospital **Country:** Korea **Length of follow-up:** not reported **Number of randomised participants:** 48 women (21 intervention, 27 control) among 170 patients with a thin endometrium **Age (mean and SD):** 36.4 ± 4.6 years in experimental group, 36.3 ± 4.3 years in control group **Inclusion criteria:** women with a thin endometrium (< 8 mm: range 5 to 7.9 mm) at the time of embryo transfer undergoing IVF **Exclusion criteria:** not reported
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 **Co-interventions:** 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). For 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 to 8 weeks when pregnancy was achieved. **Length of treatment:** not reported
Outcomes	**Primary:** clinical pregnancy **Secondary:** fertilisation rate
Notes	**Funding:** not reported **Conflict of interest:** not reported **Protocol registry:** not reported **Sample size calculation:** not reported
Risk of bias	

Kim 2010 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Comment:** information about sequence generation process insufficient to allow judgement
Allocation concealment (selection bias)	Unclear risk	**Comment:** method of concealment not described to allow a definitive judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	**Comment:** study did not use placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	**Comment:** not described, but outcome measurement not likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	**Comment:** investigators evaluated all randomly assigned women
Selective reporting (reporting bias)	Unclear risk	**Comment:** study protocol not available; no published reports describe all expected outcomes
Other bias	Low risk	**Comment:** 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)

Magdi Ammar 2017

Methods	Randomised controlled trial
Participants	**Number of centres:** 1 **Setting:** infertility clinic of the Cytogenetic and Endoscopy Unit, Zagazig University Hospital **Country:** Egypt **Length of follow-up:** 15 months **Number of participants:** 236 patients who underwent a single cycle of ovulation induction and timed intercourse **Age:** 18 to 35 years **Inclusion criteria:** primary infertility due to unexplained infertility or PCOS; both tubes and uterine cavity normal as assessed by hysterosalpingography (HSG); neither history of previous endometrial surgery nor history of smoking; willingness to participate in the study; body mass index (BMI) ranging between 18 and 25 kg/m^2 **Exclusion criteria:** endometriosis; history of ovarian hyperstimulation syndrome (OHSS); abnormal HSG/laparoscopy suggestive of pelvic adhesions with altered tubo-ovarian relationship (like pelvic endometriosis, chronic PID, and postoperative adhesions); Mullerian malformations; hypogonadotropic hypogonadism; primary amenorrhoea; premature ovarian failure; secondary infertility; failed IUI or IVF; abnormal husband semen parameters
Interventions	• **Group A:** clomiphene citrate (Clomid 50 mg) as 100 mg (2 tablets) daily for 5 days (from second day until sixth day of the cycle) • **Group B:** clomiphene citrate (Clomid 50 mg) as 100 mg (2 tablets) daily for 5 days (from second day until sixth day of the cycle) and tadalafil (CIALIS-tadalafil) oral 5 mg/d for 7 days (from fourth day until 10th day of the cycle)

Magdi Ammar 2017 *(Continued)*

	• **Group C:** human menopausal gonadotropin (hMG) (Menogon) IM was given from second day of the cycle until 1 to 3 follicles reach a size ≥ 18 mm. Dose of hMG ranged from 75 to 225 IU/mL according to the patient's response. **Co-interventions:** all participants in the 3 studied groups received luteal phase support by vaginal progesterone suppositories 200 mg (Prontogest, GMP Marcyrl) twice daily, which was started on the day of timed intercourse for 2 weeks until pregnancy test and was continued for 2 weeks longer if positive
Outcomes	**Primary** • Endometrial thickness on the day of hCG triggering • Total pregnancy rate (cases with a positive pregnancy test defined as a finding of plasma β-hCG concentration > 10 mU/mL 2 weeks after timed intercourse). All cases with positive serum pregnancy test (chemical pregnancy) were followed up by transabdominal ultrasound 6 weeks from the first day of the last menstrual period for detection of intrauterine gestational sac (clinical pregnancy).
Notes	**Funding:** not reported **Conflict of interest:** not reported **Protocol registry:** not reported **Sample size calculation:** not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote:** "Patients were divided randomly by using random number table (computer), software Open Epi version 3.21, into three groups (A, B, and C). Patients were assigned to either group by the randomization known while allocation concealment concentrated on preventing selection and confusing biases"
Allocation concealment (selection bias)	Unclear risk	**Comment:** not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	**Comment:** not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	**Comment:** not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	**Comment:** 102 (30%) participants were dropped from follow-up - those who failed to respond to the administered ovulation induction drug
Selective reporting (reporting bias)	Low risk	**Comment:** results of all outcomes described in methods are reported
Other bias	Low risk	Basal characteristics are similar between groups.

Mahran 2016

Methods	Randomised open controlled clinical trial
Participants	**Number of centres:** 2 **Setting:** fertility units of hospitals **Country:** Egypt **Length of follow-up:** not reported **Number of participant**s: 95 women; 30 (74 cycles) women in experimental group 1; 30 (72 cycles) in experimental group 2; 35 (81 cycles) in the control group **Age (mean and SD):** 27.5 ± 4.3 years in experimental group 1; 26 ± 5.4 years in experimental group 2; 26.1 ± 4 years in control group **Inclusion criteria:** women 20 to 39 years old with diagnosis of polycystic ovarian syndrome (based on the Rotterdam criteria); meeting at least 2 of the following 3 criteria: oligo or anovulation; clinical or biochemical hyperandrogenaemia; and polycystic ovaries (> 12 follicles < 10 mm and/or ovarian volume > 10 mL per ovary by vaginal ultrasound) **Exclusion criteria:** women with uterine pathology as fibroids; tubal factor of infertility (diagnosed by hysterosalpingography (HSG) or laparoscopy); male factor infertility; any contraindications for clomiphene citrate (CC) and nitric oxide (chronic liver and renal disease, known cardiac disease, and migraine); hyperprolactinaemia; thyroid dysfunction; Cushing's syndrome; congenital adrenal hyperplasia; an adrenal or ovarian tumour
Interventions	**Experimentals groups** • **Group B:** treated with CC 100 mg for 5 days starting from cycle day 5 in addition to 10 mg isosorbide mononitrate (ISMN) tablets applied vaginally from day 2 to day 15 of the cycle • **Group C:** treated with CC 100 mg for 5 days starting from fifth day of cycle in addition to 20 mg ISMN tablets applied vaginally from day 2 to day 15 of the cycle • **Control group (group A):** treated with CC 100 mg for 5 days starting from cycle day 5 **Length of treatment:** not reported
Outcomes	**Primaries:** ovulation rate per treatment cycle; pregnancy rate per treatment cycle (pregnancy diagnosed by serum β-hCG) **Secondaries:** number of mature follicles; endometrial thickness; side effects recorded with treatment
Notes	**Funding:** Department of Obstetrics and Gynecology, Minia University, Minia, Egypt **Conflict of interest:** study authors declare that there is no conflict of interest in this paper **Protocol registry:** not reported **Sample size calculation:** not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Quote:** "Patients were randomized into three groups" - "Randomization was done simply using sealed envelopes" **Comment:** study authors did not specify how the randomisation list was generated
Allocation concealment (selection bias)	Low risk	**Quote:** "Randomization was done simply using sealed envelopes"

Mahran 2016 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	**Quote:** "The subject allocation was neither blinded to the patients nor to the physicians and investigators" **Comment:** pregnancy outcome measurement not likely to be influenced by lack of blinding, but yes in the case of side effects
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	**Quote:** "The subject allocation was neither blinded to the patients nor to the physicians and investigators" **Comment:** pregnancy outcome measurement not likely to be influenced by lack of blinding, but yes in the case of side effects; reported that pregnancy was diagnosed by serum β-hCG
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	**Comment:** no participant dropout was reported (all participants were followed up).
Selective reporting (reporting bias)	Low risk	**Comment:** study authors did report all outcomes that they proposed to measure in methods
Other bias	Low risk	No significant differences between the 3 groups in demographic, hormonal, or sonographic features

