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Oestrogens alone or with amniotomy for cervical ripening or induction of labour (Review)

Thomas J, Kelly AJ, Kavanagh J

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[Intervention Review]

Oestrogens alone or with amniotomy for cervical ripening or induction of labour

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ABSTRACT

Background

It is suggested that oestrogen may promote changes in cervical favourability with minimal effect on uterine activity and could be used to induce labour or prime the cervix. A variety of oestrogen preparations (infusions, gels, creams and tablets) and routes of administrations (oral, vaginal, extra-amniotic) vaginal,extra-amniotic) have been used in inpatient and outpatient settings. Oestrogen is rarely used in clinical practice. There are no commercially available preparations of oestrogen for induction and in most cases this is prepared specifically for the study.

Objectives

To determine the effectiveness and safety of oestrogens alone, or with amniotomy, for third trimester cervical ripening and induction of labour in comparison with other methods of induction of labour.

Search methods

We searched the Cochrane Pregnancy and Childbirth Group trials register (January 2008), the Cochrane Register of Controlled Trials (*The Cochrane Library,* Issue 4, 2007), and bibliographies of relevant papers.

Selection criteria

Randomised controlled trials comparing oestrogens for third trimester cervical ripening or labour induction with placebo/no treatment or other methods listed above it on a predefined list of labour induction methods.

Data collection and analysis

Studies were assessed by at least two review authors.

Main results

Seven studies (465 women) were included. Only studies using oestrogens alone were identified; there were no trials of oestrogen with amniotomy. Three studies used intravaginal oestrogen, two used extra-amniotic oestrogen, one used an intravenous preparation, and one used oral tablets. Three studies were inpatient studies, one was an outpatient intervention and three did not state whether the setting was inpatient or outpatient. None of the studies reported the primary outcomes of rates of vaginal delivery not achieved in 24 hours. There

were insufficient data to make any meaningful conclusions when comparing oestrogen with vaginal prostaglandin (PGE2), oxytocin alone, or extra amniotic PGF2a, as to whether oestrogen is effective in inducing labour.

There was no evidence of a difference between oestrogen and placebo in the rate of caesarean section, uterine hyperstimulation with or without fetal heart rate changes, or instrumental vaginal delivery.

Authors' conclusions

There were insufficient data to quantify the safety and effectiveness of oestrogen as an induction agent; they should only be used as part of randomised control trials as there are alternative effective options for inducting labour.

PLAIN LANGUAGE SUMMARY

Oestrogens alone or with amniotomy for cervical ripening or induction of labour

There is not enough evidence, from randomised controlled trials, to show the effects and safety of oestrogen to ripen the cervix and help bring on labour.

Sometimes it is necessary to bring on labour artificially, because of safety concerns for either the pregnant woman or baby. Oestrogen is a hormone involved in the ripening of the neck of the womb (cervix) and preparing it for the birth of the baby. It is possible that oestrogen increases the release of other local hormones (prostaglandins) which help ripen the cervix. A variety of oestrogen preparations have been used (such as tablets, creams and infusions). They have been used for inductions when women are inpatients and outpatients. There is not enough research from the review of seven studies (with 465 women) to show the true effect of oestrogen. Oestrogen is not commonly used in current clinical practice as alternative agents that are known to be effective are available.

BACKGROUND

Sometimes it is necessary to bring on labour artificially because of safety concerns for the mother or baby. This review is one of a series of reviews of methods of labour induction using a standardised protocol. For more detailed information on the rationale for this methodological approach, please refer to the currently published 'generic' protocol (Hofmeyr 2000). The generic protocol describes how a number of standardised reviews will be combined to compare various methods of preparing the cervix of the uterus and inducing labour.

Studies in sheep showed that there is a pre-labour rise in oestrogen and a decrease in progesterone, both of these changes stimulate prostaglandin production and may help initiate labour. Research in humans has failed to demonstrate a similar physiological mechanism. However oestrogen has been suggested as an effective cervical ripening and induction agent, promoting changes in cervical favourability but with less effect on uterine activity and as such could be used to induce labour, or prime the cervix and uterus, prior to induction with other methods. There has been a slight resurgence of interest in oestrogens as an agent for cervical ripening in an outpatient setting, and induction of labour in outpatient versus inpatient settings are the subject of another review (Kelly 2008). Most studies have used natural oestrogen analogues such as oestradiol. More potent synthetic oestrogens such as stilbestrol are no longer used because of the long term adverse events in female children. Oestrogens are associated with a variety of adverse effects (such as an increase in thromboembolic disease) which could reduce the potential benefit of their use in pregnancy. A variety of oestrogen preparations (including tablets, infusions, gels and creams) and routes of administrations have been used (oral, rectal, vaginal, intracervical, extra-amniotic and intravenous routes). Administration of some oestrogen preparations such as tablets gels or creams will be possible in either an inpatient or outpatient setting. However, using intravenous or extraamniotic infusions are likely to only be possible in an inpatient setting. In most studies the oestrogen was prepared specifically for the study. The use of oestrogen as an induction agent is not currently in common use in clinical practice and there are no commercially available preparations of oestrogen for its use in cervical ripening or induction of labour .

OBJECTIVES

To determine, from the best available evidence, the effectiveness and safety of oestrogens alone, or with amniotomy, for third trimester cervical ripening and induction of labour in comparison with other methods of induction of labour.

METHODS

Criteria for considering studies for this review

Types of studies

Clinical trials comparing oestrogens alone or with amniotomy for cervical ripening or labour induction, with placebo/no treatment or other methods listed above it on a predefined list of methods of labour induction (see 'Data collection and analysis'); the trials included some form of random allocation to either group; and they reported one or more of the prestated outcomes.

Types of participants

Pregnant women due for third trimester induction of labour, carrying a single live fetus. Women having induction of labour in either inpatient or outpatient settings will be included.

Predefined sub-group analyses will be (see Data collection and analysis): previous caesarean section or not; nulliparity or multiparity; membranes intact or ruptured, and cervix unfavourable, favourable or undefined. Only those outcomes with data will appear in the analysis tables.

Types of interventions

There are a variety of oestrogen preparations (tablets, infusions, gels and creams) and several possible routes of administrations have been used (oral, rectal, vaginal, intracervical, extra-amniotic and intravenous routes). We will include any oestrogen used alone or with amniotomy compared with any of the 14 interventions listed above oestrogen in the generic protocol (namely: 1. placebo/no treatment; 2. vaginal prostaglandins; 3. intracervical prostaglandins; 4.intravenous oxytocin; 5.amniotomy; 6.intravenous oxytocin with amniotomy; 7. vaginal misoprostol; 8.oral misoprostol; 9.mechanical methods including extra-amniotic Foley catheter; 10.membrane sweeping; 11.extra-amniotic prostaglandins; 12.intravenous prostaglandins; 13.oral prostaglandins; and 14 mifepristone).

As a number of trials administer oestrogen via a Foley catheter into the extra amniotic space, it was decided by the authors prior to data extraction to exclude any trial where the Foley catheter balloon was inflated to any volume greater than or equal to 10 mls. At this level it was felt that there was potential for the catheter balloon to have an additional effect to the oestrogens, and that this interaction would make it difficult to measure the effect of oestrogens.

For oestrogen and amniotomy to be considered as concomitant interventions both needed to be delivered within two hours of each other. This is in accordance with other reviews on induction of labour where amniotomy is considered as a concomitant intervention. Studies of oestrogen and amniotomy with other interventions are considered separate comparisons.

It is possible to use some oestrogen preparations (such as tablets, gels or creams) by oral or vaginal route in either inpatient or outpatient settings. However, using intravenous or extraamniotic infusion are likely to only be possible in an inpatient setting.

The primary comparisons listed below are the only comparisons for which there are data. Comparisons for which no studies were identified (namely oestrogens with amniotomy and comparison with vaginal misoprostol; oral misoprostol; mechanical methods including extra-amniotic Foley catheter; membrane sweeping; intravenous prostaglandins; oral prostaglandins; and mifepristone) are not listed below.

Primary comparisons.
(1) oestrogen alone (all routes) versus placebo (all routes);
(2) oestrogen alone (all routes) versus vaginal prostaglandin;
(3) oestrogen alone (all routes) versus intracervical prostaglandin;
(4) oestrogen alone (all routes) versus oxytocin alone;
(5) oestrogen alone (all routes) versus extra-amniotic prostaglandins.

Types of outcome measures

Clinically relevant outcomes for trials of methods of cervical ripening/labour induction have been prespecified by two authors of labour induction reviews (Justus Hofmeyr and Zarko Alfirevic). Differences were settled by discussion.

Five primary outcomes were chosen as being most representative of the clinically important measures of effectiveness and complications. Sub-group analyses will be limited to the primary outcomes:
(1) vaginal delivery not achieved within 24 hours;
(2) uterine hyperstimulation with fetal heart rate (FHR) changes;
(3) caesarean section;
(4) serious neonatal morbidity or perinatal death (e.g. seizures, birth asphyxia defined by trialists, neonatal encephalopathy, disability in childhood);
(5) serious maternal morbidity or death (e.g. uterine rupture, admission to intensive care unit, septicaemia).

Perinatal and maternal morbidity and mortality are composite outcomes. This is not an ideal solution because some components are clearly less severe than others. It is possible for one intervention to cause more deaths but less severe morbidity. However, in the context of labour induction at term this is unlikely. All these events will be rare, and a modest change in their incidence will be easier to detect if composite outcomes are presented. The incidence of individual components will be explored as secondary outcomes (see below).

Secondary outcomes relate to measures of effectiveness, complications and satisfaction:

Measures of effectiveness:
(6) cervix unfavourable/unchanged after 12 to 24 hours;
(7) oxytocin augmentation.

Complications:
(8) uterine hyperstimulation without FHR changes;
(9) uterine rupture;
(10) epidural analgesia;
(11) instrumental vaginal delivery;
(12) meconium stained liquor;
(13) Apgar score < 7 at 5 minutes;
(14) neonatal intensive care unit admission;
(15) neonatal encephalopathy;
(16) perinatal death;
(17) disability in childhood;
(18) maternal side effects (all);
(19) maternal nausea;
(20) maternal vomiting;
(21) maternal diarrhoea;
(22) other maternal side-effects (e.g. thromboembolic events);
(23) postpartum haemorrhage (as defined by the trial authors);
(24) serious maternal complications (e.g. intensive care unit admission, septicaemia but excluding uterine rupture);
(25) maternal death.

Measures of satisfaction:
(26) woman not satisfied;
(27) caregiver not satisfied.

While all the above outcomes were sought, only those with data appear in the analysis tables.

The aim of treatment maybe either cervical ripening and/or induction of labour. Where the aim of treatment is cervical ripening for example in an outpatient setting rather than induction of labour, then the other primary outcomes rather than "vaginal delivery not achieved within 24 hours" are more relevant.

The terminology of uterine hyperstimulation is problematic (Curtis 1987). In the review we used the term 'uterine hyperstimulation without FHR changes' to include uterine tachysystole (> 5 contractions per 10 minutes for at least 20 minutes) and uterine hypersystole/hypertonus (a contraction lasting at least two minutes) and 'uterine hyperstimulation with FHR changes' to denote uterine hyperstimulation syndrome (tachysystole or hypersystole with fetal heart rate changes such as persistent decelerations, tachycardia or decreased short term variability).

Outcomes were included in the analysis: if reasonable measures were taken to minimise observer bias; and data were available for analysis according to original allocation.

Search methods for identification of studies

We searched the Cochrane Pregnancy and Childbirth Group trials register by contacting the Trials Search Co-ordinator (January 2008).

The Cochrane Pregnancy and Childbirth Group's trials register is maintained by the Trials Search Co-ordinator and contains trials identified from:
1. quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. monthly searches of MEDLINE;
3. handsearches of 30 journals and the proceedings of major conferences;
4. weekly current awareness search of a further 37 journals.

Details of the search strategies for CENTRAL and MEDLINE, the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service can be found in the 'Search strategies for identification of studies' section within the editorial information about the Cochrane Pregnancy and Childbirth Group.

Trials identified through the searching activities described above are given a code (or codes) depending on the topic. The codes are linked to review topics. The Trials Search Co-ordinator searches the register for each review using these codes rather than keywords.

We did not apply any language restrictions.

The initial search was performed simultaneously for all reviews of methods of inducing labour, as outlined in the generic protocol for these reviews (Hofmeyr 2000).

The reference lists of trial reports and reviews were searched by hand.

Data collection and analysis

A strategy has been developed to deal with the large volume and complexity of trial data relating to labour induction. Many methods have been studied, examining the effects of these methods when induction of labour was undertaken in a variety of clinical groups e.g. restricted to primiparous women or those with ruptured membranes. Most trials are intervention-driven, comparing two

or more methods in various categories of women. Clinicians and parents need the data arranged according to the clinical characteristics of the women undergoing induction of labour, to be able to choose which method is best for a particular clinical scenario. To extract these data from several hundred trial reports in a single step would be very difficult. We developed a two-stage method of data extraction. The initial data extraction was done in a series of primary reviews arranged by methods of induction of labour, following a standardised methodology. The data was then extracted from the primary reviews into a series of secondary reviews, arranged by the clinical characteristics of the women undergoing induction of labour.

To avoid duplication of data in the primary reviews, the labour induction methods have been listed in a specific order, from one to 23. Each primary review included comparisons between one of the methods (from two to 23) with only those methods above it on the list. Thus, the review of intravenous oxytocin (4) will include only comparisons with intracervical prostaglandins (3), vaginal prostaglandins (2) or placebo (1). Methods identified in the future will be added to the end of the list. The current list is as follows:

(1) placebo/no treatment;
(2) vaginal prostaglandins (Kelly 2003);
(3) intracervical prostaglandins (Boulvain 2008);
(4) intravenous oxytocin (Kelly 2001);
(5) amniotomy (Bricker 2000);
(6) intravenous oxytocin with amniotomy (Howarth 2001);
(7) vaginal misoprostol (Hofmeyr 2003);
(8) oral misoprostol (Alfirevic 2006);
(9) mechanical methods including extra-amniotic Foley catheter (Boulvain 2001);
(10) membrane sweeping (Boulvain 2005);
(11) extra-amniotic prostaglandins (Hutton 2001);
(12) intravenous prostaglandins (Luckas 2000);
(13) oral prostaglandins (French 2001);
(14) mifepristone (Neilson 2000);
(15) oestrogens with or without amniotomy (Thomas 2001);
(16) corticosteroids (Kavanagh 2006);
(17) relaxin (Kelly 2001a);
(18) hyaluronidase Kavanagh 2006a;
(19) castor oil, bath, and/or enema (Kelly 2001b);
(20) acupuncture (Smith 2004);
(21) breast stimulation (Kavanagh 2005);
(22) sexual intercourse (Kavanagh 2001);
(23) homoeopathic methods (Smith 2003);
(24) buccal or sublingual misoprostol (Muzonzini 2004);

(25) nitric oxide (Kelly 2008a);
(26) hypnosis.

The primary reviews will be analysed by the following subgroups:
(1) previous caesarean section or not;
(2) nulliparity or multiparity;
(3) membranes intact or ruptured;
(4) cervix favourable, unfavourable or undefined.

The secondary reviews will include all methods of labour induction for each of the categories of women for which subgroup analysis has been done in the primary reviews, and will include only five primary outcome measures. There will thus be six secondary reviews, of methods of labour induction in the following groups of women:
(1) nulliparous, intact membranes (unfavourable cervix, favourable cervix, cervix not defined);
(2) nulliparous, ruptured membranes (unfavourable cervix, favourable cervix, cervix not defined);
(3) multiparous, intact membranes (unfavourable cervix, favourable cervix, cervix not defined);
(4) multiparous, ruptured membranes (unfavourable cervix, favourable cervix, cervix not defined);
(5) previous caesarean section (intact or ruptured membranes and unfavourable cervix, favourable cervix, cervix not defined).
(6) previous caesarean section, ruptured membranes (unfavourable cervix, favourable cervix, cervix not defined).

Each time a primary review is updated with new data, those secondary reviews which include data which have changed, will also be updated.

The trials included in the primary reviews were extracted from an initial set of trials covering all interventions used in induction of labour (see above for details of search strategy). The data extraction process was conducted centrally. This was coordinated from the Clinical Effectiveness Support Unit (CESU) at the Royal College of Obstetricians and Gynaecologists, UK, in co-operation with The Pregnancy and Childbirth Group of The Cochrane Collaboration. This process allowed the data extraction process to be standardised across all the reviews.

The trials were initially reviewed on eligibility criteria, using a standardised form and the basic selection criteria specified above. Following this, data were extracted to a standardised data extraction form which was piloted for consistency and completeness. The pilot process involved the researchers at the CESU and previous reviewers in the area of induction of labour.

Information was extracted regarding the methodological quality of trials on a number of levels. This process was completed without consideration of trial results. Assessment of selection bias examined the process involved in the generation of the random sequence and the method of allocation concealment separately. These were then judged as adequate or inadequate using the criteria described in Table 1 for the purpose of the reviews.

Performance bias was examined with regards to whom was blinded in the trials i.e. participant, caregiver, outcome assessor or analyst. In many trials the caregiver, assessor and analyst were the same party. Details of the feasibility and appropriateness of blinding at all levels was sought.

Individual outcome data were included in the analysis if they meet the pre stated criteria in 'Types of outcome measures'. Included trial data were processed as described in the Cochrane Collaboration Handbook (Cochrane 2008). Data extracted from the trials were analysed on an intention to treat basis (when this was not done in the original report, re-analysis is performed if possible). Where data were missing, clarification was sought from the original authors. If the attrition was such that it might significantly affect the results, these data were excluded from the analysis. This decision rested with the reviewers of primary reviews and is clearly documented. If missing data become available, they will be included in the analyses.

Data were extracted from all eligible trials to examine how issues of quality influence effect size in a sensitivity analysis. In trials

where reporting was poor, methodological issues were reported as unclear or clarification sought.

Due to the large number of trials, double data extraction was not feasible and agreement between the three data extractors was therefore assessed on a random sample of trials.

Once the data had been extracted, they were distributed to individual reviewers for entry onto the Review Manager computer software (RevMan 2008), checked for accuracy, and analysed as above using the RevMan software. For dichotomous data, relative risks and 95% confidence intervals were calculated, and in the absence of heterogeneity, results were pooled using a fixed-effect model.