Mostafa 2003

Methods	Randomised controlled trial
Participants	**Number of centres:** 1 **Setting:** Department of Obstetrics and Gynecology, Ain Shams University, Nasr City, Cairo **Country:** Egypt **Length of follow-up:** not reported **Number of randomised participants:** 60 (30 per group) **Age (range):** 25 to 35 years **Inclusion criteria:** women who underwent IVF/ICSI indicated for infertility associated with a male factor **Exclusion criteria:** not reported
Interventions	• **Intervention:** glyceryl trinitrate skin patches 5 mg daily for 2 weeks • **Control:** participants did not receive the aforementioned drug
Outcomes	**Primaries:** pregnancy (we do not know the method used to establish pregnancy), implantation rate (number of implantations and pregnancies is equal, so we used this as the clinical pregnancy rate) **Secondary outcome:** pulsatility index **Co-interventions:** participants received the long protocol of controlled ovarian hyperstimulation. Luteal phase support was undertaken with progesterone suppositories (Cyclogest 400 mg daily) starting on the day of oocyte retrieval and for 2 weeks after embryo transfer. Two to three good quality embryos were transferred for each woman.
Notes	**Funding:** not reported **Conflict of interest:** not reported

Mostafa 2003 *(Continued)*

	Protocol registry: not reported **Sample size calculation:** not reported Published currently only as an abstract

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Quote:** "The subjects were divided randomly into two groups after embryo transfer" **Comment:** methods not adequately described
Allocation concealment (selection bias)	Unclear risk	**Quote:** "The subjects were divided randomly into two groups after embryo transfer" **Comment:** methods not adequately described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	**Comment:** methods not adequately described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	**Comment:** methods not adequately described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	**Comment:** methods not adequately described
Selective reporting (reporting bias)	Unclear risk	**Comment:** methods not adequately described
Other bias	Unclear risk	**Comment:** methods not adequately described

Ohl 2002

Methods	Randomised multi-centre double-blinded placebo-controlled trial
Participants	**Number of centres:** 3 **Setting:** Hospital Gynecology and Obstetric Services **Country:** France **Length of follow-up:** not reported **Number of randomised participants:** 138 (70 in intervention group, 68 in control group) **Age (mean and SD):** 25 to 35 years **Inclusion criteria:** women with a history of 2 or more previous implantation failures **Exclusion criteria:** hypersensitivity to nitric oxide donors; heart failure; severe anaemia; high intracranial blood pressure; high intraocular blood pressure

Ohl 2002 *(Continued)*

Interventions	• **Intervention:** 5 mg glyceryl trinitrate (GTN) patch applied once daily, beginning the morning of the day before transfer, just after transvaginal ultrasonography and colour doppler were performed • **Control:** placebo
Outcomes	**Primary outcome:** clinical pregnancy **Secondary outcomes:** newborn (equivalent "live birth"), multiple gestation or birth, spontaneous abortion/miscarriage, ectopic pregnancy, vasodilator side effects **Co-interventions:** 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)
Notes	**Funding:** not reported **Conflict of interest:** not reported **Protocol registry:** not reported **Sample size calculation:** yes. A total sample of 288 patients was calculated (144 placebo and 144 NTG) in a unilateral test at the 5% significance level with 80% power. In January 2000, whereas 164 out of 288 patients were enrolled in the study, placebo as well as NTG patches became out of date. New patches were not affordable. A new power calculation showed 53% in a unilateral test at the 5% significance level.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Comment:** investigators describe a random component in the sequence generation process. Randomisation was performed with the use of 4 randomly permuted blocks and was stratified by centre.
Allocation concealment (selection bias)	Low risk	**Comment:** participants and investigators enrolling participants could not foresee assignment because central allocation was used to conceal allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	**Comment:** double-blinded with the use of placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	**Comment:** not described, but main outcome measurement is not likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	**Comment:** intention-to-treat analysis was performed in this study, but study authors reported losses for transvaginal ultrasonography
Selective reporting (reporting bias)	Low risk	**Comment:** study protocol is not available, but it is clear that published reports include all expected outcomes, including those that were prespecified
Other bias	Low risk	**Comment:** 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)

Shaker 1993

Methods	Double-blind study with random allocation
Participants	**Number of centres:** 1 **Setting:** University Department of Obstretics Gynecology, Glasgow **Country:** UK **Length of follow-up:** not reported **Number of randomised participants:** 120 (intervention 60, placebo 60) **Age (mean and SD):** not reported **Inclusion criteria:** women having their first IVF/embryo transfer and accepted to participate **Exclusion criteria:** not reported
Interventions	• **Intervention:** 2 sublingual spray emissions of GTN 400 µg/spray or placebo spray • **Control:** placebo **Co-intervention:** all participants received in vitro fertilisation after combined long-course gonadotrophin-releasing hormone analogue and human menopausal gonadotrophin therapy
Outcomes	**Primary outcome:** pregnancy rate (outcome definition is not clear) **Secondary outcome:** side effect
Notes	**Funding:** Lipha Company supplied GTN and placebo **Conflict of interest:** not reported **Protocol registry:** not reported **Sample size calculation:** not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Comment:** insufficient information about sequence generation process to permit judgement of 'low risk' or 'high risk'
Allocation concealment (selection bias)	Unclear risk	**Comment:** insufficient information to permit judgement of 'low risk' or 'high risk'; allocation not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	**Comment:** double-blinded with use of placebo
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	**Comment:** no blinding of outcome assessment, but review authors judge that measurement of pregnancy outcome is not likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	**Comment:** investigators evaluated women randomly assigned

Shaker 1993 *(Continued)*

Selective reporting (reporting bias)	Low risk	**Comment:** study protocol is not available, but it is clear that published reports include all prespecified outcomes and some expected outcomes
Other bias	Low risk	**Comment:** 2 participant groups were comparable with respect to age, duration of infertility, and parity

Abbreviations:
BMI: body mass index.
CC: clomiphene citrate.
CD: cycle day.
ET: embryo transfer.
FSH: follicle-stimulating hormone.
GnRH: gonadotrophin-releasing hormone.
GTN: glyceryl trinitrate.
hCG: human chorionic gonadotrophin.
hMG: human menopausal gonadotrophin.
HSG: hysterosalpingography.
ICSI: intracytoplasmic sperm injection.
ICSI-ET: intracytoplasmic sperm injection – embryo transfer.
IMN: isosorbide mononitrate.
ISMN: isosorbide mononitrate.
IUI: intrauterine insemination.
IVF: in vitro fertilisation.
LH: luteinising hormone.
OHSS: ovarian hyperstimulation syndrome.
PCOS: polycystic ovary syndrome.
PI: pulsatility index.
PICO: population-intervention-comparison-outcome format.
PID: pelvic inflammatory disease.
SC: subcutaneous.
SD: standard deviation.
WHO: World Health Organization.
ZIFT: zygote intrafallopian transfer.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Alborzi 2007	Study used pentoxifylline as an immunomodulator for controlling endometriosis. As participants did not undergo AR, they **were not of interest** for this review.
Ataalla 2016	**Quote:** "Randomization was carried out by asking each patient to choose a number from 1 to 60. One of our nursing staff then put the even numbers in group I and the odd numbers in group II. After informed consent, patients in group I were allocated to receive sildenafil 50 mg/day orally and those in group II were allocated to receive placebo" **Comment:** allocation was done on the basis of a pseudo-random sequence
Balasch 1997	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); pentoxifylline was used as an immunomodulator for controlling endometriosis.
Check 2004	Eliminated because this 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 7 to vaginal oestradiol. Only 3 women in the vaginal sildenafil group completed both study arms.

Study	Reason for exclusion
Creus 2008	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.
Kamencic 2008	Study did **not report participants or outcomes of interest** for this review.
Malinova 2013	Study did **not report outcomes of interest** for this review. Time frame was too short for investigator to evaluate outcomes.
Raine-Fenning 2009	Eliminated because it is not a parallel randomised controlled trial but is rather a **cross-over** study
Rosen 1987	Study reported no comparisons of interest for this review. Study compared 0.7% isoflurane + nitrous oxide vs 1.4% isoflurane + nitrous oxide.
Sher 2000	Eliminated because this is not a parallel randomised controlled trial but is rather an**observational** study including 4 participants
Shin 2002	Eliminated because this is**not a parallel randomised** controlled trial but is rather a controlled clinical trial

AR: assisted reproduction.
PTX: pentoxifylline.

Characteristics of studies awaiting assessment *[ordered by study ID]*

Casper 2013

Methods	Randomised parallel double-blind controlled trial
Participants	Women 21 to 40 years of age with intact normal ovaries, early follicular phase (2 days)
Interventions	**Experimental group:** 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
Outcomes	**Primary outcome measures:** delay in LH surge by at least 2 days **Secondary outcome measures:** side effect profile of nimodipine or placebo
Notes	**Starting date:** July 2012

Penzias 2012

Methods	Randomised parallel double-blind controlled trial
Participants	Women 25 to 40 years of age at time of enrolment, with both ovaries intact by history and ultrasound assessment early follicular phase
Interventions	**Experimental group:** nimodipine 30 mg liquid oral, 4 times a day for 8 total doses in prefilled syringes
Outcomes	**Primary outcome measures:** delay in LH surge

Penzias 2012 *(Continued)*	**Secondary outcome measures:** side effect profile of nimodipine, clinical pregnancy (positive pregnancy test and ultrasound evidence of foetal heart rate)
Notes	**Starting date:** September 2012

hCG: human chorionic gonadotrophin.
LH: luteinising hormone.

Characteristics of ongoing studies *[ordered by study ID]*

NCT02072291

Trial name or title	Nifedipine treatment on uterine contractility in in vitro fertilisation
Methods	Randomised parallel double-blind controlled trial
Participants	Women 18 to 45 years of age undergoing frozen embryo transfer
Interventions	**Experimental group:** nifedipine 5 mg single dose **Control group:** placebo
Outcomes	**Primary outcome measures:** uterine contractility after treatment (time frame 30 minutes after treatment) (designated as safety issue: no) **Secondary outcome measures:** implantation and pregnancy rates (time frame 4 weeks) (designated as safety issue: no)
Starting date	24 February 2014
Contact information	Assaf Ben-Meir, MD; 972-2-6776425; assaf.benmeir@gmail.com
Notes	We wrote to the study author, and he mentioned: "The study is still under recruitment so I don't have final results. Hopefully soon".

DATA AND ANALYSES

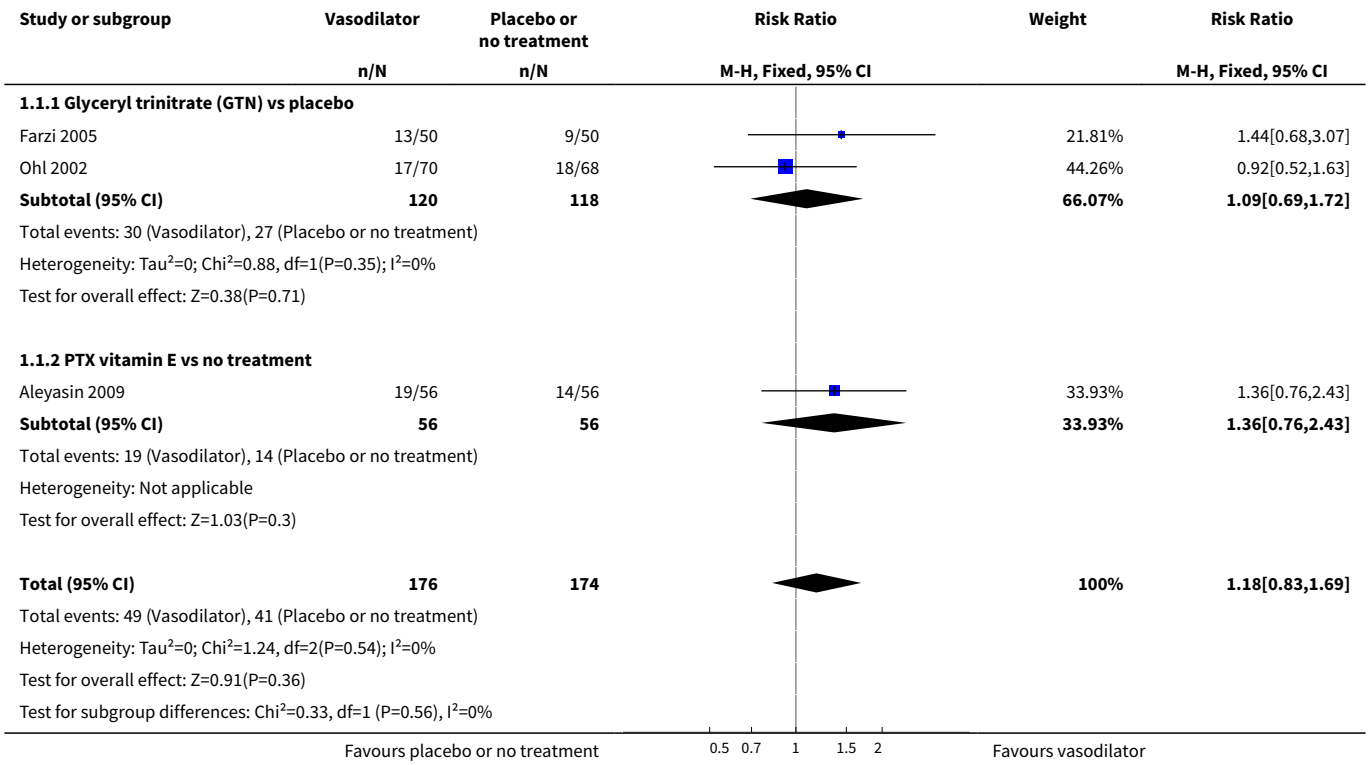
Comparison 1. Vasodilator vs placebo or no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Live birth	3	350	Risk Ratio (M-H, Fixed, 95% CI)	1.18 [0.83, 1.69]
1.1 Glyceryl trinitrate (GTN) vs placebo	2	238	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.69, 1.72]
1.2 PTX vitamin E vs no treatment	1	112	Risk Ratio (M-H, Fixed, 95% CI)	1.36 [0.76, 2.43]
2 Vasodilator side effects	4	418	Risk Ratio (M-H, Fixed, 95% CI)	2.35 [1.51, 3.66]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Glyceryl trinitrate (GTN) vs placebo	2	258	Risk Ratio (M-H, Fixed, 95% CI)	2.05 [0.97, 4.36]
2.2 Sildenafil vs placebo or no treatment	1	70	Risk Ratio (M-H, Fixed, 95% CI)	1.88 [0.91, 3.85]
2.3 Isosorbid mononitrate vs placebo	1	90	Risk Ratio (M-H, Fixed, 95% CI)	3.3 [1.44, 7.58]
3 Specific vasodilator side effects	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Hypotension	1	90	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.58, 2.14]
3.2 Headache	2	160	Risk Ratio (M-H, Fixed, 95% CI)	4.12 [1.87, 9.06]
3.3 Tachycardia	1	90	Risk Ratio (M-H, Fixed, 95% CI)	3.83 [1.25, 11.75]
3.4 Dizziness	1	90	Risk Ratio (M-H, Fixed, 95% CI)	1.57 [0.76, 3.26]
3.5 Hot flushes	2	160	Risk Ratio (M-H, Fixed, 95% CI)	2.40 [0.96, 5.99]
4 Clinical pregnancy	11	1054	Risk Ratio (M-H, Fixed, 95% CI)	1.45 [1.19, 1.77]
4.1 Glyceryl trinitrate (GTN) vs placebo or no treatment	4	418	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.80, 1.43]
4.2 Sildenafil vs placebo or no treatment	2	139	Risk Ratio (M-H, Fixed, 95% CI)	1.47 [0.68, 3.20]
4.3 Sildenafil + oestrogen vs no treatment	1	48	Risk Ratio (M-H, Fixed, 95% CI)	1.84 [0.84, 4.01]
4.4 PTX + vitamin E vs no treatment	1	112	Risk Ratio (M-H, Fixed, 95% CI)	1.45 [0.98, 2.16]
4.5 Amlodipine vs placebo	1	60	Risk Ratio (M-H, Fixed, 95% CI)	3.67 [1.14, 11.84]
4.6 Isosorbide mononitrate vs placebo	1	120	Risk Ratio (M-H, Fixed, 95% CI)	2.8 [1.08, 7.29]
4.7 Tadalafil vs no treatment	1	157	Risk Ratio (M-H, Fixed, 95% CI)	2.08 [1.12, 3.86]
5 Thickened endometrium	5	477	Mean Difference (IV, Random, 95% CI)	2.11 [1.16, 3.07]
5.1 Isosorbid mononitrate vs placebo	2	210	Mean Difference (IV, Random, 95% CI)	1.26 [0.38, 2.14]
5.2 Amlodipine vs placebo	1	60	Mean Difference (IV, Random, 95% CI)	1.80 [0.66, 2.94]
5.3 Sildenafil vs placebo or no treatment	1	50	Mean Difference (IV, Random, 95% CI)	2.61 [2.13, 3.09]
5.4 Tadalafil vs no treatment	1	157	Mean Difference (IV, Random, 95% CI)	3.57 [3.01, 4.13]