The predefined criteria for sensitivity analysis included all aspects of quality assessment as mentioned above, including aspects of selection, performance and attrition bias.

Primary analysis was limited to the prespecified outcomes and sub-group analyses. In the event of differences in unspecified outcomes or sub-groups being found, these were analysed post hoc, but clearly identified as such to avoid drawing unjustified conclusions.

RESULTS

Description of studies

In total, 25 studies were considered; 18 were excluded and seven (with a total of 465 women) were included. For further details of study characteristics refer to 'characteristics of included/excluded studies'.

All included studies compared oestrogen alone with other interventions, no included studies compared oestrogen with amniotomy with any other interventions.

- Excluded studies:

Six studies involved complex interventions, with oestrogen or placebo being combined with an extra amniotic Foley catheter (Gordon 1977; Peedicayil 1989; Pedersen 1981; Roztocil 1998; Stewart 1981; Thiery 1979). In one study oestrogen or a placebo was then followed by oral prostaglandin E2 (Luther 1980).

Eight studies did not report any prespecified outcomes in an extractable format (Griffin 2003; Klopper 1973; Magnani 1986; Mamo 1994; Moran 1994; Palmero 1997; Pedersen 1981; Thiery 1978).

One study involved induction after failed induction (Martin 1955).

One study involved intra amniotic administration of oestrogen after the onset of labour (Klopper 1969).

One study involved induction with Dehydroepiandrosterone sulphate (Sasaki 1982).

- Included studies:

The oestrogen preparations used varied. One study (Klopper 1962) used oral tablets, one used intravenous infusion (Pinto 1967), two used extra-amniotic oestrogen (Peedicayil 1990, Quinn 1981) and three used intravaginal oestrogen cream (Larmon 2002, Magann 1995, Tromans 1981)

Five studies compared oestrogen with placebo. The oestrogen was delivered as oral tablets in one trial (Klopper 1962), as an intravenous infusion in another (Peedicayil 1990), as an extra-amniotic formulation in two studies (Pinto 1967; Quinn 1981) and a vaginal oestrogen cream in one study (Larmon 2002).

One study compared intravaginal oestrogen cream with intravaginal PGE2 (Tromans 1981).

One study compared intravaginal oestrogen cream with intracervical PGE2 (Larmon 2002). Different to other included studies these interventions were given as a weekly outpatient treatment until the onset of spontaneous labour.

One study compared intracervical oestrogen with intracervical PGE2 (Magann 1995).

The same study compared intracervical oestrogen with oxytocin (Magann 1995).

One study compared extra-amniotic oestrogen with extra-amniotic PGF2a (Quinn 1981).

Three studies had three arms and hence reported in two comparisons (Magann 1995; Larmon 2002; Quinn 1981).

Three studies (Pinto 1967; Quinn 1981,Tromans 1981 that included a total of 185 women) stated they were undertaken in an inpatient setting, the first two of these studies used extra-amniotic formulation the third used intravaginal cream. One study using intravaginal cream in the intervention arm (Larmon 2002 with 87 women) was undertaken in an outpatient setting. Three studies did not state if the study had been conducted in an inpatient or outpatient setting, the first used oral oestradiol tablets (Klopper 1962), the second (Magann 1995) used vaginal cream, and the third (Peedicayil 1990) used extra-amniotic oestrogen.

Risk of bias in included studies

- Randomisation and concealment

One trial used computer-generated random number sequences (Magann 1995), one trial used random number tables (Larmon 2002), one trial allocated depending on the date of admission (Tromans 1981) and one trial used alternation as a means of allocation (Pinto 1967). The remaining studies were unclear regarding the method of generation of the randomisation sequence.

Concealment was achieved by sealed opaque envelopes in one trial (Magann 1995), opaque numbered envelopes in another (Larmon 2002) and using coded drug boxes or bottles in two further trials (Peedicayil 1990; Quinn 1981). The remaining studies were unclear regarding concealment or used open allocation as a result of inadequate randomisation methods.

- Blinding

Double blinding was accomplished in all four placebo controlled trials (Klopper 1962; Peedicayil 1990; Pinto 1967; Quinn 1981), and was not possible in the remaining trials due to the nature of the active comparison.

Effects of interventions

None of the studies compared oestrogen with amniotomy. None of the studies reported the primary outcome of rates of either vaginal delivery not achieved in 24 hours, or the measure of effectiveness of the cervix unfavourable/unchanged after 12 to 24 hours. There were insufficient data to make any meaningful conclusions when comparing oestrogen with vaginal PGE2, intracervical PGE2, oxytocin alone or extra amniotic PGF2a, as to whether oestrogen is effective for inducing labour.

All the outcomes listed under 'Types of outcome measures' and sub-groups defined in 'Types of participants' were sought. Only those with data appear in the analysis tables.
Data discussed applies to the 'all women' group and unless stated there was no difference between any of the prespecified sub-groups.

(1) Oestrogen alone (all routes) versus placebo (all routes) (five studies: 306 women)

There was no evidence of a difference between the rate of caesarean section between oestrogen and placebo (14.7% versus 14.6%, relative risk (RR) 1.00, 95% confidence interval (CI) 0.6 to 1.68). There was no evidence of a difference between rates of uterine hyperstimulation with or without fetal heart rate changes or instrumental vaginal delivery.

(2) Oestrogen alone (all routes) versus vaginal prostaglandin (one study: 60 women)

There were insufficient data to make any meaningful conclusions when comparing oestrogen with vaginal PGE2.

(3) Oestrogen alone (all routes) versus intracervical prostaglandin (two studies: 151 women)

There was no evidence of a difference between the rate of caesarean section between oestrogen and intracervical PGE2 (44.1% versus 33.8%, RR 1.33, 95% CI 0.90 to 1.95).There were insufficient data to make any meaningful conclusions when comparing oestrogen with intracervical PGE2.

(4) Oestrogen alone (all routes) versus oxytocin alone (one study: 66 women)

There were insufficient data to make any meaningful conclusions when comparing oestrogen with oxytocin alone.

(5) Oestrogen alone (all routes) versus extra amniotic prostaglandins (one study: 30 women)

There were insufficient data to make any meaningful conclusions when comparing oestrogen with extra amniotic PGF2a.

DISCUSSION

There were insufficient data to draw any conclusions regarding the efficacy of oestrogen alone as an induction agent. No trails considered the use of oestrogen with amniotomy and none of the included trials reported on vaginal delivery not achieved within 24 hours.

The delivery of oestrogen within the included trials is varied (oral, intravenous, vaginal, and extra-amniotic), and no attempt was made to sub-divide the routes of administration. The effect of different delivery methods would not be possible to quantify unless much larger numbers of trials were available. In most studies it is specified that the oestrogen preparation was made specifically for the study and was not from a commercially available form. There is very limited information about the use of oestrogens in an outpatient setting. In this context the aim of treatment has been to promote cervical ripening rather than induce labour, and the outcome of achieving a delivery within 24 hours is not the most relevant outcome.

AUTHORS' CONCLUSIONS

Implications for practice

Oestrogens should not currently be used for induction of labour or cervical ripening as their effectiveness and safety cannot be quantified at present and there are alternative effective treatment options.

Implications for research

Future studies evaluating the effectiveness of oestrogen need to be of good methodological quality and should report on all the outcomes listed in the generic protocol of the induction of labour reviews.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Klopper 1962

Methods	No mention of method of randomisation or concealment.
Participants	44 nulliparous women, > 37 weeks pregnant. Not stated if IP or OP setting
Interventions	10 mg oral oestradiol (20 mg initially, followed by 10 mg 6 hourly) vs placebo.
Outcomes	Caesarean section.
Notes	Not stated if inpatient or outpatient setting, University of Aberdeen, UK. Two trials reported, only smaller first trial is definite RCT. Funding not stated but Intervention and placebo donated by pharmaceutical company Organnon.

Klopper 1962 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Larmon 2002

Methods	Randomisation by random number tables, concealment by opaque numbered envelopes.
Participants	87 pregnant women> 37 weeks, unfavourable cervix (Bishops score <6), outpatient setting.
Interventions	0.5 mg PGE2 intracervical gel versus 4 mg vaginal oestrogen gel versus inert gel. All given weekly until spontaneous labour or membrane rupture. No maximum specified.
Outcomes	Caesarean section, oxytocin augmentation, instrumental vaginal delivery, meconium stained liquor, neonatal intensive care unit admission, serious maternal complications.
Notes	Outpatient setting. University of Mississippi Medical centre, USA. Funded in part by the Vicksburg Medical Foundation, Mississippi.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Magann 1995

Methods	Computer generated sequence, allocation by sealed opaque envelopes.
Participants	99 pregnant women (33 in each treatment group), with intact membranes, Bishops score < 4. Setting not stated but probably an inpatient setting.
Interventions	4 mg vaginal oestradiol cream (6 hourly, max 3 doses) vs 0.5 mg intracervical PGE2 gel (6 hourly, max 3 doses) vs IV oxytocin (starting at 1mU/min increased every 30 minutes).
Outcomes	Caesarean section, instrumental vaginal delivery.
Notes	University of Mississippi Medical centre, USA. Setting not stated but probably an inpatient setting. Source of funding not stated.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Peedicayil 1990

Methods	Randomisation method unclear, concealment by coded drug boxes.
Participants	50 Multiparae, unfavourable cervix (Bishops score < 3), singleton, cephalic, > 37 weeks. Not stated if IP or OP.
Interventions	150 mg extra amniotic oestradiol vs extra amniotic placebo.
Outcomes	Caesarean section, perinatal mortality, instrumental vaginal delivery.
Notes	Christian medical college and hospital, Vellore, India. Setting not stated but probably an inpatient. Source of funding not stated. Unclear from report to what volume the catheter was inflated to.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Pinto 1967

Methods	Alternation used for allocation.
Participants	100 pregnant women > 36 weeks. Inpatients.
Interventions	200 mg single dose of IV oestradiol vs IV placebo.
Outcomes	Caesarean section.
Notes	University of Buenos Aires, Argentina. Inpatient setting. Source of funding not stated.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	High risk	C - Inadequate

Quinn 1981

Methods	Randomisation method not mentioned. Drugs prepared in coded bottles.
Participants	25 Nulliparous women with modified Bishops score, 3. Inpatients for procedure.
Interventions	15 mg extra amniotic oestradiol vs 10 mg extra amniotic PGF2a

Quinn 1981 *(Continued)*

	vs extra amniotic placebo.
Outcomes	Uterine hyperstimulation, caesarean section, instrumental vaginal delivery, perinatal death.
Notes	Dalhousie university, Halifax, Canada. Inpatient setting. Source of funding not stated. Prostaglandin supplied by Upjohn pty Ltd and Hoechst Australia Ltd supplied the Tylose gel.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Tromans 1981

Methods	Allocation by date of admission.
Participants	60 women with singleton cephalic pregnancy, > 37 weeks, presentation unfavourable cervix < 4 on modified Bishops score. Inpatients.
Interventions	150 mg intravaginal oestradiol vs 4 mg vaginal PGE2 Both in a tylose gel.
Outcomes	Uterine hyperstimulation, caesarean section, epidural analgesia.
Notes	Royal Liverpool Hospital, UK. Inpatient setting. Source of funding not stated.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	High risk	C - Inadequate

SRM=artificial rupture of the membranes
IV = intravenous
IP = inpatient
min = minimum
max = maximum
OP = outpatient
RCT = randomised controlled trial
vs = versus

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

Study	Reason for exclusion
Gordon 1977	Complex intervention. Both groups had extra-amniotic Foley catheter (balloon inflated to 20 mls) with either extra-amniotic oestrogen or placebo.

Study	Reason for exclusion
Griffin 2003	No prespecified outcomes reported in usable format. 35 women randomised to either 12 mg oestradiol twice a day for two days or placebo as outpatients prior to Induction of labour. The main outcome measured was change (improvement) in Bishops score. Published as abstract.
Klopper 1969	Not an induction trial, but uterine activity study. ARM given and then intra-amniotic oestriol sulphate at onset of labour to test if myometrial activity is modified.
Klopper 1973	Uterine activity study. No pre-specified outcomes reported.
Luther 1980	Complex intervention. groups randomised to either 10 mg intramuscular estradiol valerate or placebo followed by oral prostaglandin E2.
Magnani 1986	Report of two trials. First trial compares vaginal oestrogen with placebo, but no pre-specified outcomes are reported. The second trial involves a complex intervention of oestrogen or placebo followed by extra-amniotic prostaglandin 12 hours later.
Mamo 1994	No pre-specified outcomes reported.
Martin 1955	IOL for failed abortion.
Moran 1994	No prespecified outcomes reported. 28 women included, 17 received rectal estriol and 11 received placebo. The outcome was measurement of plasma progesterone levels.
Palmero 1997	No pre-specified outcomes reported.
Pedersen 1981	No pre-specified outcomes reported.
Peedicayil 1989	Complex intervention, Both groups had extra-amniotic Foley catheter (balloon inflated to 10mls) with either extra-amniotic oestrogen or placebo.
Roztocil 1998	Complex intervention. Second phase allocated on Bishops score.
Sasaki 1982	Induction with Dehydroepiandrosterone sulphate versus placebo.
Stewart 1981	Complex intervention. Both groups had extra-amniotic Foley catheter (balloon inflated to 20 mls) with either extra-amniotic oestrogen or placebo.
Thiery 1978	No pre-specified outcomes reported.
Thiery 1979	Complex intervention. Both groups had extra-amniotic Foley catheter (balloon inflated to 20 mls) with either extra-amniotic oestrogen or placebo.
Williams 1988	Indications for induction included fetal death.

ARM = artificial rupture of the membranes
IOL = induction of labour

DATA AND ANALYSES

Comparison 1. Oestrogen versus placebo: all women

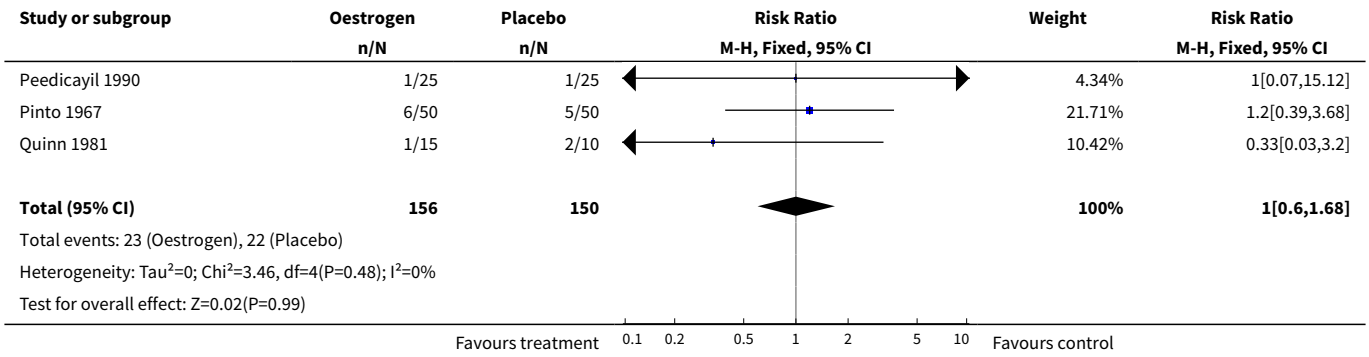
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Uterine hyperstimulation with FHR changes	1	25	Risk Ratio (M-H, Fixed, 95% CI)	3.44 [0.18, 64.88]
3 Caesarean section	5	306	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.60, 1.68]
4 Serious neonatal morbidity or perinatal death	2	75	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.07, 15.12]
7 Oxytocin augmentation	1	87	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.61, 1.43]
8 Uterine hyperstimulation without FHR changes	1	25	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
11 Instrumental vaginal delivery	3	162	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.46, 1.22]
12 Meconium stained liquor	1	87	Risk Ratio (M-H, Fixed, 95% CI)	0.49 [0.13, 1.83]
14 Neonatal intensive care unit admission	1	87	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.06, 15.13]
16 Perinatal death	2	75	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 7.81]
20 Serious maternal complications	1	87	Risk Ratio (M-H, Fixed, 95% CI)	2.93 [0.85, 10.10]

Analysis 1.2. Comparison 1 Oestrogen versus placebo: all women, Outcome 2 Uterine hyperstimulation with FHR changes.

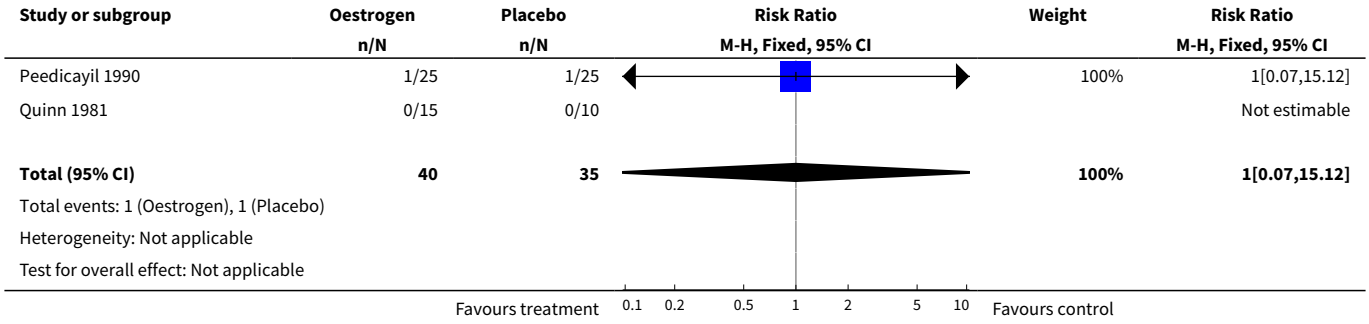
Study or subgroup	Oestrogen n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Quinn 1981	2/15	0/10		100%	3.44[0.18,64.88]
Total (95% CI)	**15**	**10**		**100%**	**3.44[0.18,64.88]**
Total events: 2 (Oestrogen), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.82(P=0.41)					

Analysis 1.3. Comparison 1 Oestrogen versus placebo: all women, Outcome 3 Caesarean section.