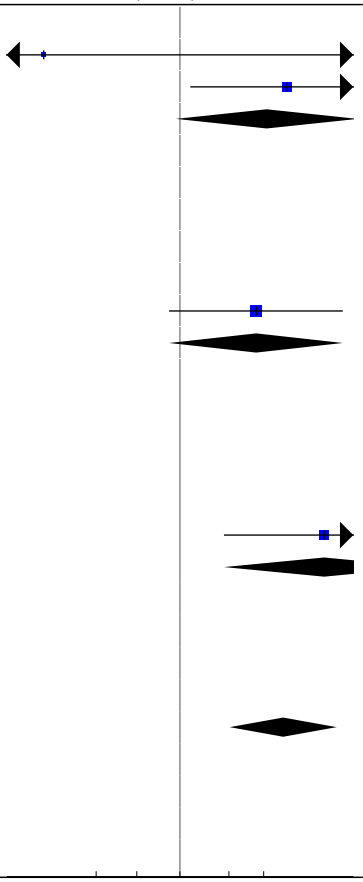
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6 Other adverse effects	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 Multiple gestation or birth: NTG or isosorbide mononitrate vs placebo and PTX + tocopherol vs no treatment	3	370	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.55, 2.42]
6.2 Spontaneous abortion/miscarriage NTG vs placebo and PTX + tocopherol vs no treatment	3	350	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.37, 1.86]
6.3 Ectopic pregnancy: NTG vs placebo and PTX + tocopherol vs no treatment	2	250	Risk Ratio (M-H, Fixed, 95% CI)	1.48 [0.25, 8.69]

Analysis 1.1. Comparison 1 Vasodilator vs placebo or no treatment, Outcome 1 Live birth.



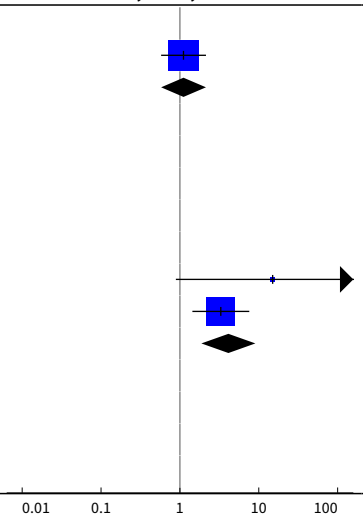
Analysis 1.2. Comparison 1 Vasodilator vs placebo or no treatment, Outcome 2 Vasodilator side effects.

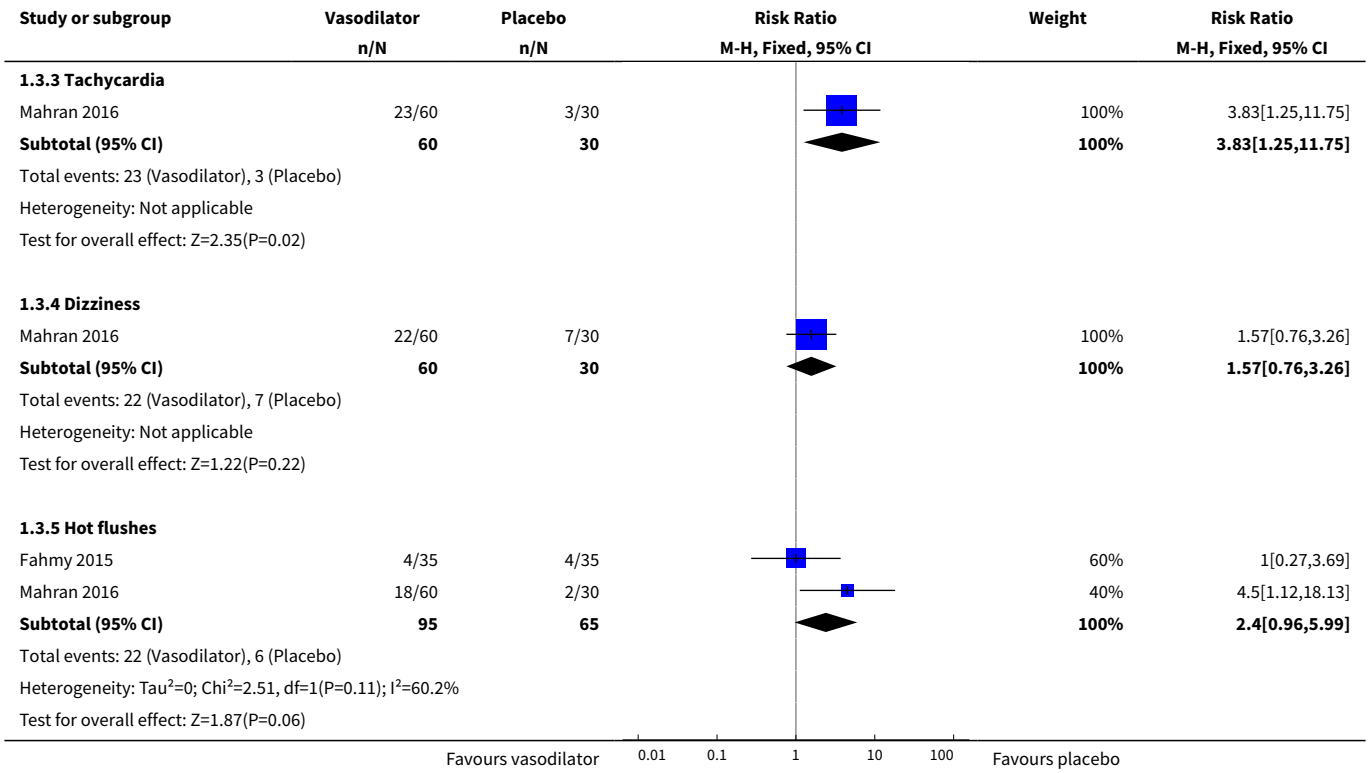
Study or subgroup	Vasodilator n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.2.1 Glyceryl trinitrate (GTN) vs placebo					
Ohl 2002	0/70	1/68		6.56%	0.32[0.01,7.82]
Shaker 1993	17/60	7/60		30.19%	2.43[1.09,5.43]
Subtotal (95% CI)	**130**	**128**		**36.75%**	**2.05[0.97,4.36]**
Total events: 17 (Vasodilator), 8 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=1.46, df=1(P=0.23); I^2=31.51%					
Test for overall effect: Z=1.87(P=0.06)					
1.2.2 Sildenafil vs placebo or no treatment					
Fahmy 2015	15/35	8/35		34.5%	1.88[0.91,3.85]
Subtotal (95% CI)	**35**	**35**		**34.5%**	**1.88[0.91,3.85]**
Total events: 15 (Vasodilator), 8 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.71(P=0.09)					
1.2.3 Isosorbid mononitrate vs placebo					
Mahran 2016	33/60	5/30		28.75%	3.3[1.44,7.58]
Subtotal (95% CI)	**60**	**30**		**28.75%**	**3.3[1.44,7.58]**
Total events: 33 (Vasodilator), 5 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.81(P=0)					
Total (95% CI)	**225**	**193**		**100%**	**2.35[1.51,3.66]**
Total events: 65 (Vasodilator), 21 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=2.51, df=3(P=0.47); I^2=0%					
Test for overall effect: Z=3.78(P=0)					
Test for subgroup differences: Chi^2=1.12, df=1 (P=0.57), I^2=0%					



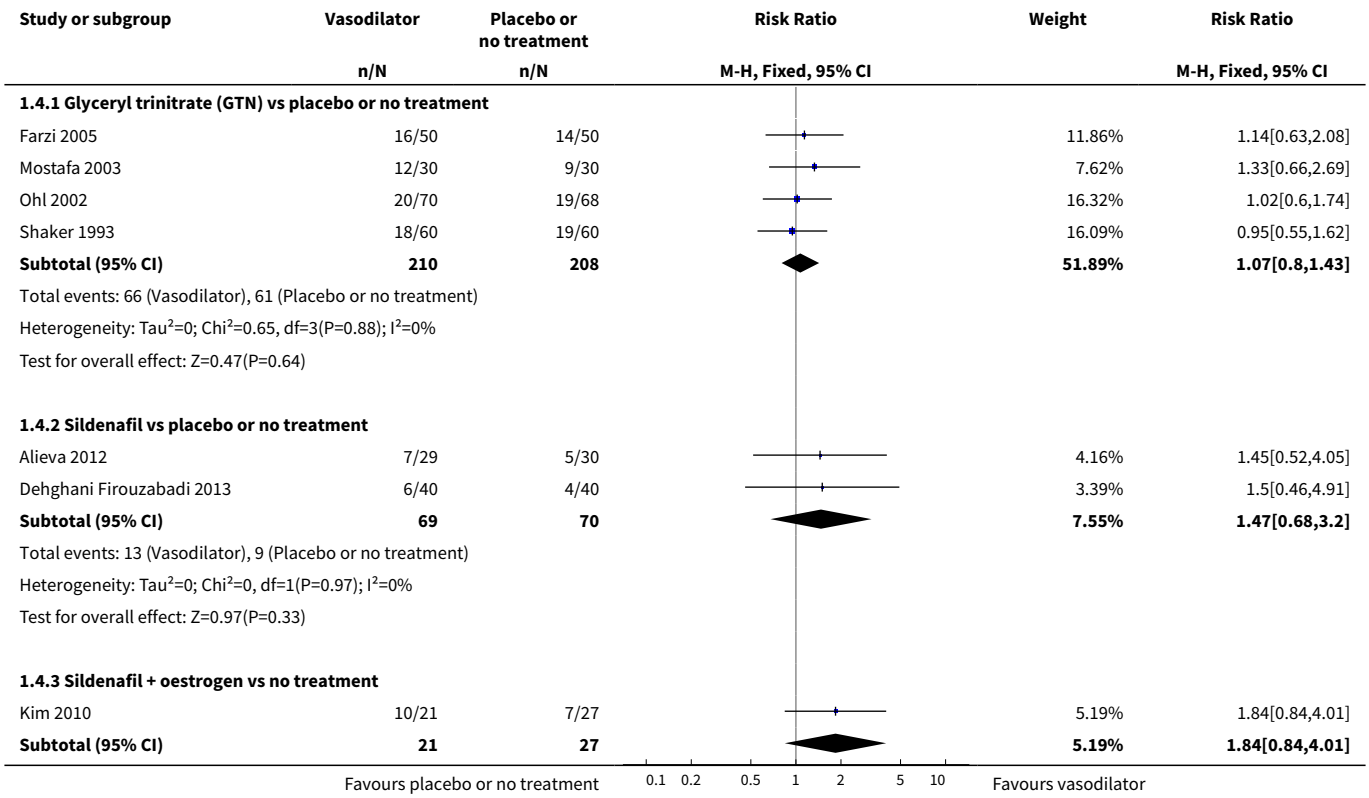
Analysis 1.3. Comparison 1 Vasodilator vs placebo or no treatment, Outcome 3 Specific vasodilator side effects.

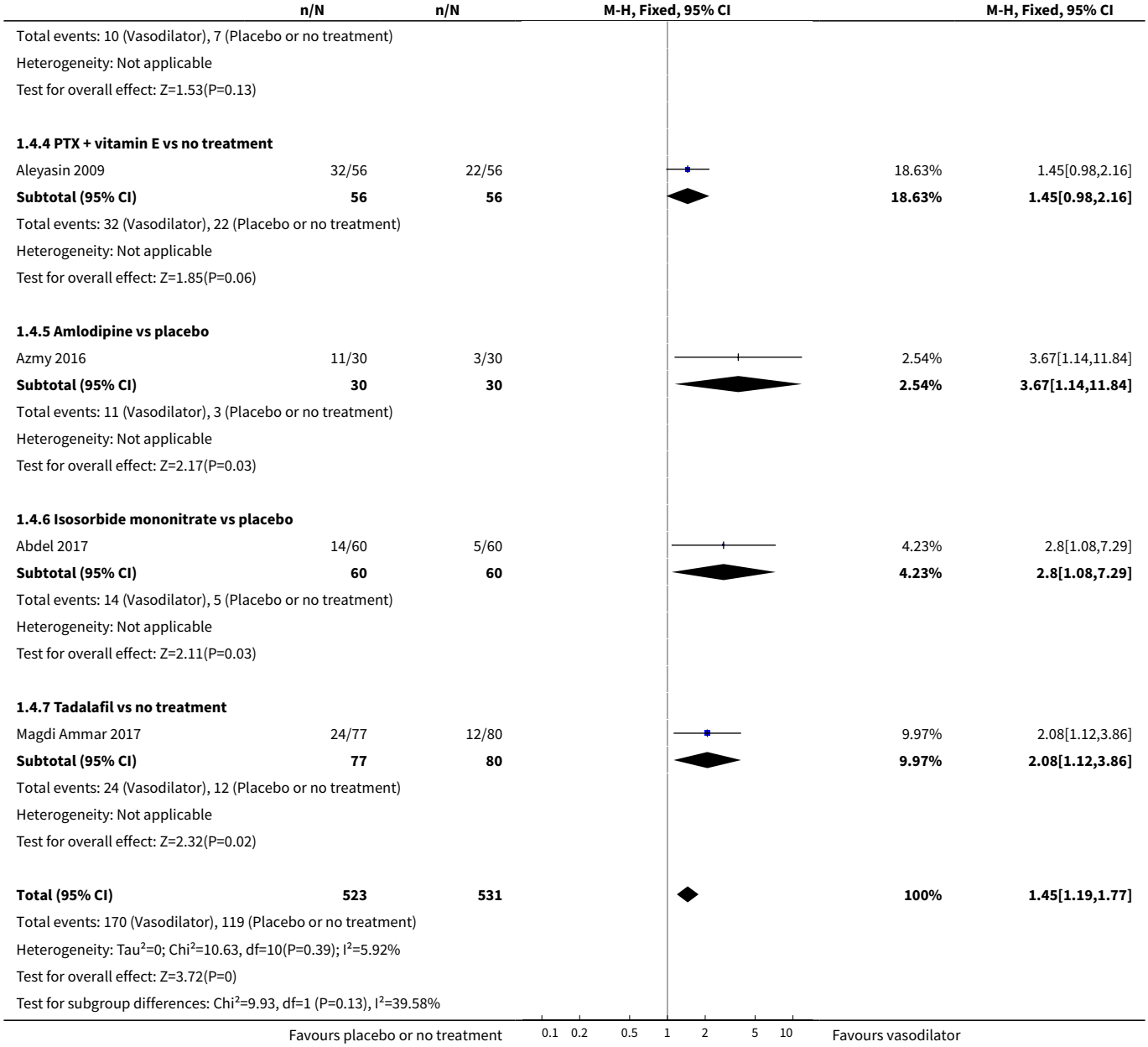
Study or subgroup	Vasodilator n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.3.1 Hypotension					
Mahran 2016	20/60	9/30		100%	1.11[0.58,2.14]
Subtotal (95% CI)	**60**	**30**		**100%**	**1.11[0.58,2.14]**
Total events: 20 (Vasodilator), 9 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.32(P=0.75)					
1.3.2 Headache					
Fahmy 2015	7/35	0/35		6.98%	15[0.89,252.96]
Mahran 2016	33/60	5/30		93.02%	3.3[1.44,7.58]
Subtotal (95% CI)	**95**	**65**		**100%**	**4.12[1.87,9.06]**
Total events: 40 (Vasodilator), 5 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=1.08, df=1(P=0.3); I^2=7.04%					
Test for overall effect: Z=3.52(P=0)					