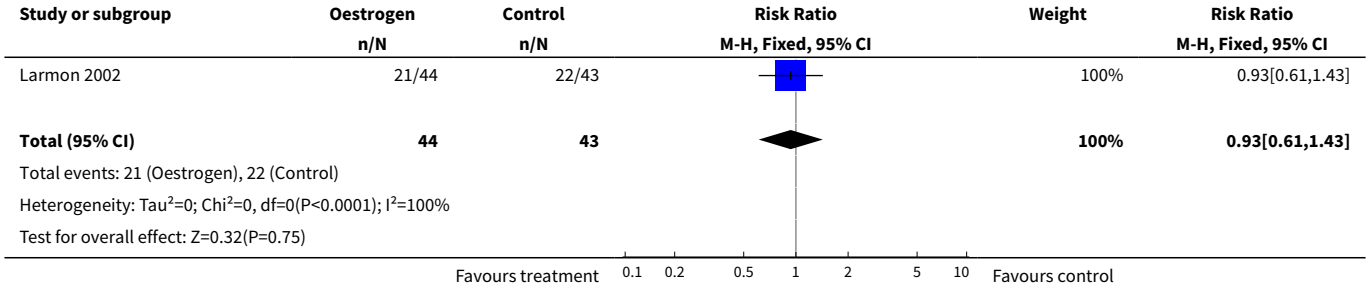
Study or subgroup	Oestrogen n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Klopper 1962	0/22	3/22		15.2%	0.14[0.01,2.61]
Larmon 2002	15/44	11/43		48.32%	1.33[0.69,2.56]



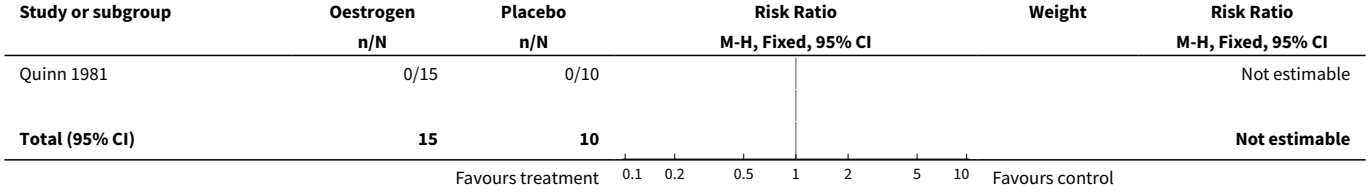
Analysis 1.4. Comparison 1 Oestrogen versus placebo: all women, Outcome 4 Serious neonatal morbidity or perinatal death.

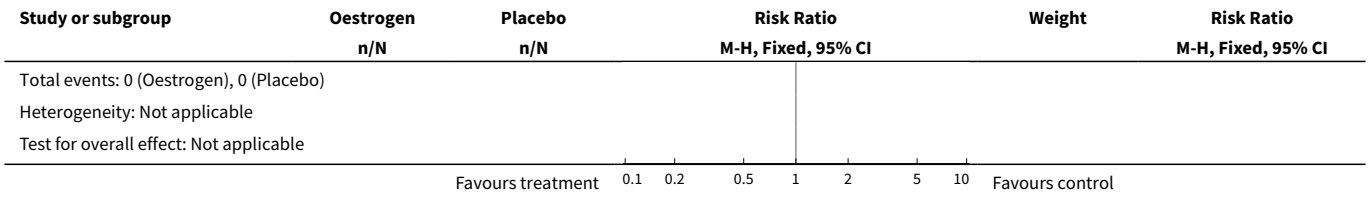


Analysis 1.7. Comparison 1 Oestrogen versus placebo: all women, Outcome 7 Oxytocin augmentation.

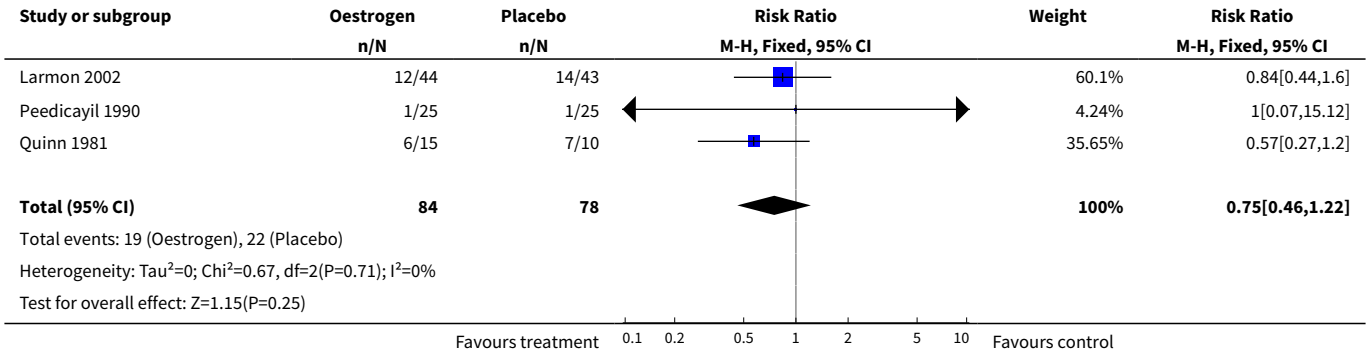


Analysis 1.8. Comparison 1 Oestrogen versus placebo: all women, Outcome 8 Uterine hyperstimulation without FHR changes.

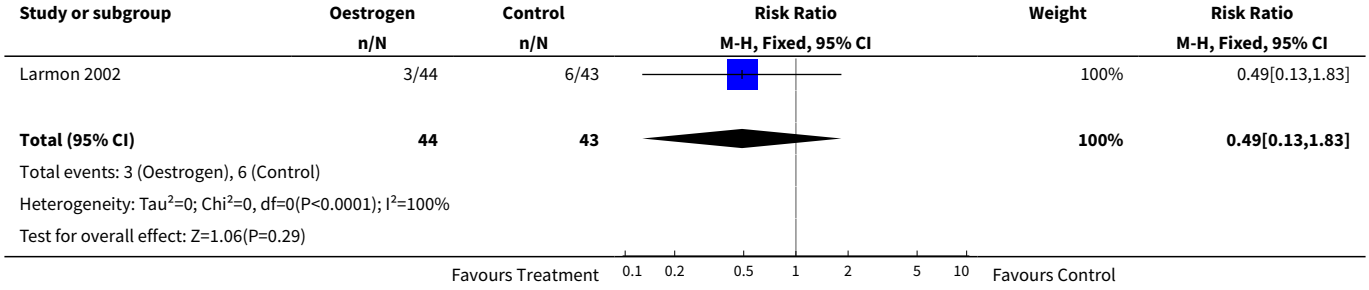




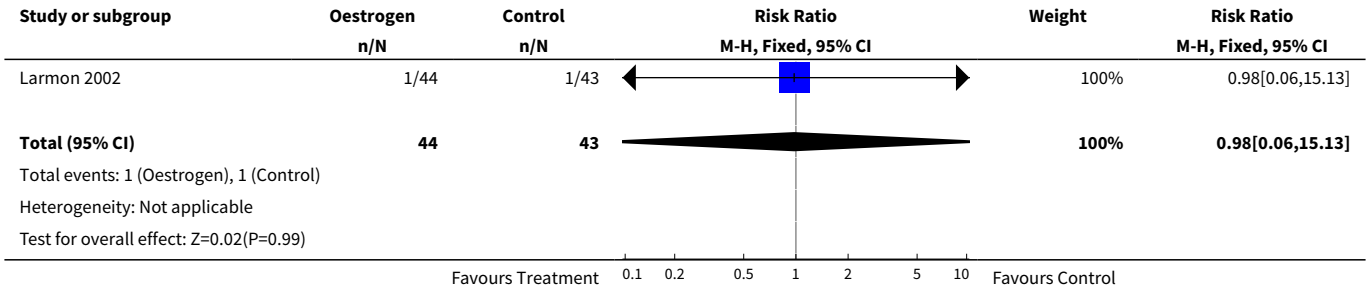
Analysis 1.11. Comparison 1 Oestrogen versus placebo: all women, Outcome 11 Instrumental vaginal delivery.



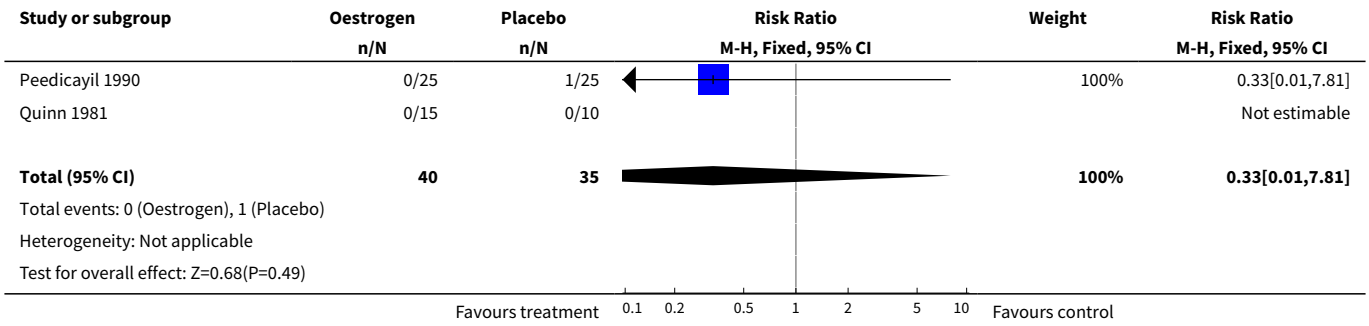
Analysis 1.12. Comparison 1 Oestrogen versus placebo: all women, Outcome 12 Meconium stained liquor.



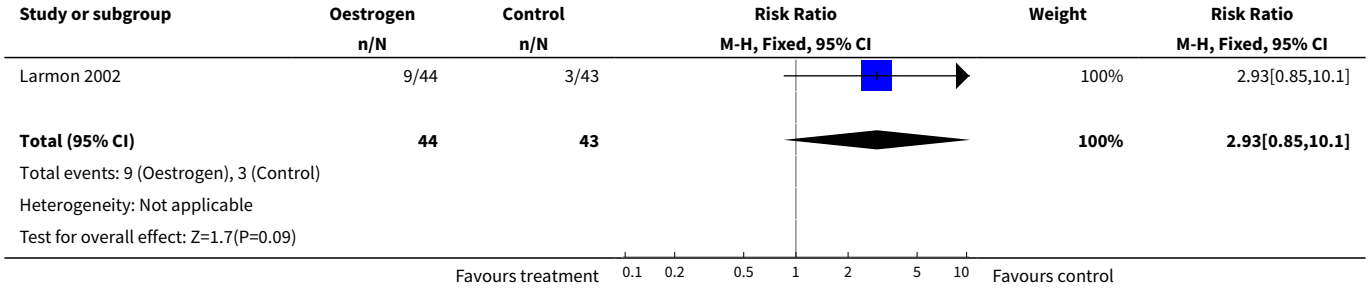
Analysis 1.14. Comparison 1 Oestrogen versus placebo: all women, Outcome 14 Neonatal intensive care unit admission.



Analysis 1.16. Comparison 1 Oestrogen versus placebo: all women, Outcome 16 Perinatal death.



Analysis 1.20. Comparison 1 Oestrogen versus placebo: all women, Outcome 20 Serious maternal complications.



Comparison 2. Oestrogen versus placebo: all women, unfavourable

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Uterine hyperstimulation with FHR changes	1	25	Risk Ratio (M-H, Fixed, 95% CI)	3.44 [0.18, 64.88]
3 Caesarean section	3	162	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.63, 2.09]
4 Serious neonatal morbidity or perinatal death	2	75	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.07, 15.12]
7 Oxytocin augmentation	1	87	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.61, 1.43]
8 Uterine hyperstimulation without FHR changes	1	25	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
11 Instrumental vaginal delivery	3	162	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.46, 1.22]
12 Meconium stained liquor	1	87	Risk Ratio (M-H, Fixed, 95% CI)	0.49 [0.13, 1.83]
14 Neonatal intensive care unit admission	1	87	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.06, 15.13]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
16 Perinatal death	2	75	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 7.81]
20 Serious maternal complications	1	87	Risk Ratio (M-H, Fixed, 95% CI)	2.93 [0.85, 10.10]

Analysis 2.2. Comparison 2 Oestrogen versus placebo: all women, unfavourable, Outcome 2 Uterine hyperstimulation with FHR changes.

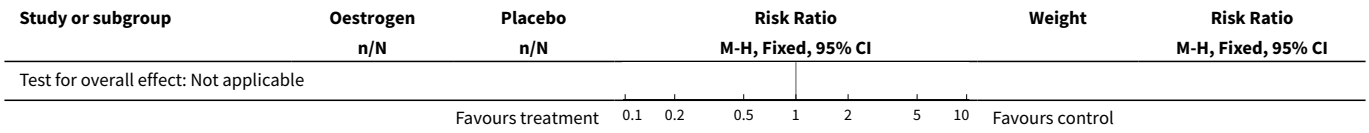
Study or subgroup	Oestrogen n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Quinn 1981	2/15	0/10		100%	3.44[0.18,64.88]
Total (95% CI)	**15**	**10**		**100%**	**3.44[0.18,64.88]**
Total events: 2 (Oestrogen), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.82(P=0.41)					

Analysis 2.3. Comparison 2 Oestrogen versus placebo: all women, unfavourable, Outcome 3 Caesarean section.

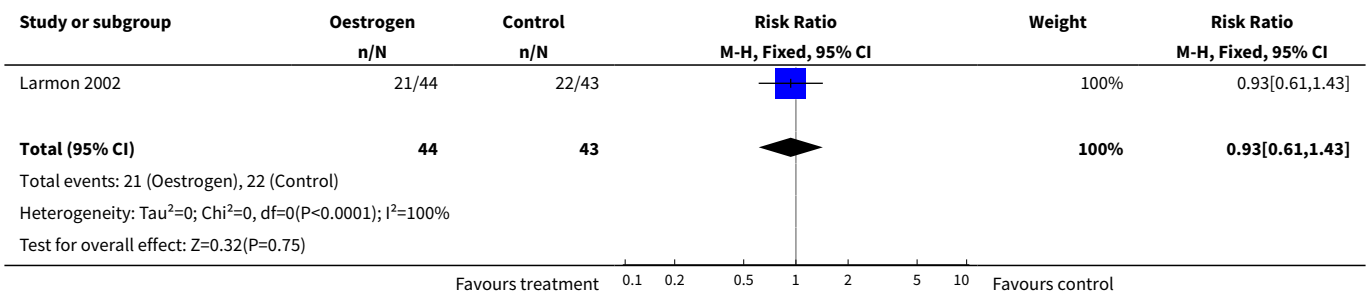
Study or subgroup	Oestrogen n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Larmon 2002	15/44	11/43		76.59%	1.33[0.69,2.56]
Peedicayil 1990	1/25	1/25		6.88%	1[0.07,15.12]
Quinn 1981	1/15	2/10		16.52%	0.33[0.03,3.2]
Total (95% CI)	**84**	**78**		**100%**	**1.14[0.63,2.09]**
Total events: 17 (Oestrogen), 14 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=1.36, df=2(P=0.51); I^2=0%					
Test for overall effect: Z=0.44(P=0.66)					

Analysis 2.4. Comparison 2 Oestrogen versus placebo: all women, unfavourable, Outcome 4 Serious neonatal morbidity or perinatal death.

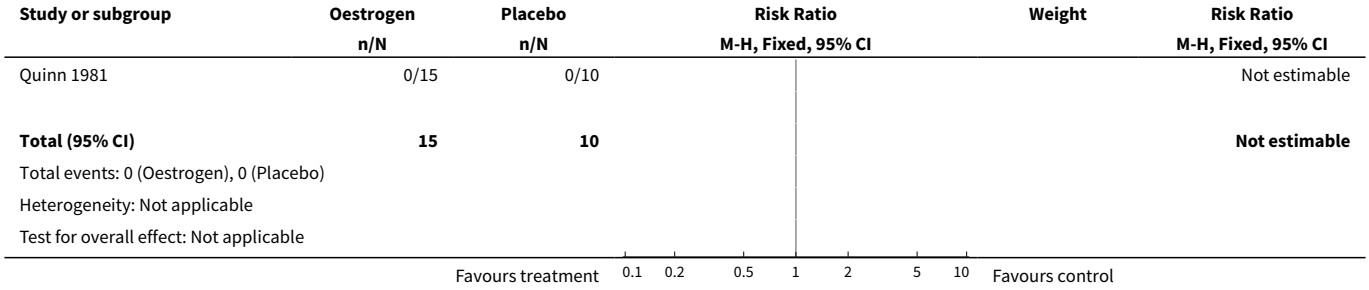
Study or subgroup	Oestrogen n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Peedicayil 1990	1/25	1/25		100%	1[0.07,15.12]
Quinn 1981	0/15	0/10			Not estimable
Total (95% CI)	**40**	**35**		**100%**	**1[0.07,15.12]**
Total events: 1 (Oestrogen), 1 (Placebo)					
Heterogeneity: Not applicable					



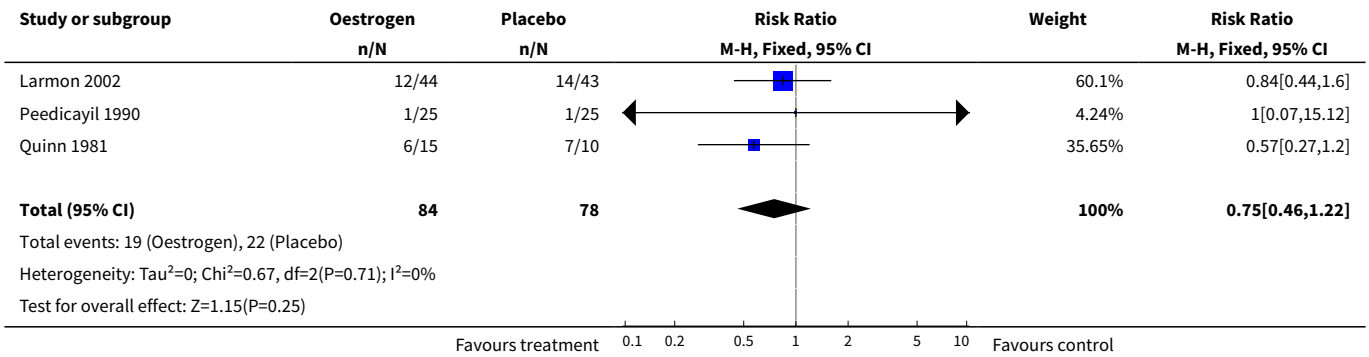
Analysis 2.7. Comparison 2 Oestrogen versus placebo: all women, unfavourable, Outcome 7 Oxytocin augmentation.



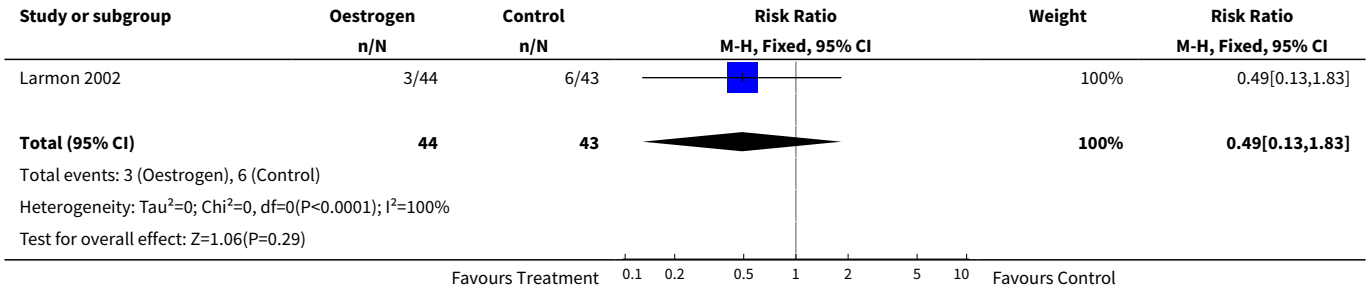
Analysis 2.8. Comparison 2 Oestrogen versus placebo: all women, unfavourable, Outcome 8 Uterine hyperstimulation without FHR changes.



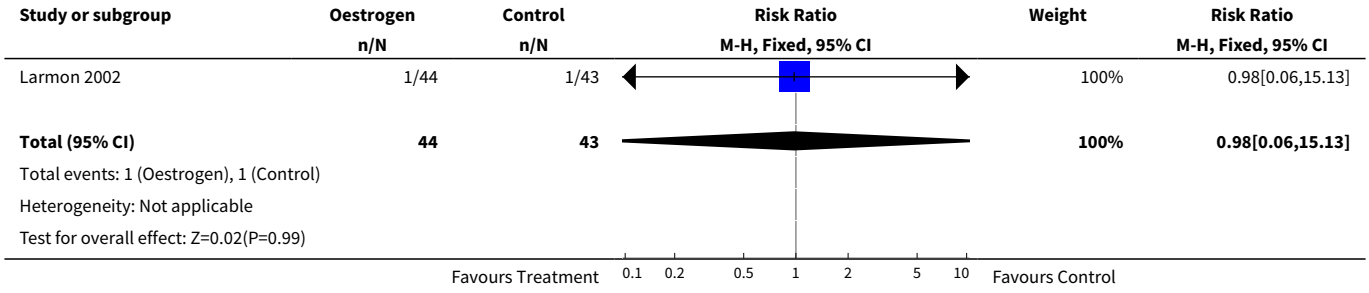
Analysis 2.11. Comparison 2 Oestrogen versus placebo: all women, unfavourable, Outcome 11 Instrumental vaginal delivery.



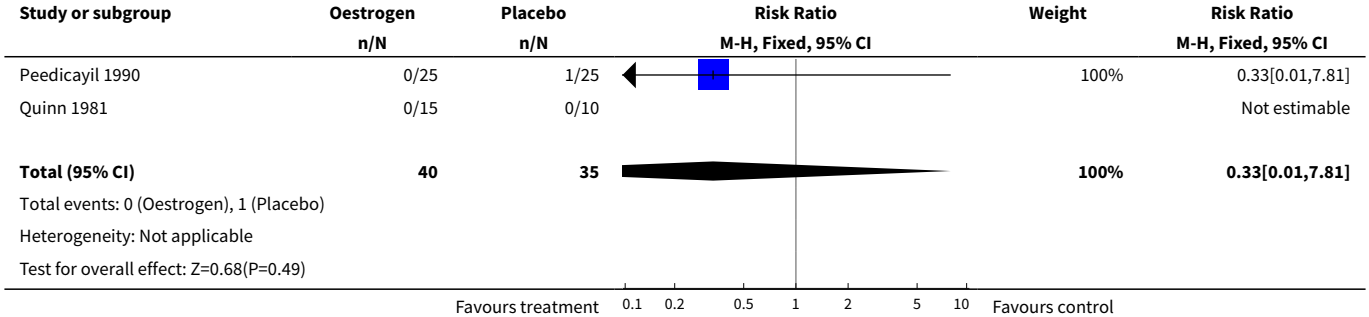
Analysis 2.12. Comparison 2 Oestrogen versus placebo: all women, unfavourable, Outcome 12 Meconium stained liquor.



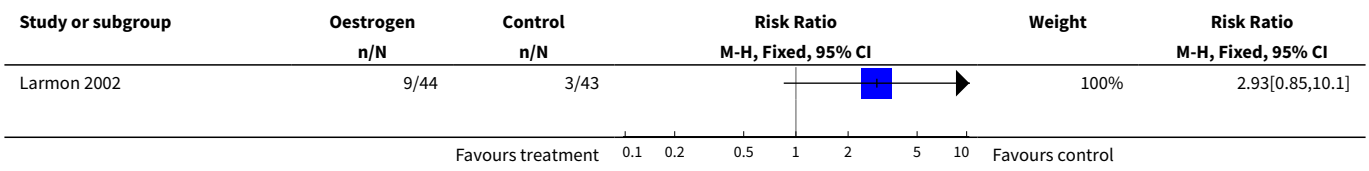
Analysis 2.14. Comparison 2 Oestrogen versus placebo: all women, unfavourable, Outcome 14 Neonatal intensive care unit admission.

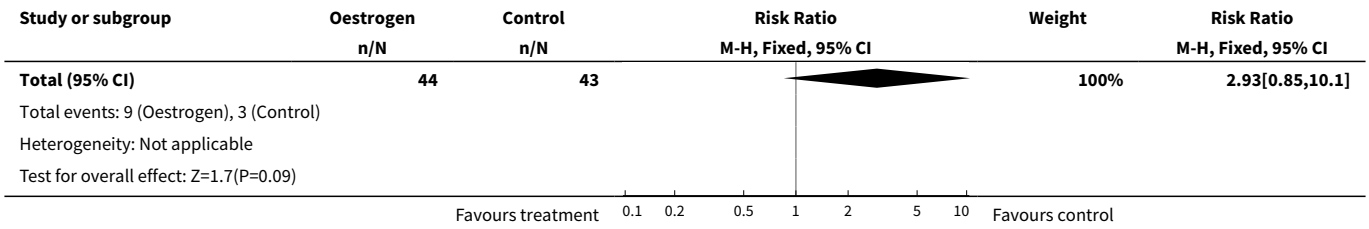


Analysis 2.16. Comparison 2 Oestrogen versus placebo: all women, unfavourable, Outcome 16 Perinatal death.



Analysis 2.20. Comparison 2 Oestrogen versus placebo: all women, unfavourable, Outcome 20 Serious maternal complications.

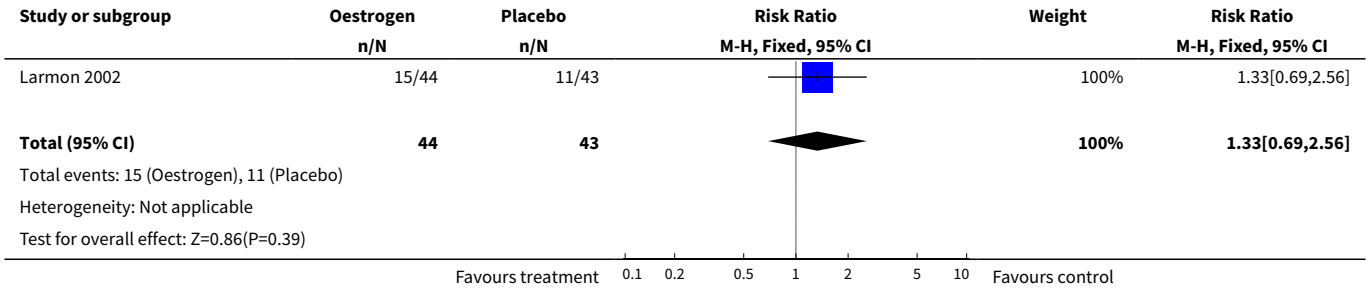




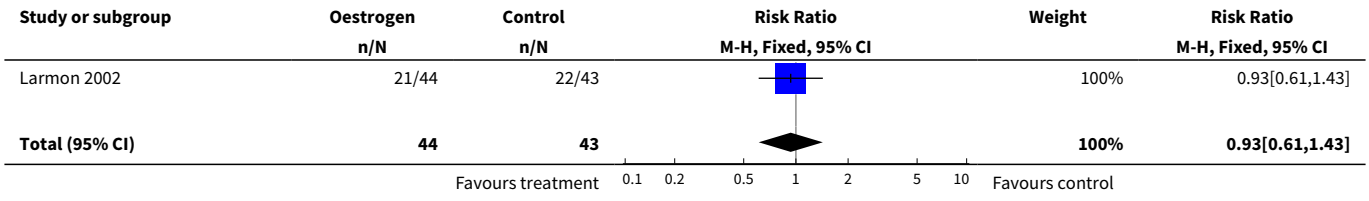
Comparison 3. Oestrogen versus placebo: all women, intact membranes, unfavourable

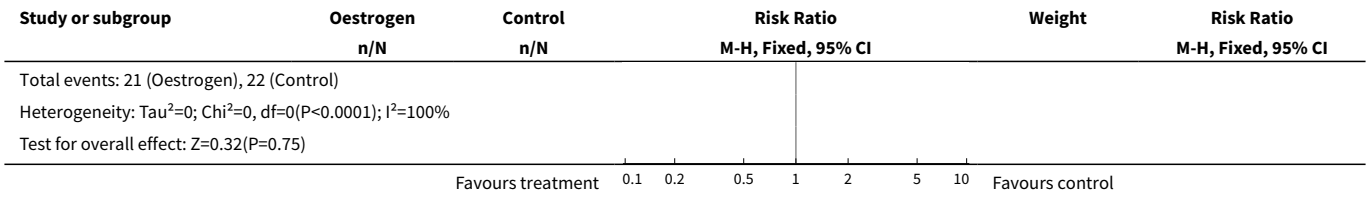
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Caesarean section	1	87	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [0.69, 2.56]
7 Oxytocin augmentation	1	87	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.61, 1.43]
11 Instrumental vaginal delivery	1	87	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.44, 1.60]
12 Meconium stained liquor	1	87	Risk Ratio (M-H, Fixed, 95% CI)	0.49 [0.13, 1.83]
14 Neonatal intensive care unit admission	1	87	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.06, 15.13]
20 Serious maternal complications	1	87	Risk Ratio (M-H, Fixed, 95% CI)	2.93 [0.85, 10.10]

Analysis 3.3. Comparison 3 Oestrogen versus placebo: all women, intact membranes, unfavourable, Outcome 3 Caesarean section.

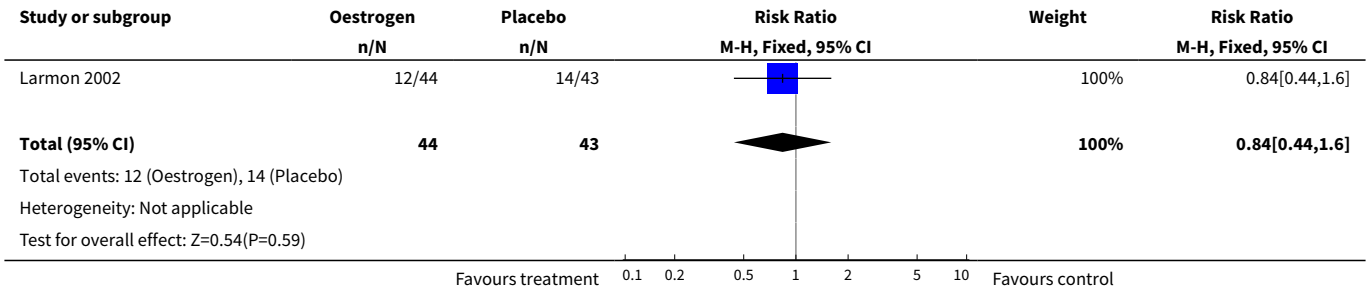


Analysis 3.7. Comparison 3 Oestrogen versus placebo: all women, intact membranes, unfavourable, Outcome 7 Oxytocin augmentation.

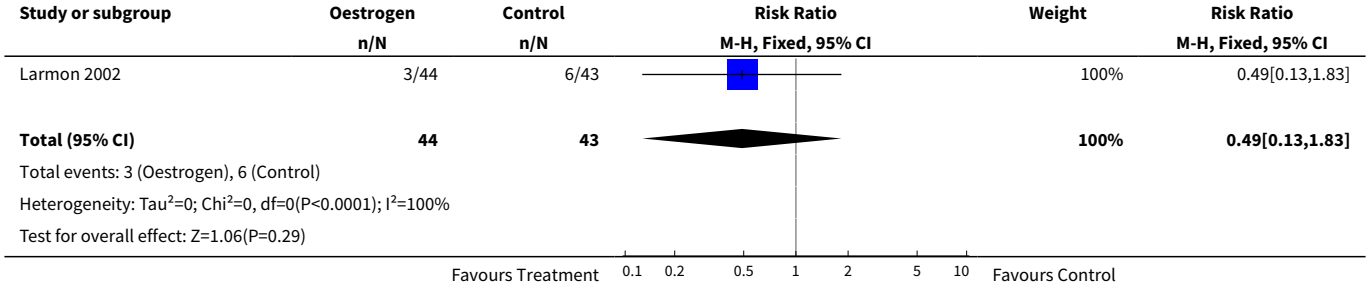




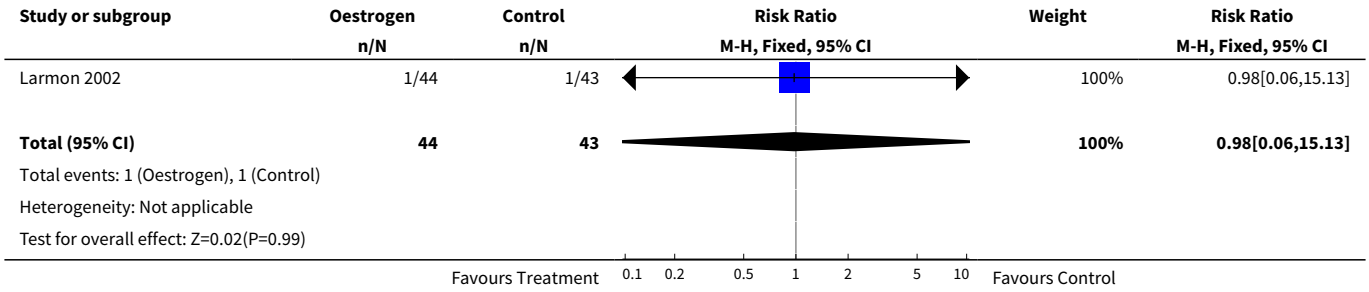
Analysis 3.11. Comparison 3 Oestrogen versus placebo: all women, intact membranes, unfavourable, Outcome 11 Instrumental vaginal delivery.



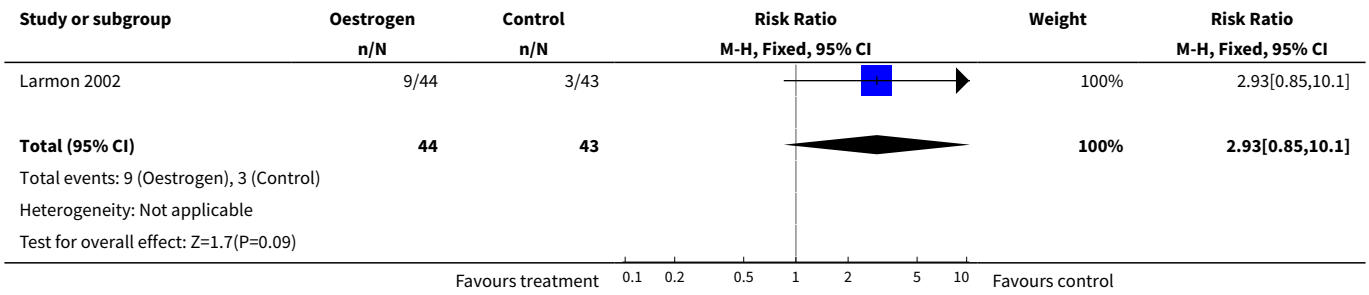
Analysis 3.12. Comparison 3 Oestrogen versus placebo: all women, intact membranes, unfavourable, Outcome 12 Meconium stained liquor.



Analysis 3.14. Comparison 3 Oestrogen versus placebo: all women, intact membranes, unfavourable, Outcome 14 Neonatal intensive care unit admission.



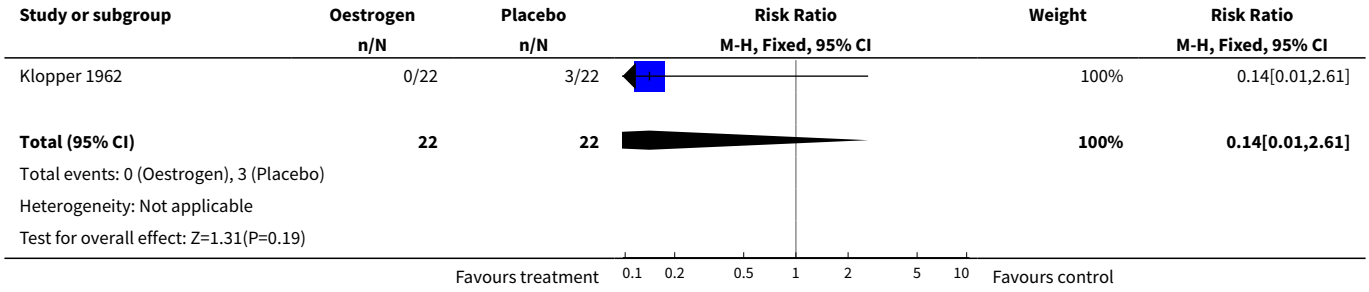
Analysis 3.20. Comparison 3 Oestrogen versus placebo: all women, intact membranes, unfavourable, Outcome 20 Serious maternal complications.