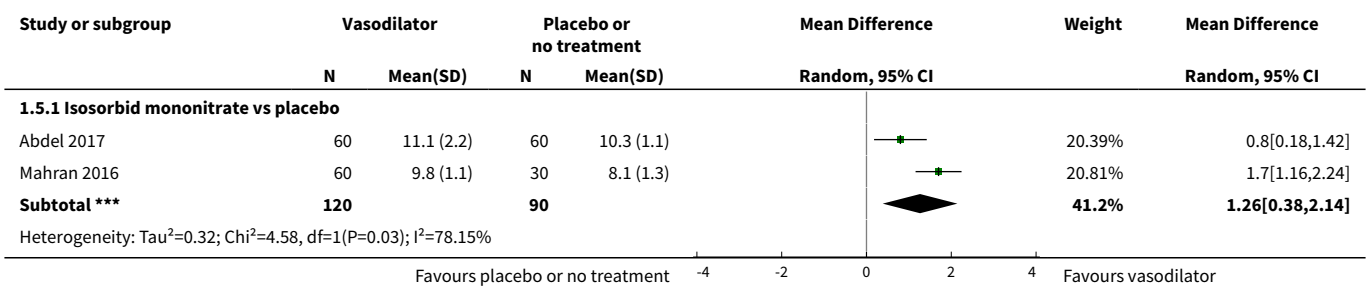


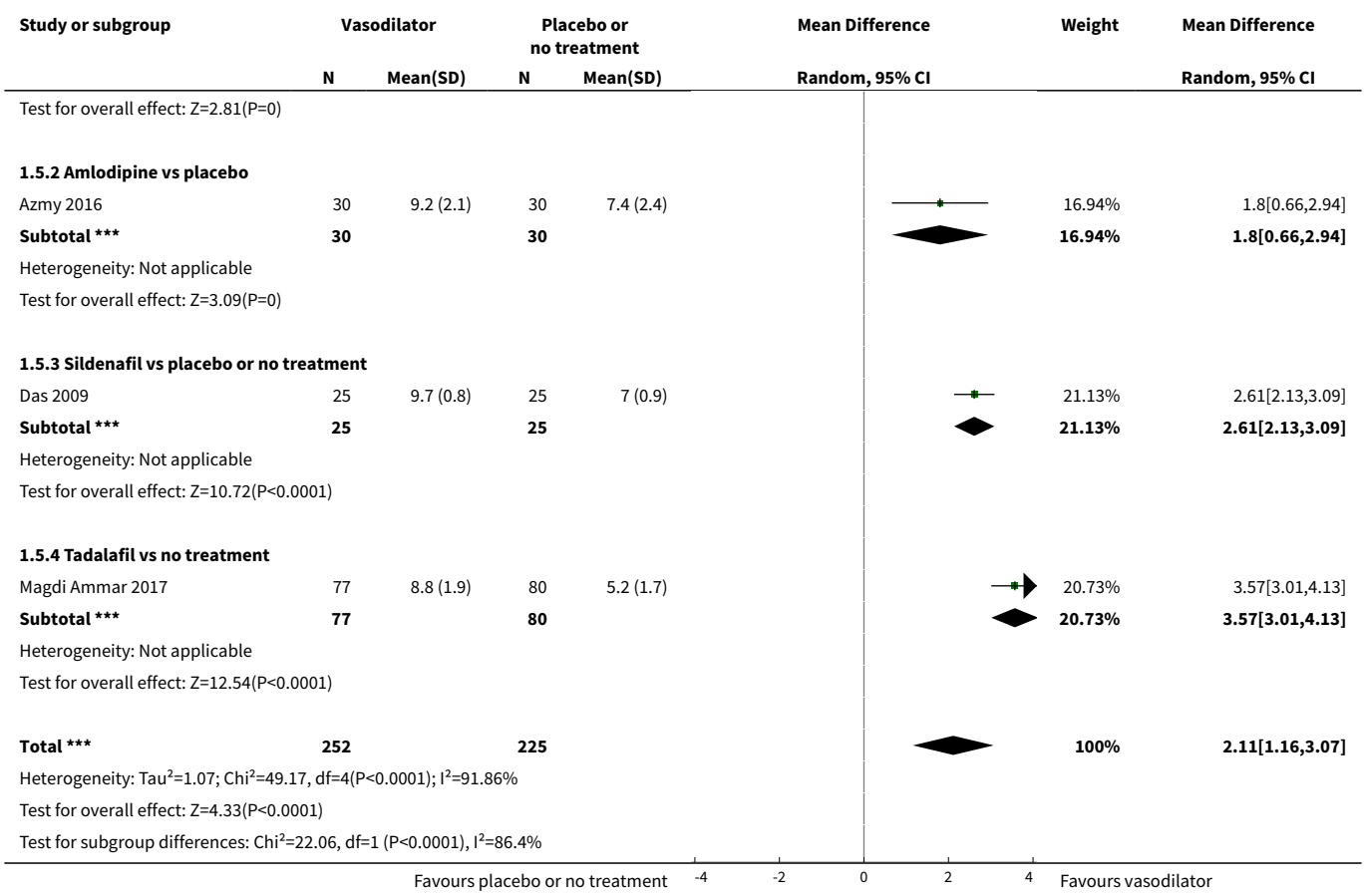
Analysis 1.4. Comparison 1 Vasodilator vs placebo or no treatment, Outcome 4 Clinical pregnancy.



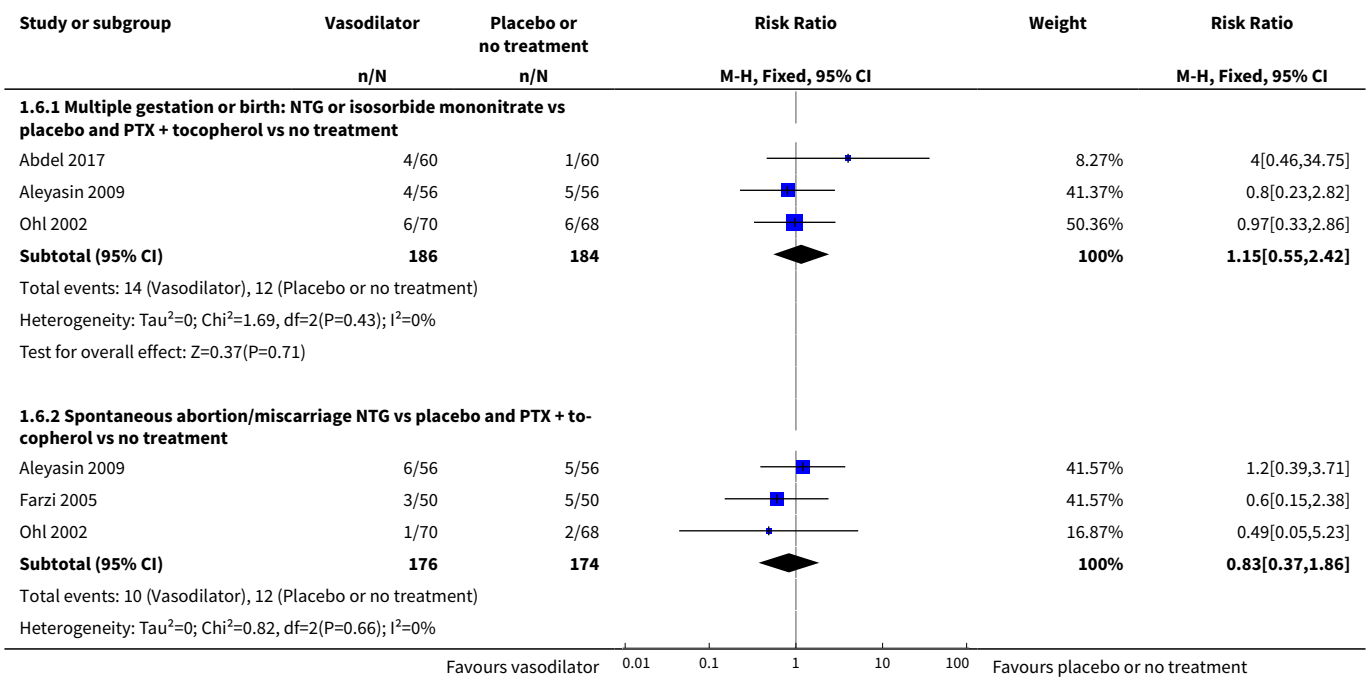


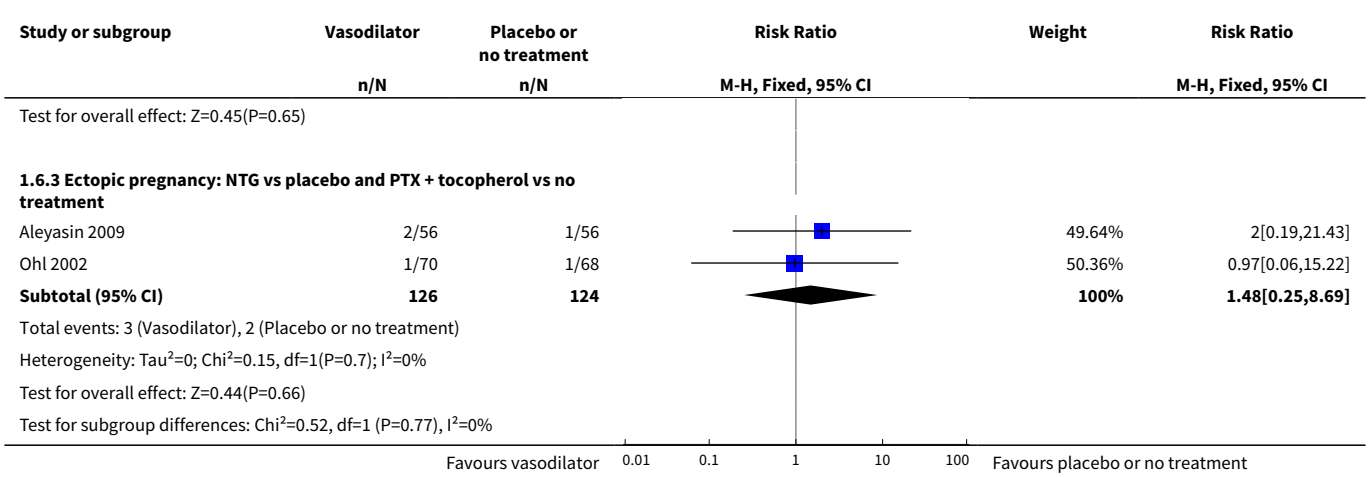
Analysis 1.5. Comparison 1 Vasodilator vs placebo or no treatment, Outcome 5 Thickened endometrium.