Comparison 4. Oestrogen versus placebo: all women, intact membranes, variable or undefined cervix

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Caesarean section	1	44	Risk Ratio (M-H, Fixed, 95% CI)	0.14 [0.01, 2.61]

Analysis 4.3. Comparison 4 Oestrogen versus placebo: all women, intact membranes, variable or undefined cervix, Outcome 3 Caesarean section.



Comparison 5. Oestrogen versus placebo: all primiparae

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Uterine hyperstimulation with FHR changes	1	25	Risk Ratio (M-H, Fixed, 95% CI)	3.44 [0.18, 64.88]
3 Caesarean section	2	69	Risk Ratio (M-H, Fixed, 95% CI)	0.22 [0.04, 1.32]
4 Serious neonatal morbidity or perinatal death	1	25	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8 Uterine hyperstimulation without FHR changes	1	25	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
11 Instrumental vaginal delivery	1	25	Risk Ratio (M-H, Fixed, 95% CI)	0.57 [0.27, 1.20]
16 Perinatal death	1	25	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 5.2. Comparison 5 Oestrogen versus placebo: all primiparae, Outcome 2 Uterine hyperstimulation with FHR changes.

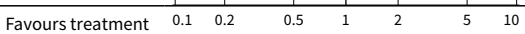
Study or subgroup	Oestrogen n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Quinn 1981	2/15	0/10		100%	3.44[0.18,64.88]
Total (95% CI)	**15**	**10**		**100%**	**3.44[0.18,64.88]**
Total events: 2 (Oestrogen), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.82(P=0.41)					

Analysis 5.3. Comparison 5 Oestrogen versus placebo: all primiparae, Outcome 3 Caesarean section.

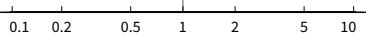
Study or subgroup	Oestrogen n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Klopper 1962	0/22	3/22		59.32%	0.14[0.01,2.61]
Quinn 1981	1/15	2/10		40.68%	0.33[0.03,3.2]
Total (95% CI)	**37**	**32**		**100%**	**0.22[0.04,1.32]**
Total events: 1 (Oestrogen), 5 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.21, df=1(P=0.64); I^2=0%					
Test for overall effect: Z=1.65(P=0.1)					

Analysis 5.4. Comparison 5 Oestrogen versus placebo: all primiparae, Outcome 4 Serious neonatal morbidity or perinatal death.

Study or subgroup	Oestrogen n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Quinn 1981	0/15	0/10			Not estimable
Total (95% CI)	**15**	**10**			**Not estimable**
Total events: 0 (Oestrogen), 0 (Placebo)					
Heterogeneity: Not applicable					

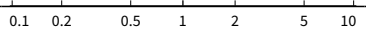


Study or subgroup	Oestrogen n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Test for overall effect: Not applicable					



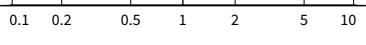
Analysis 5.8. Comparison 5 Oestrogen versus placebo: all primiparae, Outcome 8 Uterine hyperstimulation without FHR changes.

Study or subgroup	Oestrogen n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Quinn 1981	0/15	0/10			Not estimable
Total (95% CI)	**15**	**10**			**Not estimable**
Total events: 0 (Oestrogen), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					



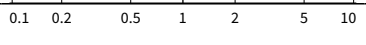
Analysis 5.11. Comparison 5 Oestrogen versus placebo: all primiparae, Outcome 11 Instrumental vaginal delivery.

Study or subgroup	Oestrogen n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Quinn 1981	6/15	7/10		100%	0.57[0.27,1.2]
Total (95% CI)	**15**	**10**		**100%**	**0.57[0.27,1.2]**
Total events: 6 (Oestrogen), 7 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.48(P=0.14)					



Analysis 5.16. Comparison 5 Oestrogen versus placebo: all primiparae, Outcome 16 Perinatal death.

Study or subgroup	Oestrogen n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Quinn 1981	0/15	0/10			Not estimable
Total (95% CI)	**15**	**10**			**Not estimable**
Total events: 0 (Oestrogen), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					



Comparison 6. Oestrogen versus placebo: all primiparae, unfavourable cervix

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Uterine hyperstimulation with FHR changes	1	25	Risk Ratio (M-H, Fixed, 95% CI)	3.44 [0.18, 64.88]
3 Caesarean section	1	25	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.03, 3.20]
4 Serious neonatal morbidity or perinatal death	1	25	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8 Uterine hyperstimulation without FHR changes	1	25	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
11 Instrumental vaginal delivery	1	25	Risk Ratio (M-H, Fixed, 95% CI)	0.57 [0.27, 1.20]
16 Perinatal death	1	25	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

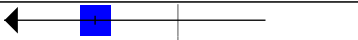
Analysis 6.2. Comparison 6 Oestrogen versus placebo: all primiparae, unfavourable cervix, Outcome 2 Uterine hyperstimulation with FHR changes.

Study or subgroup	Oestrogen n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Quinn 1981	2/15	0/10		100%	3.44[0.18,64.88]
Total (95% CI)	**15**	**10**		**100%**	**3.44[0.18,64.88]**
Total events: 2 (Oestrogen), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.82(P=0.41)					

Favours treatment — Favours control

Analysis 6.3. Comparison 6 Oestrogen versus placebo: all primiparae, unfavourable cervix, Outcome 3 Caesarean section.

Study or subgroup	Oestrogen n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Quinn 1981	1/15	2/10		100%	0.33[0.03,3.2]
Total (95% CI)	**15**	**10**		**100%**	**0.33[0.03,3.2]**
Total events: 1 (Oestrogen), 2 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.95(P=0.34)					



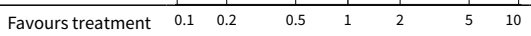
Favours treatment — Favours control

Analysis 6.4. Comparison 6 Oestrogen versus placebo: all primiparae, unfavourable cervix, Outcome 4 Serious neonatal morbidity or perinatal death.

Study or subgroup	Oestrogen n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Quinn 1981	0/15	0/10			Not estimable
Total (95% CI)	**15**	**10**			**Not estimable**
Total events: 0 (Oestrogen), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					

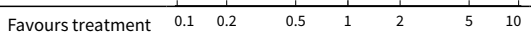
Analysis 6.8. Comparison 6 Oestrogen versus placebo: all primiparae, unfavourable cervix, Outcome 8 Uterine hyperstimulation without FHR changes.

Study or subgroup	Oestrogen n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Quinn 1981	0/15	0/10			Not estimable
Total (95% CI)	**15**	**10**			**Not estimable**
Total events: 0 (Oestrogen), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					



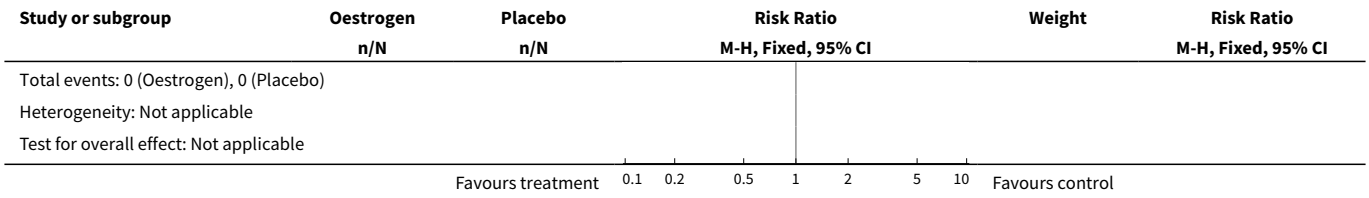
Analysis 6.11. Comparison 6 Oestrogen versus placebo: all primiparae, unfavourable cervix, Outcome 11 Instrumental vaginal delivery.

Study or subgroup	Oestrogen n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Quinn 1981	6/15	7/10		100%	0.57[0.27,1.2]
Total (95% CI)	**15**	**10**		**100%**	**0.57[0.27,1.2]**
Total events: 6 (Oestrogen), 7 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.48(P=0.14)					



Analysis 6.16. Comparison 6 Oestrogen versus placebo: all primiparae, unfavourable cervix, Outcome 16 Perinatal death.

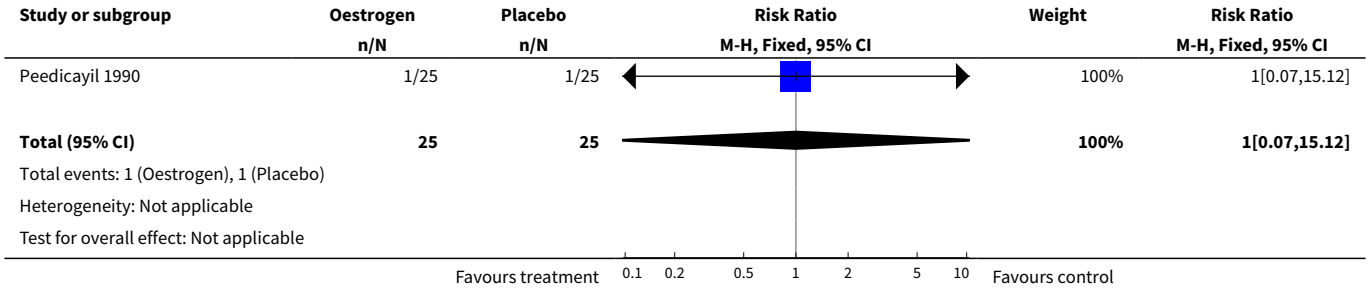
Study or subgroup	Oestrogen n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Quinn 1981	0/15	0/10			Not estimable
Total (95% CI)	**15**	**10**			**Not estimable**



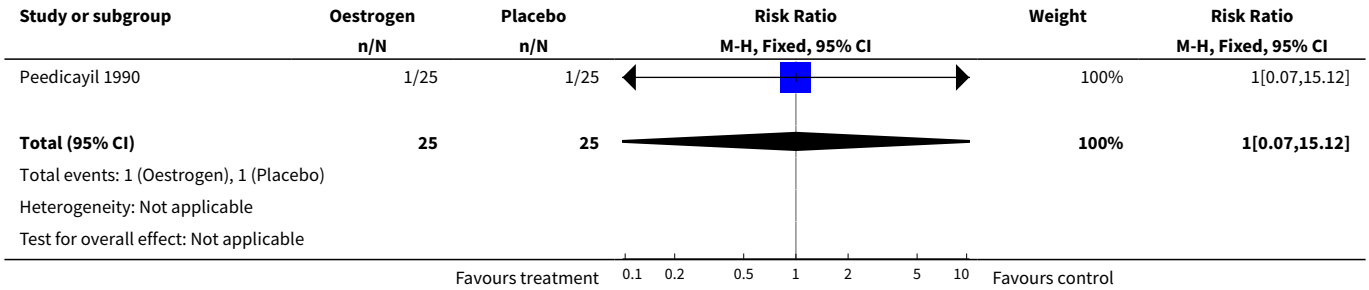
Comparison 7. Oestrogen versus placebo: all multiparae

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Caesarean section	1	50	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.07, 15.12]
4 Serious neonatal morbidity or perinatal death	1	50	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.07, 15.12]
11 Instrumental vaginal delivery	1	50	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.07, 15.12]
16 Perinatal death	1	50	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 7.81]

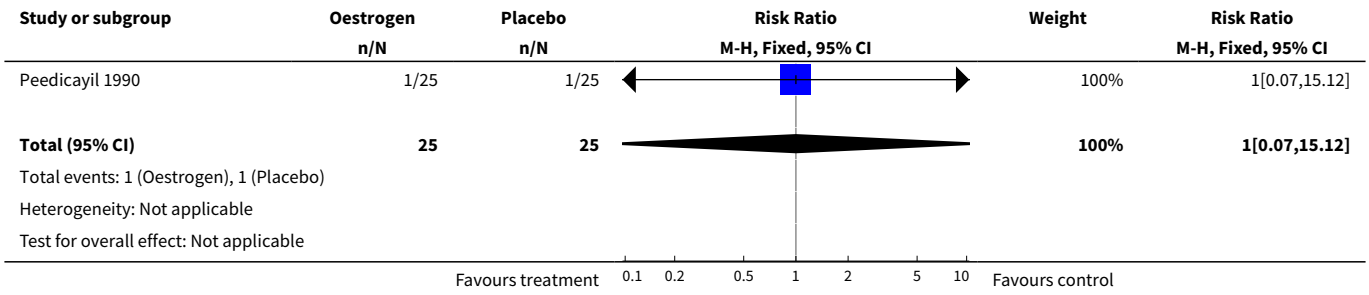
Analysis 7.3. Comparison 7 Oestrogen versus placebo: all multiparae, Outcome 3 Caesarean section.



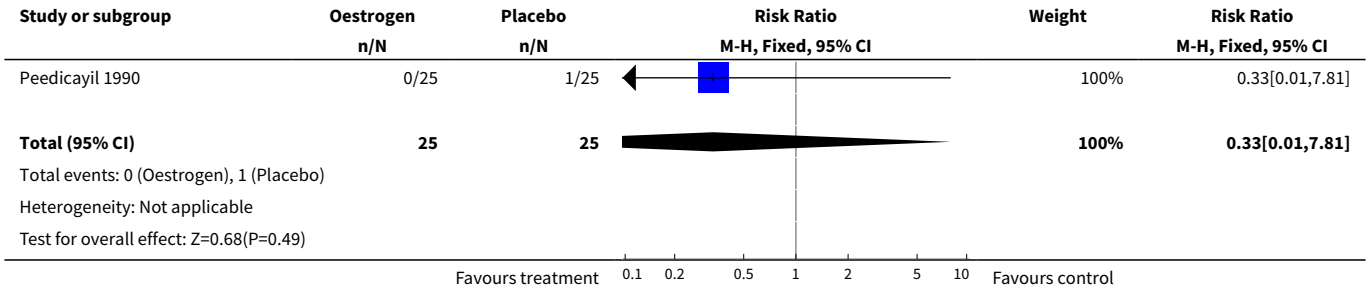
Analysis 7.4. Comparison 7 Oestrogen versus placebo: all multiparae, Outcome 4 Serious neonatal morbidity or perinatal death.



Analysis 7.11. Comparison 7 Oestrogen versus placebo: all multiparae, Outcome 11 Instrumental vaginal delivery.



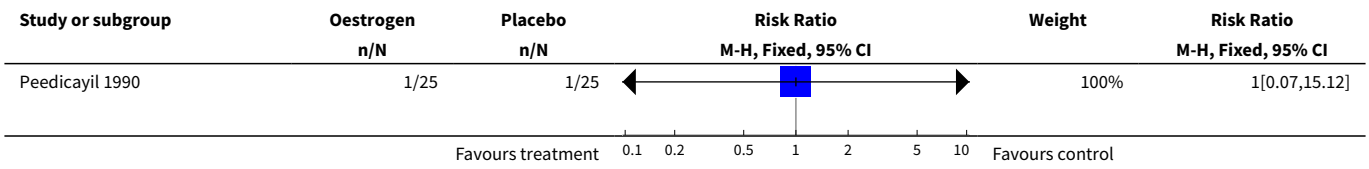
Analysis 7.16. Comparison 7 Oestrogen versus placebo: all multiparae, Outcome 16 Perinatal death.

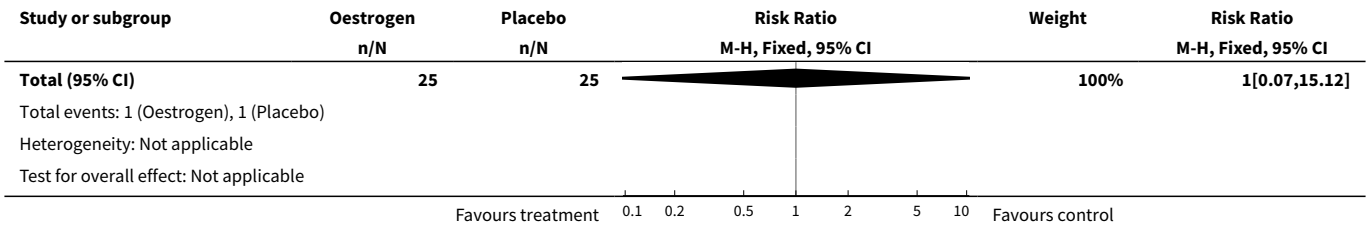


Comparison 8. Oestrogen versus placebo: all multiparae, unfavourable cervix

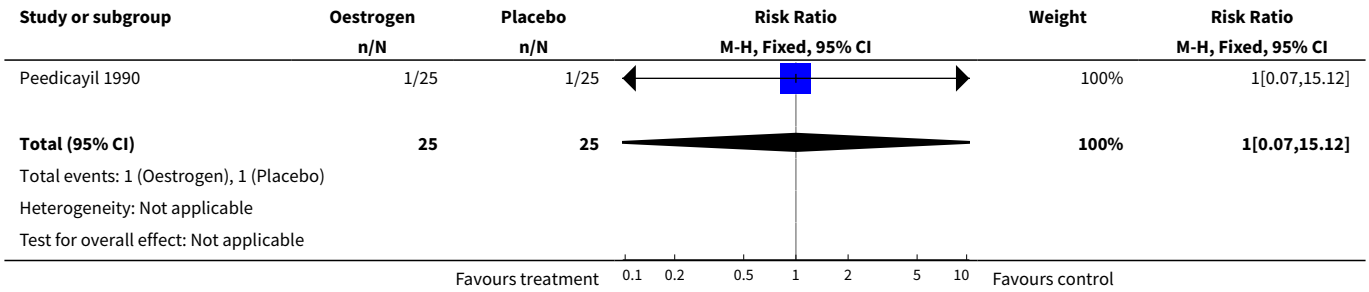
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Caesarean section	1	50	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.07, 15.12]
4 Serious neonatal morbidity or perinatal death	1	50	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.07, 15.12]
11 Instrumental vaginal delivery	1	50	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.07, 15.12]
16 Perinatal death	1	50	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 7.81]

Analysis 8.3. Comparison 8 Oestrogen versus placebo: all multiparae, unfavourable cervix, Outcome 3 Caesarean section.

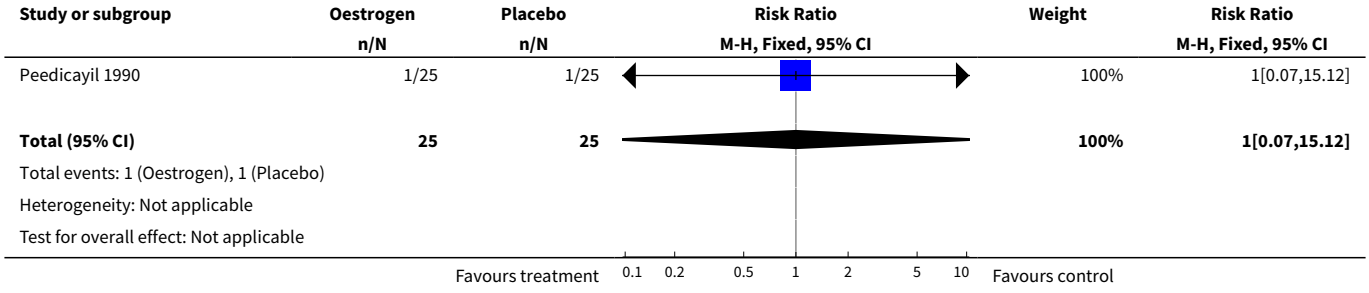




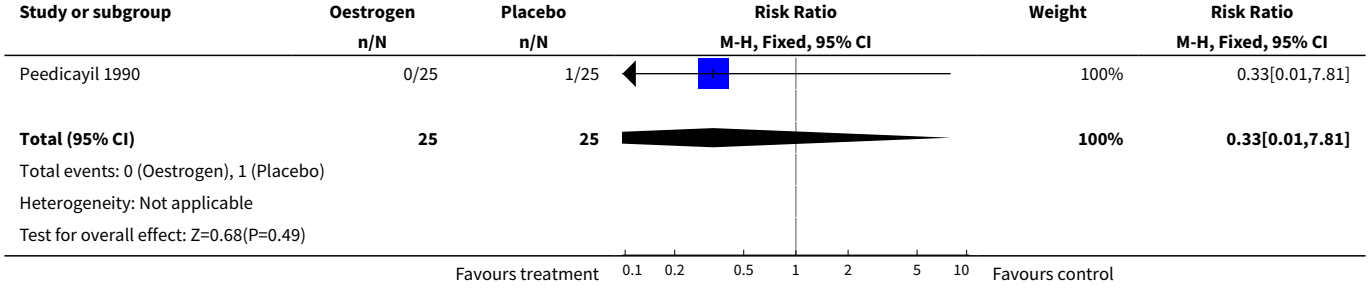
Analysis 8.4. Comparison 8 Oestrogen versus placebo: all multiparae, unfavourable cervix, Outcome 4 Serious neonatal morbidity or perinatal death.



Analysis 8.11. Comparison 8 Oestrogen versus placebo: all multiparae, unfavourable cervix, Outcome 11 Instrumental vaginal delivery.



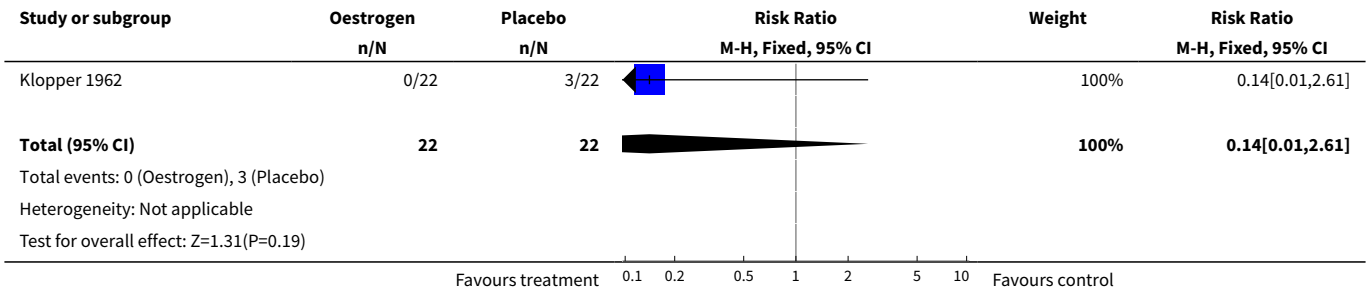
Analysis 8.16. Comparison 8 Oestrogen versus placebo: all multiparae, unfavourable cervix, Outcome 16 Perinatal death.



Comparison 9. Oestrogen versus placebo: all primiparae, intact membranes, variable or undefined cervix

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Caesarean section	1	44	Risk Ratio (M-H, Fixed, 95% CI)	0.14 [0.01, 2.61]

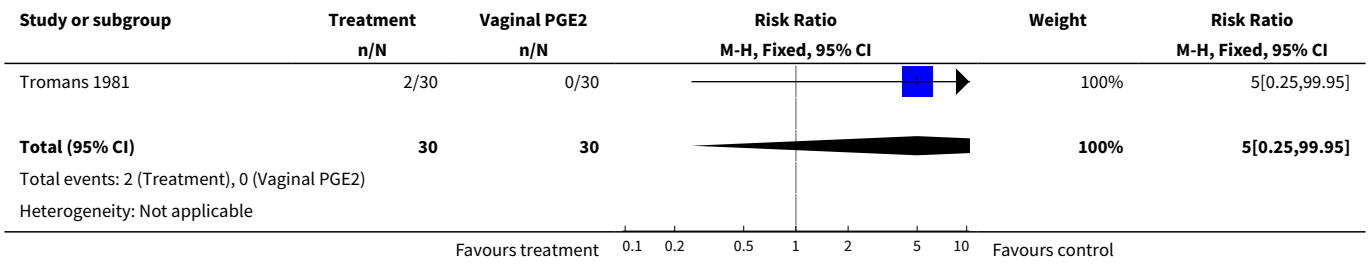
Analysis 9.3. Comparison 9 Oestrogen versus placebo: all primiparae, intact membranes, variable or undefined cervix, Outcome 3 Caesarean section.

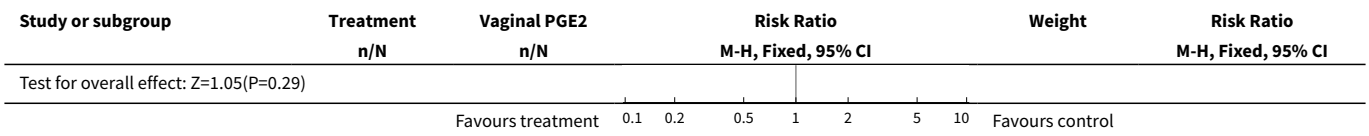


Comparison 10. Oestrogen versus vaginal prostaglandins: all women

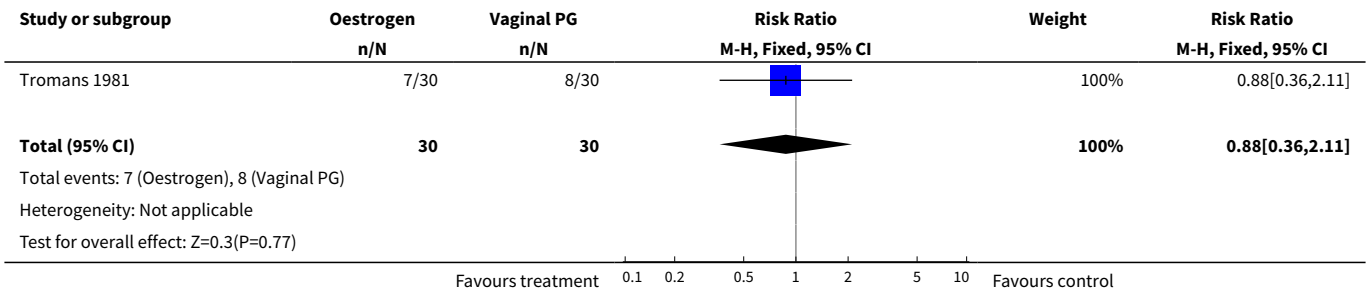
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Uterine hyperstimulation with FHR changes	1	60	Risk Ratio (M-H, Fixed, 95% CI)	5.0 [0.25, 99.95]
3 Caesarean section	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.36, 2.11]
8 Uterine hyperstimulation without FHR changes	1	60	Risk Ratio (M-H, Fixed, 95% CI)	4.6 [2.02, 10.49]
10 Epidural analgesia	1	60	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.78, 1.29]

Analysis 10.2. Comparison 10 Oestrogen versus vaginal prostaglandins: all women, Outcome 2 Uterine hyperstimulation with FHR changes.

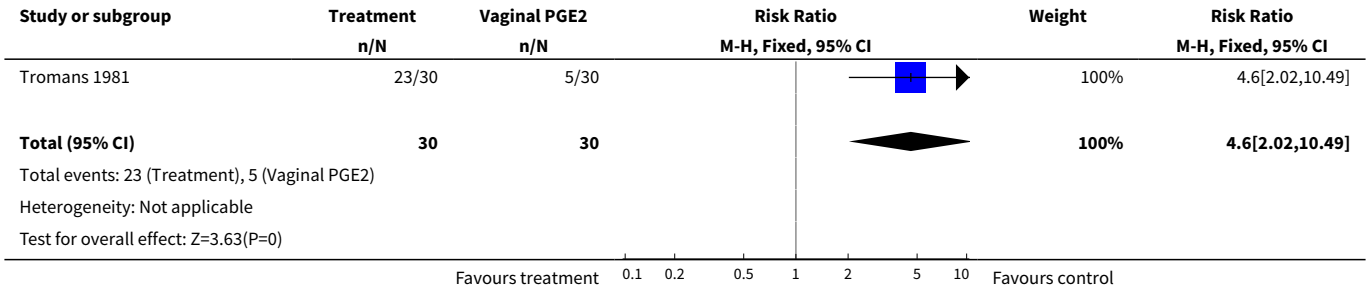




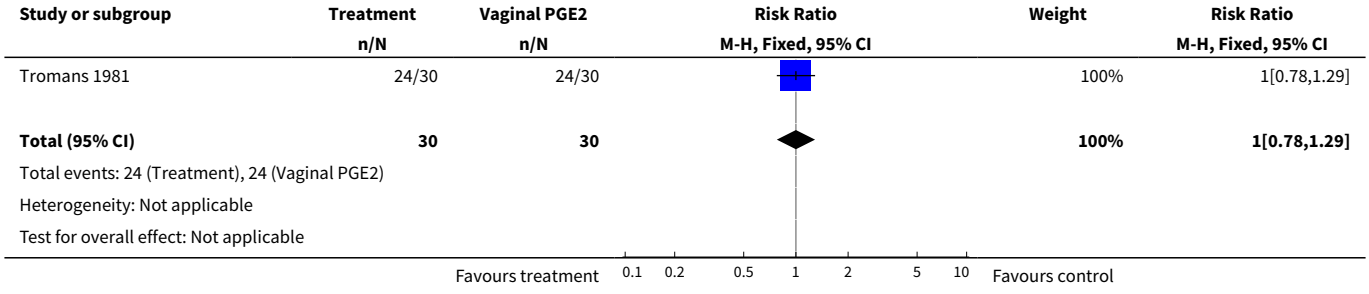
Analysis 10.3. Comparison 10 Oestrogen versus vaginal prostaglandins: all women, Outcome 3 Caesarean section.



Analysis 10.8. Comparison 10 Oestrogen versus vaginal prostaglandins: all women, Outcome 8 Uterine hyperstimulation without FHR changes.



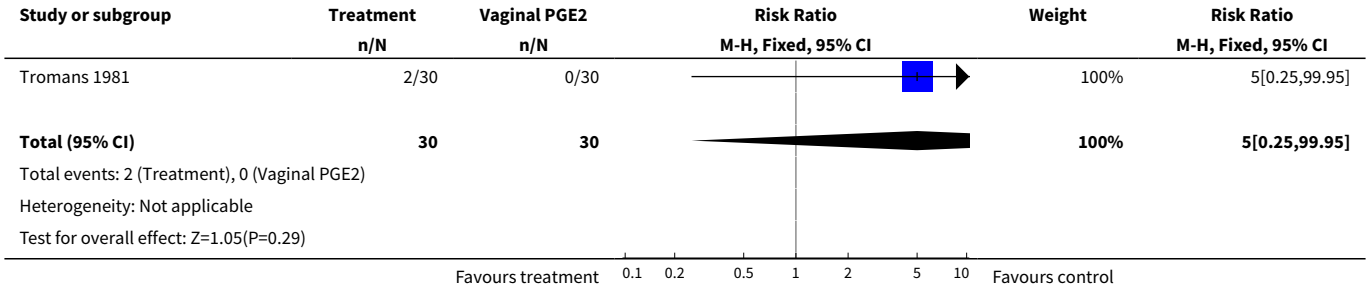
Analysis 10.10. Comparison 10 Oestrogen versus vaginal prostaglandins: all women, Outcome 10 Epidural analgesia.



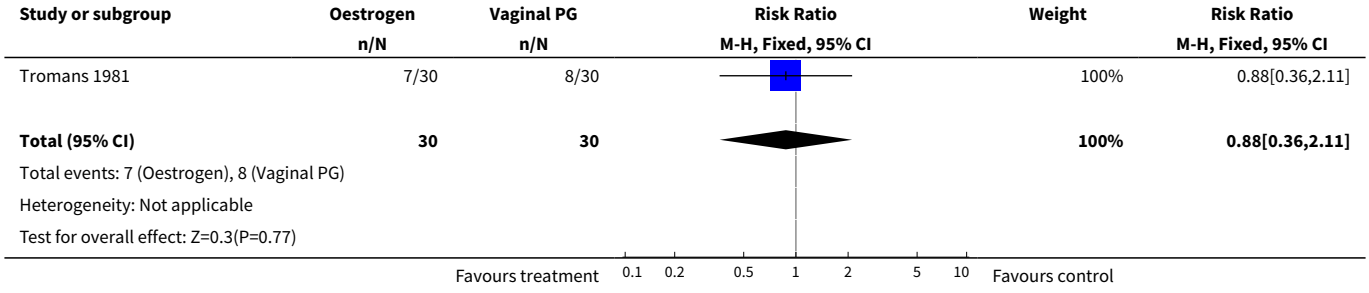
Comparison 11. Oestrogen versus vaginal prostaglandins: all women, unfavourable cervix

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Uterine hyperstimulation with FHR changes	1	60	Risk Ratio (M-H, Fixed, 95% CI)	5.0 [0.25, 99.95]
3 Caesarean section	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.36, 2.11]
8 Uterine hyperstimulation without FHR changes	1	60	Risk Ratio (M-H, Fixed, 95% CI)	4.6 [2.02, 10.49]
10 Epidural analgesia	1	60	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.78, 1.29]

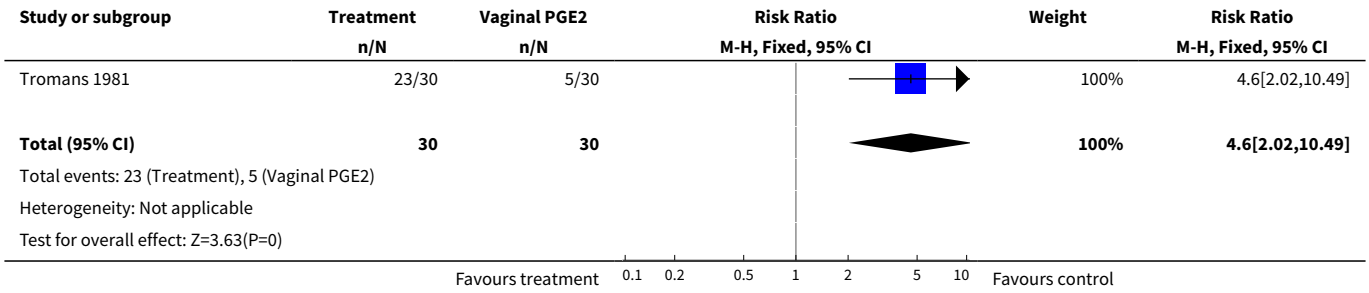
Analysis 11.2. Comparison 11 Oestrogen versus vaginal prostaglandins: all women, unfavourable cervix, Outcome 2 Uterine hyperstimulation with FHR changes.



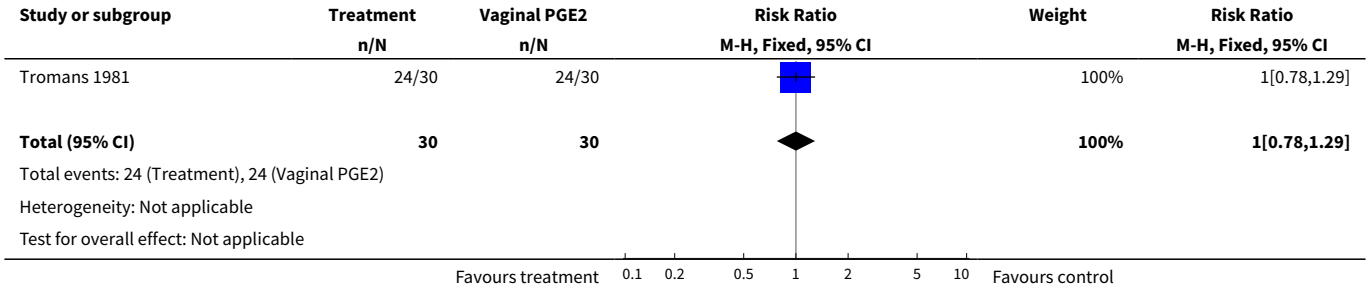
Analysis 11.3. Comparison 11 Oestrogen versus vaginal prostaglandins: all women, unfavourable cervix, Outcome 3 Caesarean section.



Analysis 11.8. Comparison 11 Oestrogen versus vaginal prostaglandins: all women, unfavourable cervix, Outcome 8 Uterine hyperstimulation without FHR changes.