Analysis 1.6. Comparison 1 Vasodilator vs placebo or no treatment, Outcome 6 Other adverse effects.





APPENDICES

Appendix 1. Cochrane Gynaecology and Fertility Group (CGFG) specialised register search

Searched 24 October 2017

PROCITE platform

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 "endometrial" or "endometrial vascularity" or "Endometrium" or "endometrium profile" 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" or "endometrial" or "endometrial vascularity" or "Endometrium" or "endometrium profile "

AND

Keywords CONTAINS "vasodilation" or "Vasodilator Agents" or "Nifedipine" or"*Nitric Oxide" or "nitroglyceril" or "nitroglycerin" or "glycerine trinitrate" or "glyceryl trinitrate" or "Sildenafil" or "viagra" or "pentoxifylline" or "GTN" or Title CONTAINS "vasodilation" or "Vasodilator Agents" or "Nifedipine" or"*Nitric Oxide" or "nitroglyceril" or "nitroglycerin" or "glycerine trinitrate" or "glyceryl trinitrate" or "Sildenafil" or "viagra" or "pentoxifylline" or "GTN" (121 hits)

Appendix 2. CENTRAL search strategy

Searched 24 October 2017

Web platform

#1 MESH DESCRIPTOR Embryo Transfer EXPLODE ALL TREES 967

#2 MESH DESCRIPTOR Fertilization in Vitro EXPLODE ALL TREES 1861

#3 MESH DESCRIPTOR Sperm Injections, Intracytoplasmic EXPLODE ALL TREES 481

#4 (embryo* adj2 transfer*):TI,AB,KY 2454

#5 (vitro fertili?ation):TI,AB,KY 2149

#6 ivf:TI,AB,KY 3521

#7 icsi:TI,AB,KY 1628

#8 (intracytoplasmic sperm injection*):TI,AB,KY 1315

#9 (blastocyst* adj2 transfer*):TI,AB,KY 253

#10 MESH DESCRIPTOR Reproductive Techniques, Assisted EXPLODE ALL TREES 2848

#11 (assisted reproduct*):TI,AB,KY 829

#12 (artificial insemination):TI,AB,KY 182

#13 MESH DESCRIPTOR Insemination, Artificial EXPLODE ALL TREES 345

#14 IUI:TI,AB,KY 550

#15 (intrauterine insemination*):TI,AB,KY 714

#16 (ovulation induc*):TI,AB,KY 1915

#17 (ovar* adj2 stimulat*):TI,AB,KY 1373

#18 superovulat*:TI,AB,KY 176

#19 (ovarian hyperstimulation):TI,AB,KY 950

#20 COH:TI,AB,KY 247

#21 infertil*:TI,AB,KY 4472

#22 subfertil*:TI,AB,KY 598

#23 (ovar* adj2 induction):TI,AB,KY 178

#24 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 9284

#25 endometrium:TI,AB,KY 2554

#26 endometrial:TI,AB,KY 3556

#27 #25 OR #26 4212

#28 #24 OR #27 12417

#29 MESH DESCRIPTOR Vasodilator Agents EXPLODE ALL TREES 21709

#30 MESH DESCRIPTOR Nifedipine EXPLODE ALL TREES 1982

#31 MESH DESCRIPTOR nitroglycerin EXPLODE ALL TREES 1713

#32 MESH DESCRIPTOR Endothelium-Dependent Relaxing Factors EXPLODE ALL TREES 1711

#33 MESH DESCRIPTOR Nitric Oxide EXPLODE ALL TREES 1705

#34 MESH DESCRIPTOR Pentoxifylline EXPLODE ALL TREES 440

#35 MESH DESCRIPTOR Nimodipine EXPLODE ALL TREES 216

#36 vasodilator*:TI,AB,KY 6128

#37 nifedipine:TI,AB,KY 3462

#38 (glyceryl trinitrate or glyceryltrinitrate):TI,AB,KY 1504

#39 (GTN or NTG):TI,AB,KY 876

#40 nitroglycerin:TI,AB,KY 2754

#41 (nitric oxide):TI,AB,KY 5189

#42 nimodipine:TI,AB,KY 653

#43 (isosorbide monohydrate or Isosorbide Mononitrate):TI,AB,KY 279

#44 pentoxifylline:TI,AB,KY 926

#45 sildenafil:TI,AB,KY 1182

#46 Viagra:TI,AB,KY 136

#47 #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 30879

#48 #28 AND #47 101

Appendix 3. MEDLINE search strategy

Searched from 1946 to 24 October 2017

Ovid platform

1 exp embryo transfer/ or exp fertilization in vitro/ or exp sperm injections, intracytoplasmic/ (40351)
2 embryo transfer$.tw. (10959)
3 vitro fertili?ation.tw. (22214)
4 ivf-et.tw. (2469)
5 ivf.tw. (22183)
6 icsi.tw. (7351)
7 intracytoplasmic sperm injection$.tw. (6445)
8 (blastocyst adj2 transfer$).tw. (822)
9 exp reproductive techniques, assisted/ or exp insemination, artificial/ or exp ovulation induction/ (66621)
10 assisted reproduct$.tw. (12915)
11 artificial insemination.tw. (6214)
12 iui.tw. (1657)
13 intrauterine insemination$.tw. (2383)
14 ovulation induc$.tw. (4249)
15 (ovari$ adj2 stimulat$).tw. (6492)
16 superovulat$.tw. (3385)
17 ovarian hyperstimulation.tw. (4997)
18 COH.tw. (1563)
19 infertil$.tw. (57074)
20 subfertil$.tw. (4807)
21 (ovari$ adj2 induction).tw. (280)
22 endometrium.tw. (26929)
23 endometrial.tw. (55007)
24 or/1-23 (189642)
25 exp vasodilator agents/ or exp nifedipine/ or exp nitroglycerin/ or exp endothelium-dependent relaxing factors/ or exp nitric oxide/ (430137)
26 exp Pentoxifylline/ (4260)
27 exp Nimodipine/ (2758)
28 vasodilator$.tw. (36048)
29 nifedipine.tw. (20421)
30 (glyceryl trinitrate or glyceryltrinitrate).tw. (2532)
31 (GTN or NTG).tw. (4958)
32 nitroglycerin.tw. (10595)
33 nitric oxide.tw. (136969)
34 nimodipine.tw. (3970)
35 (isosorbide monohydrate or Isosorbide Mononitrate).tw. (380)
36 pentoxifylline.tw. (4417)
37 sildenafil.tw. (6158)
38 Viagra.tw. (1091)
39 or/25-38 (519322)
40 24 and 39 (1497)
41 randomized controlled trial.pt. (497429)
42 controlled clinical trial.pt. (99269)
43 randomized.ab. (434012)
44 placebo.tw. (208217)

45 clinical trials as topic.sh. (195636)
46 randomly.ab. (299126)
47 trial.ti. (195999)
48 (crossover or cross-over or cross over).tw. (80875)
49 or/41-48 (1240559)
50 exp animals/ not humans.sh. (4680511)
51 49 not 50 (1143253)
52 40 and 51 (115)