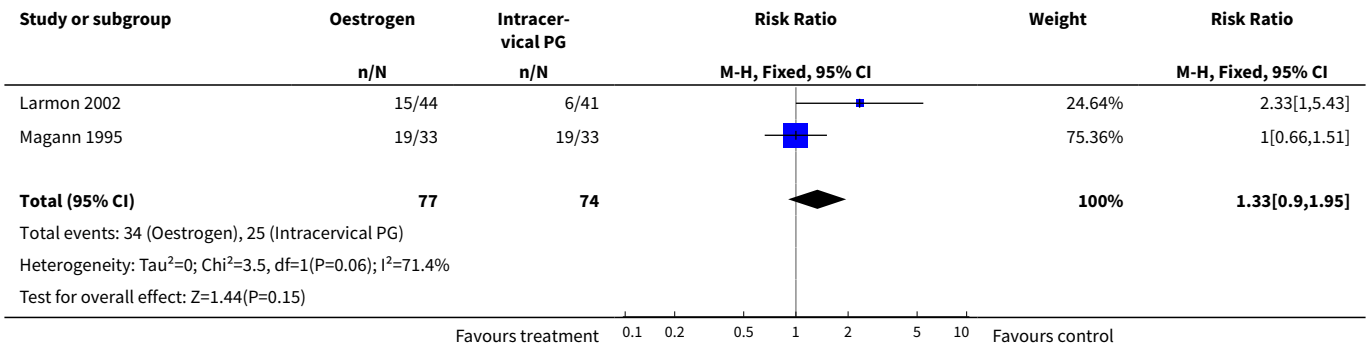
Analysis 11.10. Comparison 11 Oestrogen versus vaginal prostaglandins: all women, unfavourable cervix, Outcome 10 Epidural analgesia.



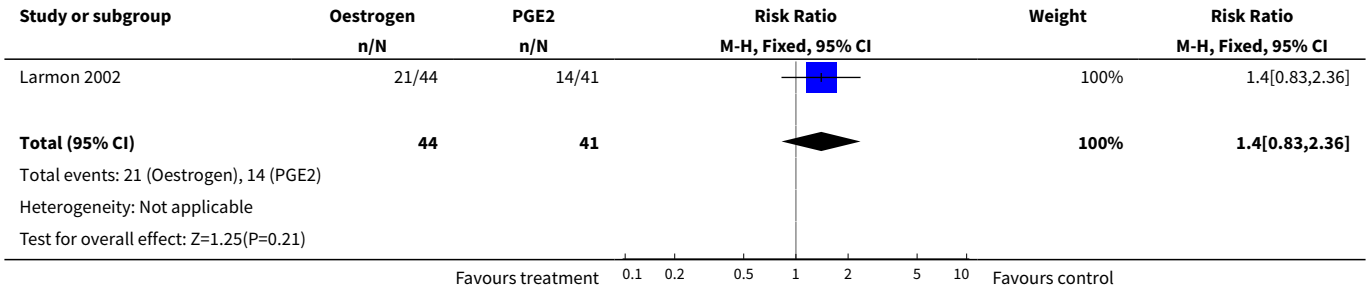
Comparison 15. Oestrogen versus intracervical prostaglandins: all women

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Caesarean section	2	151	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [0.90, 1.95]
7 Oxytocin augmentation	1	85	Risk Ratio (M-H, Fixed, 95% CI)	1.40 [0.83, 2.36]
11 Instrumental vaginal delivery	2	151	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.39, 1.23]
12 Meconium stained liquor	1	85	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.17, 2.94]
14 Neonatal intensive care unit admission	1	85	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.06, 14.42]
20 Serious maternal complications	1	85	Risk Ratio (M-H, Fixed, 95% CI)	2.80 [0.81, 9.62]

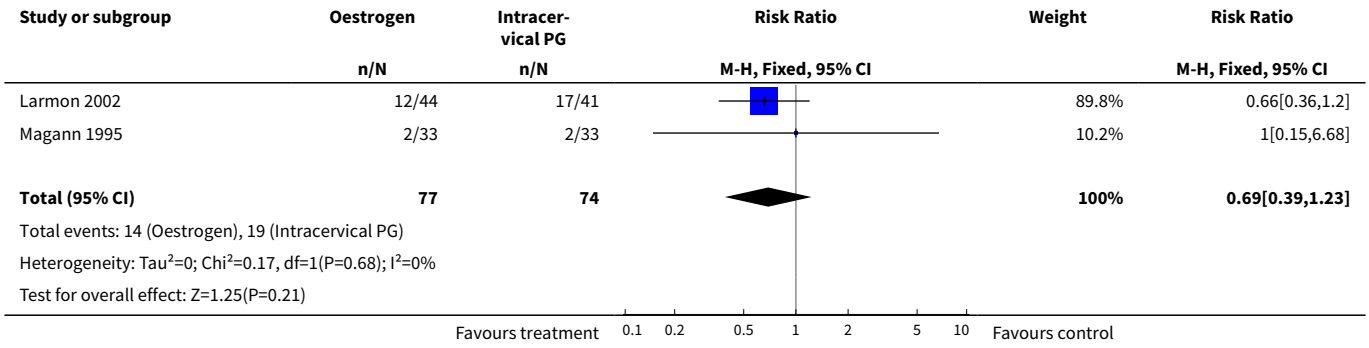
Analysis 15.3. Comparison 15 Oestrogen versus intracervical prostaglandins: all women, Outcome 3 Caesarean section.



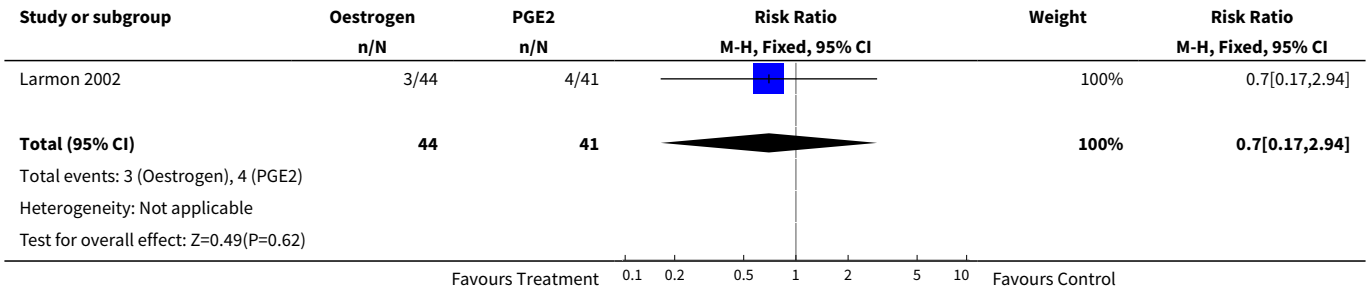
Analysis 15.7. Comparison 15 Oestrogen versus intracervical prostaglandins: all women, Outcome 7 Oxytocin augmentation.



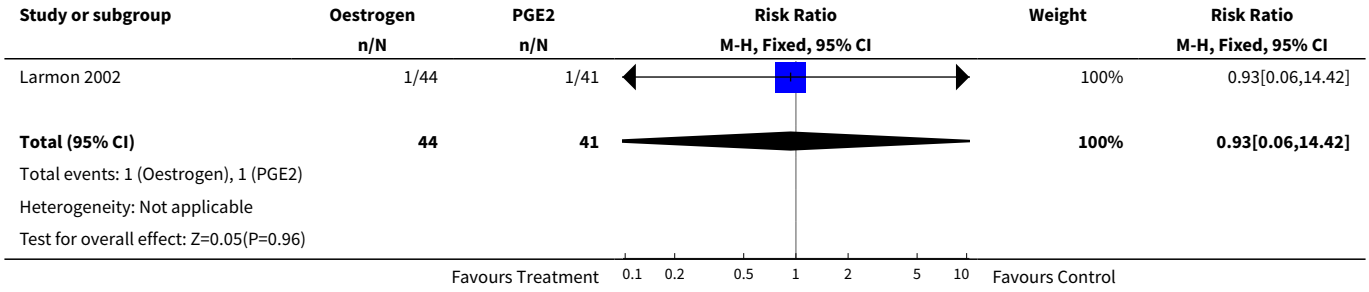
Analysis 15.11. Comparison 15 Oestrogen versus intracervical prostaglandins: all women, Outcome 11 Instrumental vaginal delivery.



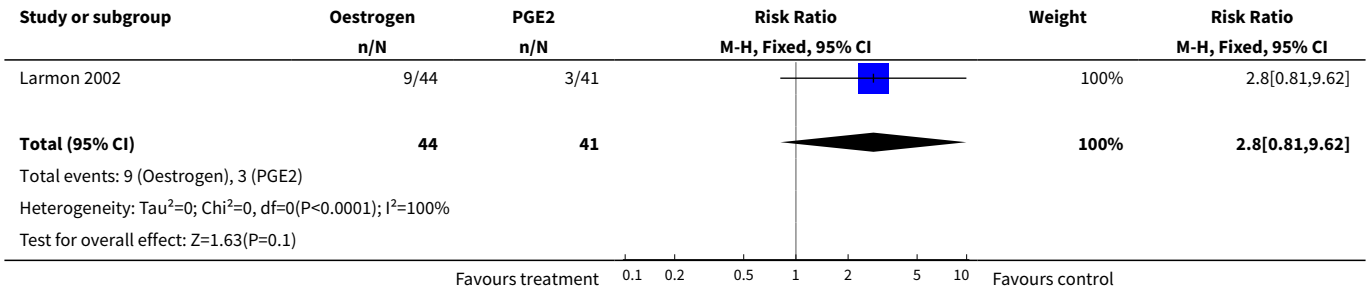
Analysis 15.12. Comparison 15 Oestrogen versus intracervical prostaglandins: all women, Outcome 12 Meconium stained liquor.



Analysis 15.14. Comparison 15 Oestrogen versus intracervical prostaglandins: all women, Outcome 14 Neonatal intensive care unit admission.



Analysis 15.20. Comparison 15 Oestrogen versus intracervical prostaglandins: all women, Outcome 20 Serious maternal complications.

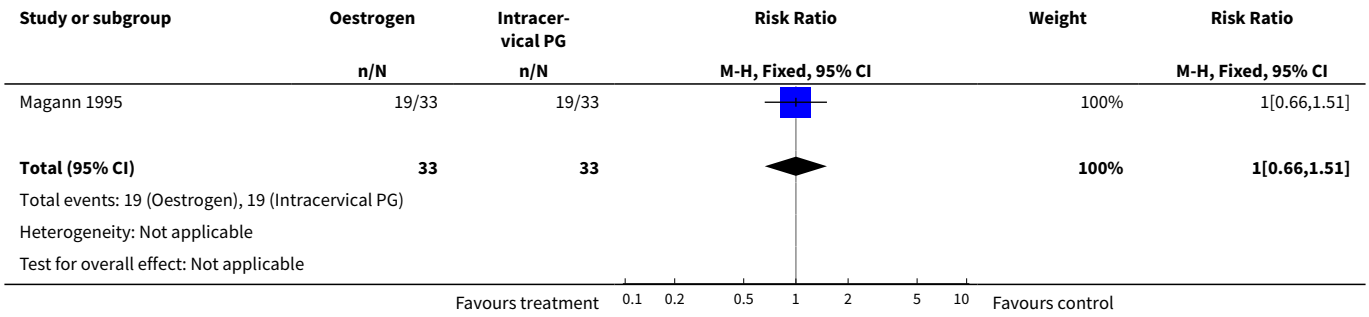


Comparison 16. Oestrogen versus intracervical prostaglandins: all women, unfavourable cervix

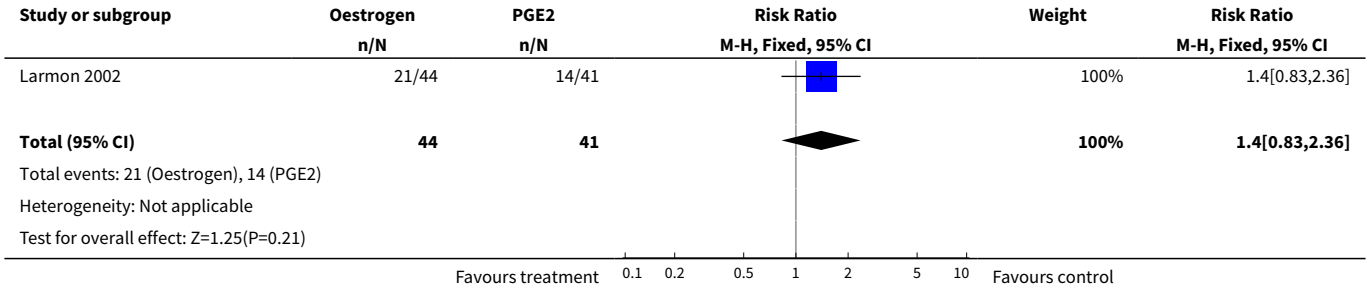
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Caesarean section	1	66	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.66, 1.51]
7 Oxytocin augmentation	1	85	Risk Ratio (M-H, Fixed, 95% CI)	1.40 [0.83, 2.36]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11 Instrumental vaginal delivery	2	151	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.39, 1.23]
12 Meconium stained liquor	1	85	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.17, 2.94]
14 Neonatal intensive care unit admission	1	85	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.06, 14.42]
20 Serious maternal complications	1	85	Risk Ratio (M-H, Fixed, 95% CI)	2.80 [0.81, 9.62]

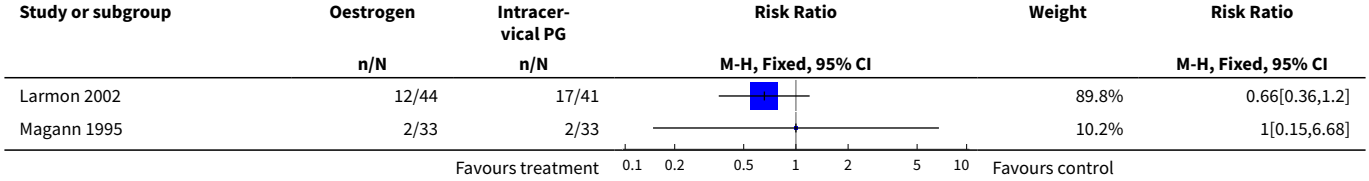
Analysis 16.3. Comparison 16 Oestrogen versus intracervical prostaglandins: all women, unfavourable cervix, Outcome 3 Caesarean section.

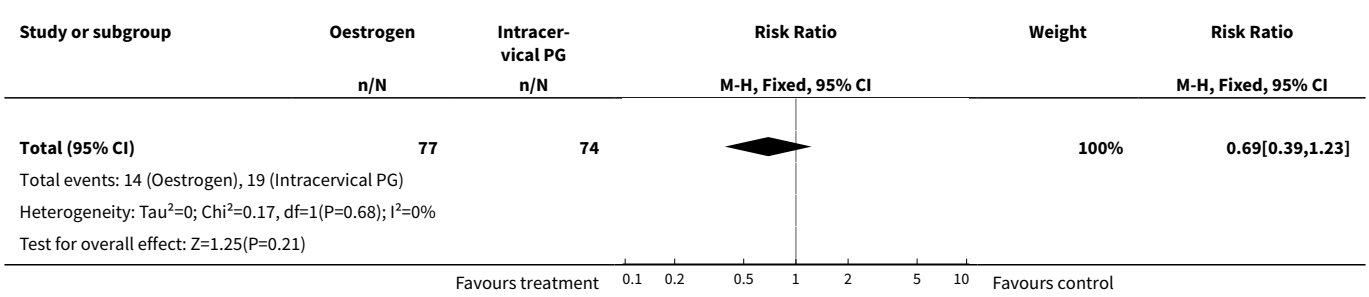


Analysis 16.7. Comparison 16 Oestrogen versus intracervical prostaglandins: all women, unfavourable cervix, Outcome 7 Oxytocin augmentation.

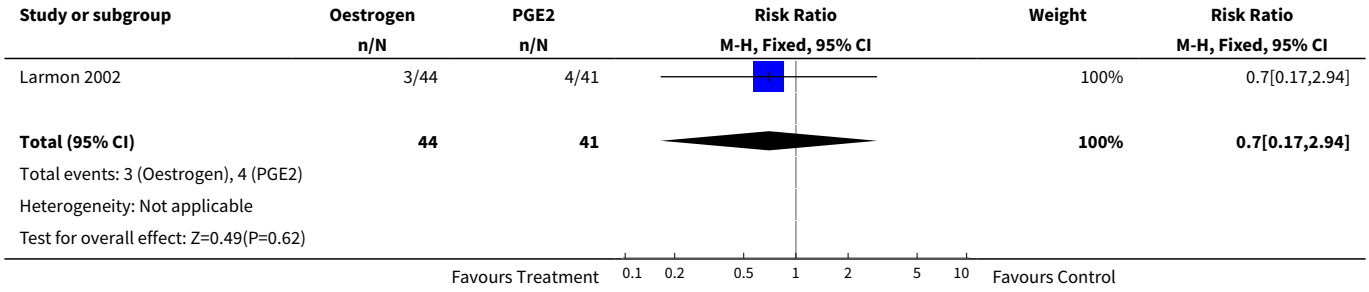


Analysis 16.11. Comparison 16 Oestrogen versus intracervical prostaglandins: all women, unfavourable cervix, Outcome 11 Instrumental vaginal delivery.