Appendix 4. Embase search strategy

Searched from 1980 to 24 October 2017

Ovid platform

1 exp embryo transfer/ or exp fertilization in vitro/ or exp intracytoplasmic sperm injection/ (58902)
2 embryo$ transfer$.tw. (18051)
3 in vitro fertili?ation.tw. (26605)
4 icsi.tw. (13920)
5 intracytoplasmic sperm injection$.tw. (8391)
6 (blastocyst adj2 transfer$).tw. (1933)
7 ivf.tw. (34828)
8 exp infertility therapy/ or exp artificial insemination/ or exp intrauterine insemination/ or exp ovulation induction/ (86522)
9 assisted reproduct$.tw. (19022)
10 artificial insemination.tw. (5557)
11 iui.tw. (2804)
12 intrauterine insemination$.tw. (3306)
13 ovulation induc$.tw. (5219)
14 (ovari$ adj2 stimulat$).tw. (9678)
15 superovulat$.tw. (3524)
16 ovarian hyperstimulation.tw. (6759)
17 COH.tw. (2126)
18 infertil$.tw. (73043)
19 subfertil$.tw. (6033)
20 (endometrium or endometrial).tw. (82219)
21 (ovari$ adj2 induction).tw. (335)
22 or/1-21 (239111)
23 exp vasodilator agent/ (544768)
24 exp nifedipine/ (46662)
25 exp glyceryl trinitrate/ (35843)
26 exp Pentoxifylline/ (12593)
27 exp Nimodipine/ (9635)
28 nitroglycerin.tw. (11414)
29 exp nitric oxide/ (142551)
30 exp endothelium derived relaxing factor/ (4005)
31 vasodilator$.tw. (41034)
32 nifedipine.tw. (22609)
33 (GTN or NTG).tw. (6429)
34 (glyceryl trinitrate$ or glyceryltrinitrate$).tw. (2869)
35 nitric oxide.tw. (162284)
36 nimodipine.tw. (4775)
37 (isosorbide monohydrate or Isosorbide Mononitrate).tw. (540)
38 pentoxifylline.tw. (5071)
39 sildenafil.tw. (8858)
40 Viagra.tw. (4223)
41 exp sildenafil/ (19077)
42 or/23-41 (626118)
43 22 and 42 (2495)
44 Clinical Trial/ (953339)
45 Randomized Controlled Trial/ (475152)
46 exp randomization/ (76149)
47 Single Blind Procedure/ (29912)
48 Double Blind Procedure/ (141466)

49 Crossover Procedure/ (53656)
50 Placebo/ (301908)
51 Randomi?ed controlled trial$.tw. (169788)
52 Rct.tw. (26090)
53 random allocation.tw. (1708)
54 randomly allocated.tw. (28609)
55 allocated randomly.tw. (2279)
56 (allocated adj2 random).tw. (787)
57 Single blind$.tw. (19980)
58 Double blind$.tw. (176576)
59 ((treble or triple) adj blind$).tw. (725)
60 placebo$.tw. (257756)
61 prospective study/ (410882)
62 or/44-61 (1824183)
63 case study/ (50599)
64 case report.tw. (341442)
65 abstract report/ or letter/ (1014796)
66 or/63-65 (1398612)
67 62 not 66 (1777862)
68 43 and 67 (396)

Appendix 5. PsycINFO search strategy

Searched from 1806 to 24 October 2017

Ovid platform

1 exp reproductive technology/ (1654)
2 in vitro fertili?ation.tw. (672)
3 ivf-et.tw. (17)
4 (ivf or et).tw. (123274)
5 icsi.tw. (67)
6 intracytoplasmic sperm injection$.tw. (50)
7 (blastocyst adj2 transfer$).tw. (4)
8 assisted reproduct$.tw. (819)
9 artificial insemination.tw. (243)
10 iui.tw. (31)
11 intrauterine insemination$.tw. (23)
12 ovulation induc$.tw. (27)
13 (ovari$ adj2 stimulat$).tw. (55)
14 ovarian hyperstimulation.tw. (11)
15 COH.tw. (97)
16 superovulat$.tw. (6)
17 infertil$.tw. (3149)
18 subfertil$.tw. (82)
19 (ovari$ adj2 induction).tw. (7)
20 (endometrial or endometrium).tw. (353)
21 or/1-20 (127886)
22 exp vasodilator drugs/ (513)
23 (isosorbide monohydrate or Isosorbide Mononitrate).tw. (8)
24 pentoxifylline.tw. (74)
25 nifedipine.tw. (490)
26 nimodipine.tw. (449)
27 nitroglycerin.tw. (162)
28 exp Nitric Oxide/ (3354)
29 nitric oxide.tw. (5340)
30 vasodilator$.tw. (620)
31 (GTN or NTG).tw. (164)
32 (glyceryl trinitrate or glyceryltrinitrate).tw. (93)
33 exp Sildenafil/ (305)
34 sildenafil.tw. (574)
35 Viagra.tw. (243)
36 or/22-35 (8088)

37 21 and 36 (310)
38 random.tw. (51200)
39 control.tw. (395909)
40 double-blind.tw. (21045)
41 clinical trials/ (10626)
42 placebo/ (4994)
43 exp Treatment/ (697142)
44 or/38-43 (1081717)
45 37 and 44 (122)

Appendix 6. CINAHL search strategy

Searched from 1961 to 24 October 2017

Ebsco platform

#	Query	Results
S60	S47 AND S59	41
S59	S48 OR S49 OR S50 OR S51 OR S52 OR S53 OR S54 OR S55 OR S56 OR S57 OR S58	1,170,446
S58	TX allocat* random*	7,342
S57	(MH "Quantitative Studies")	16,570
S56	(MH "Placebos")	10,412
S55	TX placebo*	47,780
S54	TX random* allocat*	7,342
S53	(MH "Random Assignment")	44,365
S52	TX randomi* control* trial*	133,408
S51	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*))	913,662
S50	TX clinic* n1 trial*	212,726
S49	PT Clinical trial	80,060
S48	(MH "Clinical Trials+")	223,465
S47	S27 AND S46	113
S46	S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43 OR S44 OR S45	20,949
S45	TX (isosorbide monohydrate or Isosorbide Mononitrate)	Display
S44	TX GTN or TX NTG	440
S43	TX glyceryltrinitrate	Display

(Continued)

S42	TX Nimodipine	366
S41	(MM "Nimodipine")	136
S40	TX Pentoxifylline	Display
S39	(MM "Pentoxifylline")	214
S38	TX Viagra	395
S37	TX sildenafil	Display
S36	TX nitric oxide	11,740
S35	TX nitroglycerin	1,599
S34	TX glyceryl trinitrate	Display
S33	TX nifedipine	1,027
S32	TX vasodilator*	5,440
S31	(MM "Nitric Oxide")	Display
S30	(MM "Nitroglycerin")	540
S29	(MM "Nifedipine")	350
S28	(MM "Vasodilator Agents")	1,817
S27	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26	Display
S26	TX endometrial	6,396

WHAT'S NEW

Date	Event	Description
20 March 2018	New search has been performed	In this version, we have added 5 studies (Abdel 2017; Azmy 2016; Fahmy 2015; Magdi Ammar 2017; Mahran 2016).
20 March 2018	New citation required but conclusions have not changed	The addition of 5 new studies has not led to a change in the conclusions of this review.

CONTRIBUTIONS OF AUTHORS

For the 2018 update:

RBG 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.

XB conceived of the study; co-ordinated the whole review process; provided general advice on all processes; solved discrepancies; and approved the final version of the review.

DG participated in study selection; provided general advice on study design; collaborated in the writing process of the review; and approved the final version of the review.

AV participated in study selection and assessment and data extraction; and approved the final version of the review.

FR participated in assessment and extraction of data; and approved the final version of the review actualisation.

MJM participated in assessment of potentially eligible studies; performed data analysis; collaborated in the writing process of the review; and approved the final version of the review.

DECLARATIONS OF INTEREST

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

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In this version, we added the word "safety" to the objectives.

In the previous version, review authors performed the analysis while applying a random-effects model; however for this update, review authors used a fixed-effect model because clinical and statistical heterogeneity between studies was minimal.

We did not perform a sensitivity analysis by calculating the odds ratio (OR), as the rate of events were common (> 20%) and in this case, the OR may overestimate the intervention effect.

We added a post hoc subgroup analysis to evaluate studies that used only vasodilators versus no co-intervention.

INDEX TERMS

Medical Subject Headings (MeSH)

*Pregnancy Rate; Embryo Implantation [*drug effects]; Infertility, Female [*therapy]; Live Birth; Randomized Controlled Trials as Topic; Vasodilator Agents [*therapeutic use]

MeSH check words

Female; Humans; Pregnancy