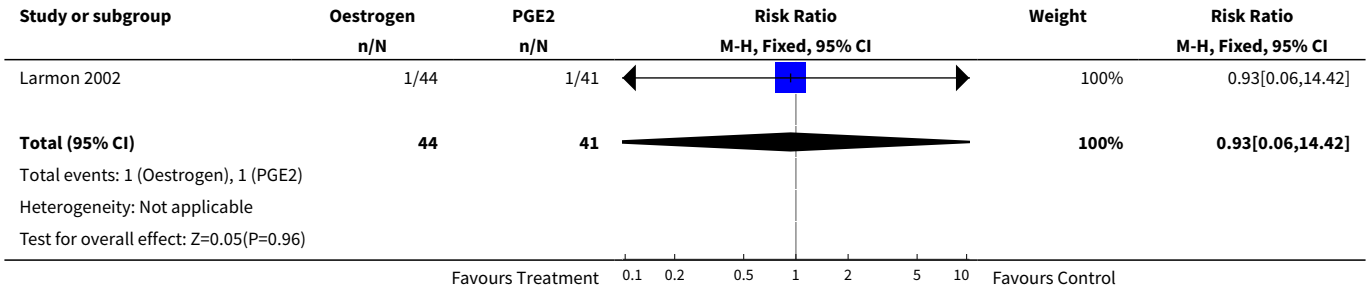




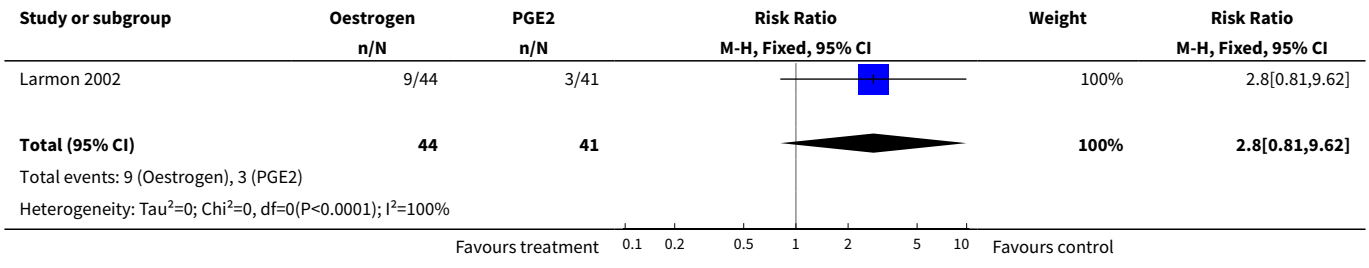
Analysis 16.12. Comparison 16 Oestrogen versus intracervical prostaglandins: all women, unfavourable cervix, Outcome 12 Meconium stained liquor.

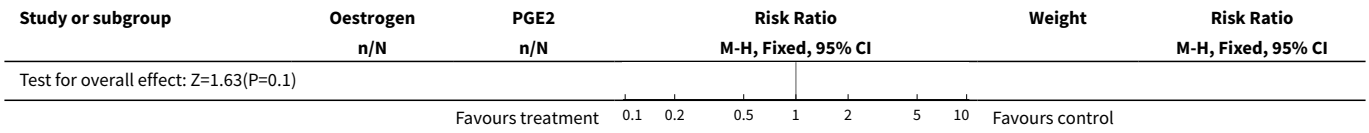


Analysis 16.14. Comparison 16 Oestrogen versus intracervical prostaglandins: all women, unfavourable cervix, Outcome 14 Neonatal intensive care unit admission.



Analysis 16.20. Comparison 16 Oestrogen versus intracervical prostaglandins: all women, unfavourable cervix, Outcome 20 Serious maternal complications.

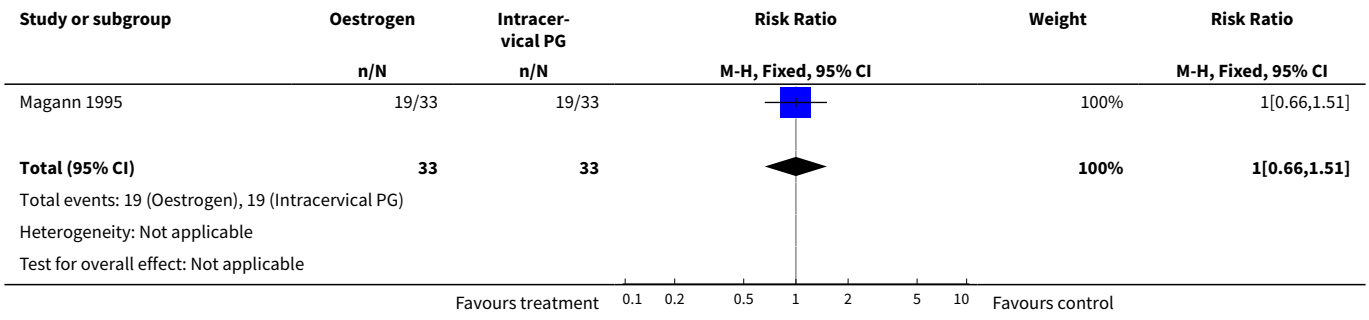




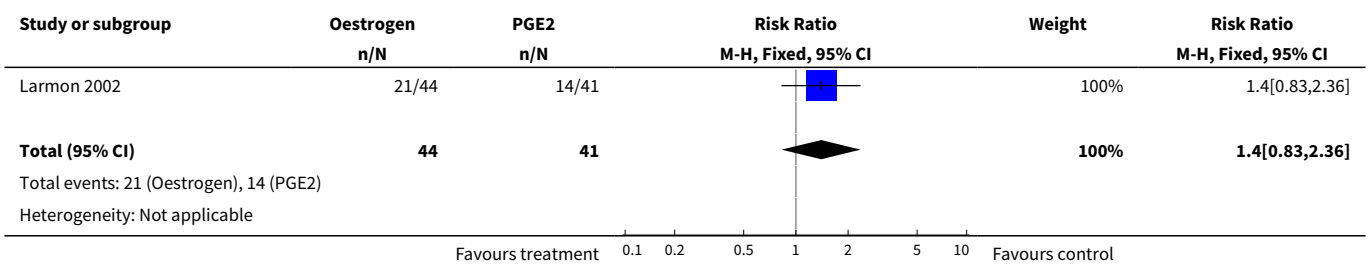
Comparison 17. Oestrogen versus intracervical prostaglandins: all women, intact membranes, unfavourable cervix

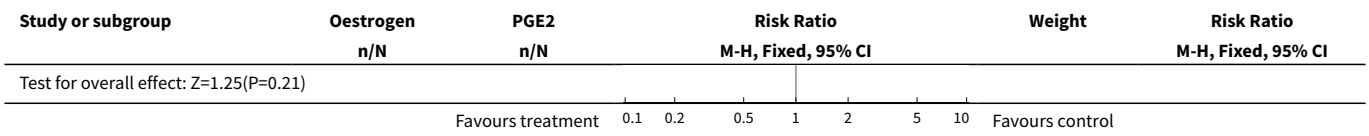
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
3 Caesarean section	1	66	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.66, 1.51]
7 Oxytocin augmentation	1	85	Risk Ratio (M-H, Fixed, 95% CI)	1.40 [0.83, 2.36]
11 Instrumental vaginal delivery	2	151	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.39, 1.23]
12 Meconium stained liquor	1	85	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.17, 2.94]
14 Neonatal intensive care unit admission	1	85	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.06, 14.42]
20 Serious maternal complications	1	85	Risk Ratio (M-H, Fixed, 95% CI)	2.80 [0.81, 9.62]

Analysis 17.3. Comparison 17 Oestrogen versus intracervical prostaglandins: all women, intact membranes, unfavourable cervix, Outcome 3 Caesarean section.

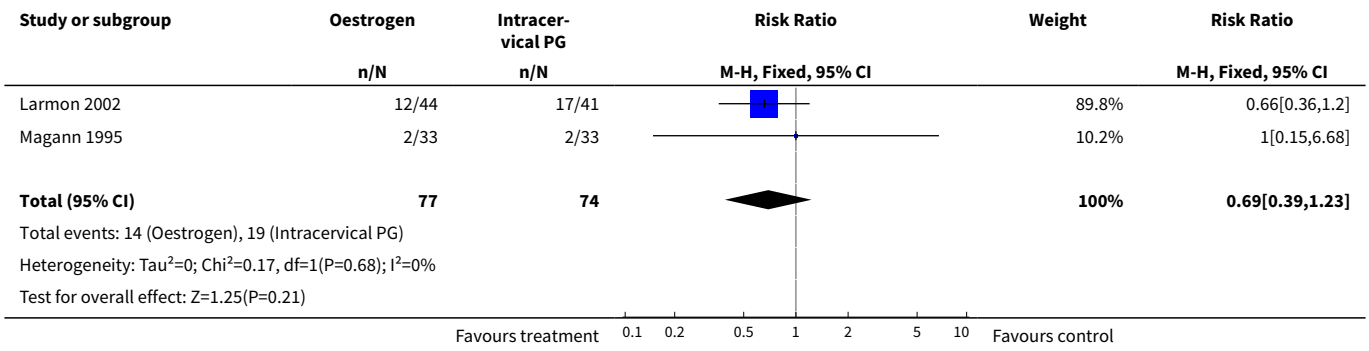


Analysis 17.7. Comparison 17 Oestrogen versus intracervical prostaglandins: all women, intact membranes, unfavourable cervix, Outcome 7 Oxytocin augmentation.

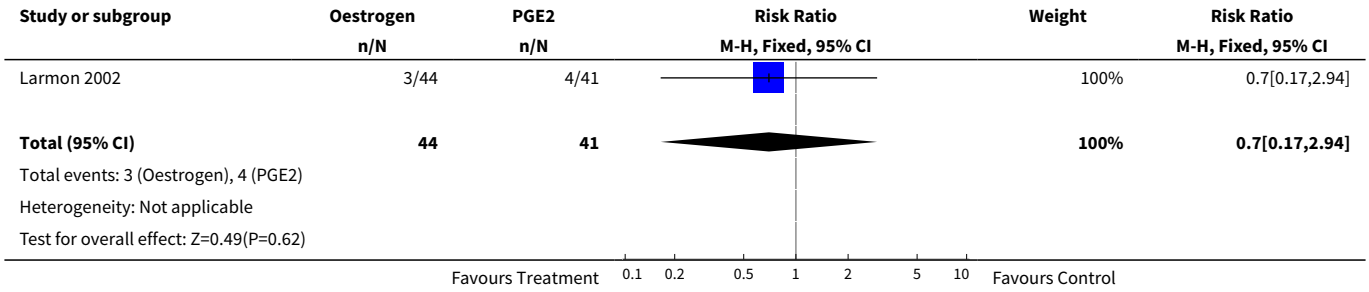




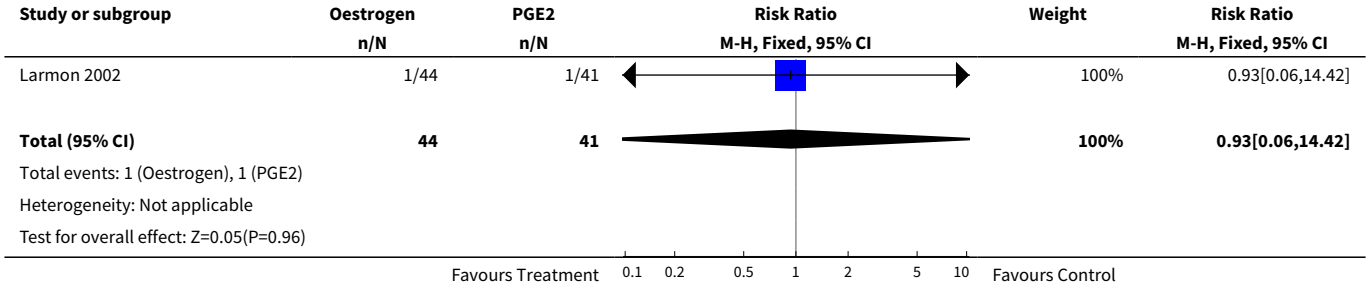
Analysis 17.11. Comparison 17 Oestrogen versus intracervical prostaglandins: all women, intact membranes, unfavourable cervix, Outcome 11 Instrumental vaginal delivery.



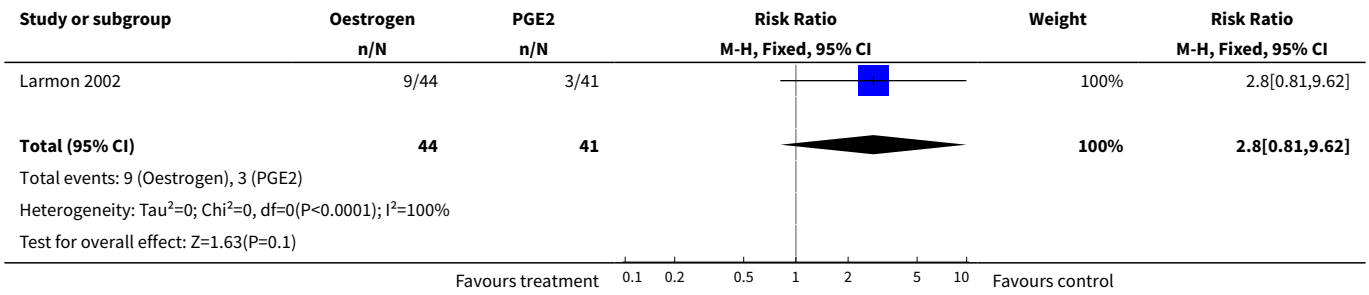
Analysis 17.12. Comparison 17 Oestrogen versus intracervical prostaglandins: all women, intact membranes, unfavourable cervix, Outcome 12 Meconium stained liquor.



Analysis 17.14. Comparison 17 Oestrogen versus intracervical prostaglandins: all women, intact membranes, unfavourable cervix, Outcome 14 Neonatal intensive care unit admission.



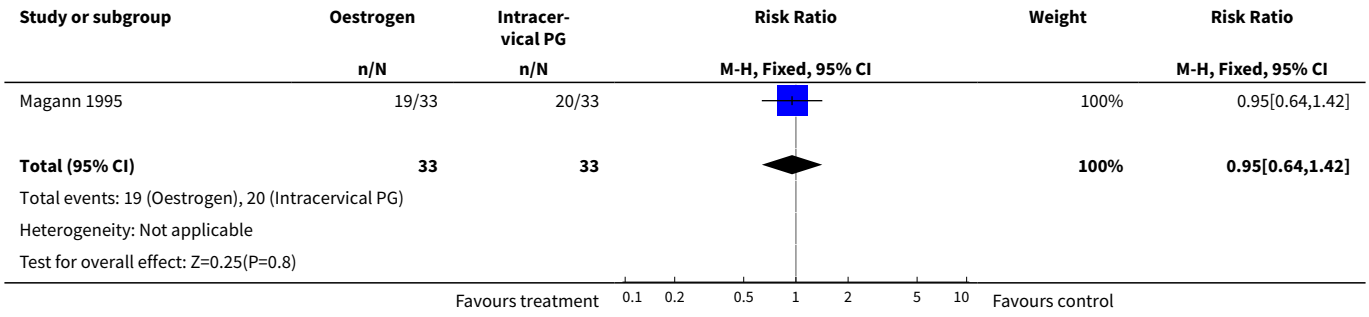
Analysis 17.20. Comparison 17 Oestrogen versus intracervical prostaglandins: all women, intact membranes, unfavourable cervix, Outcome 20 Serious maternal complications.



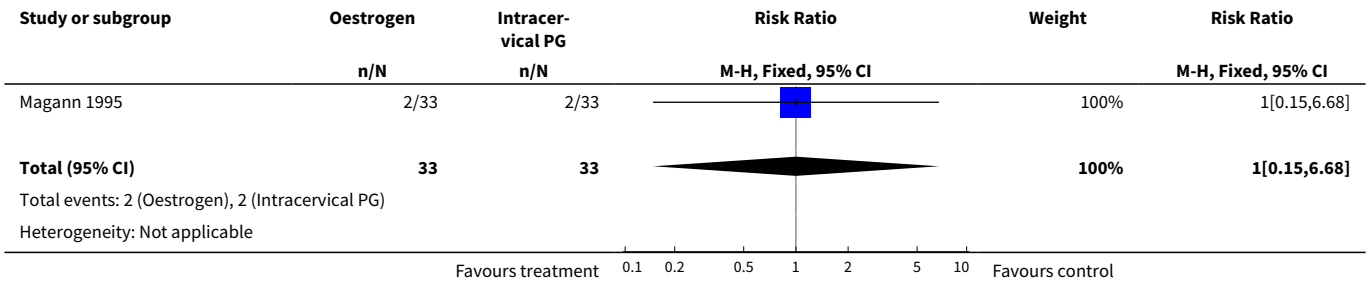
Comparison 20. Oestrogen versus oxytocin alone: all women

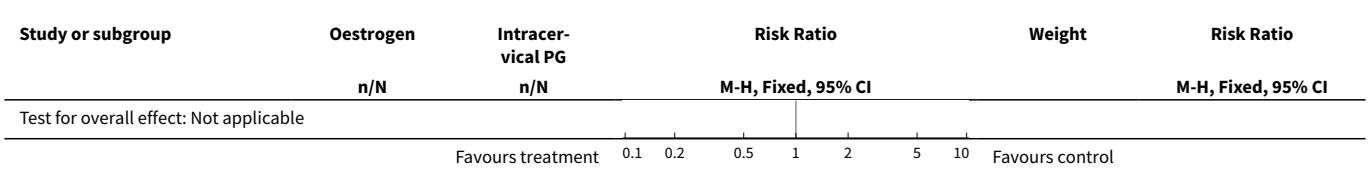
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Caesarean section	1	66	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.64, 1.42]
11 Instrumental vaginal delivery	1	66	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.15, 6.68]

Analysis 20.3. Comparison 20 Oestrogen versus oxytocin alone: all women, Outcome 3 Caesarean section.



Analysis 20.11. Comparison 20 Oestrogen versus oxytocin alone: all women, Outcome 11 Instrumental vaginal delivery.

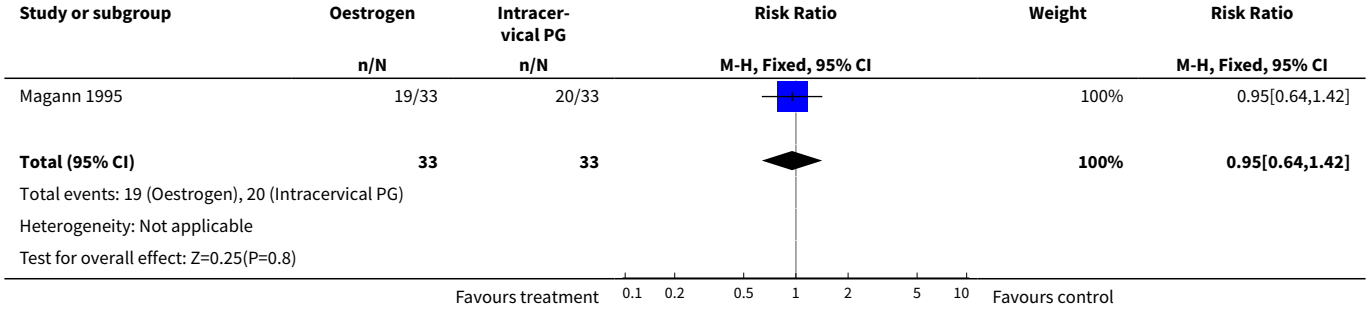




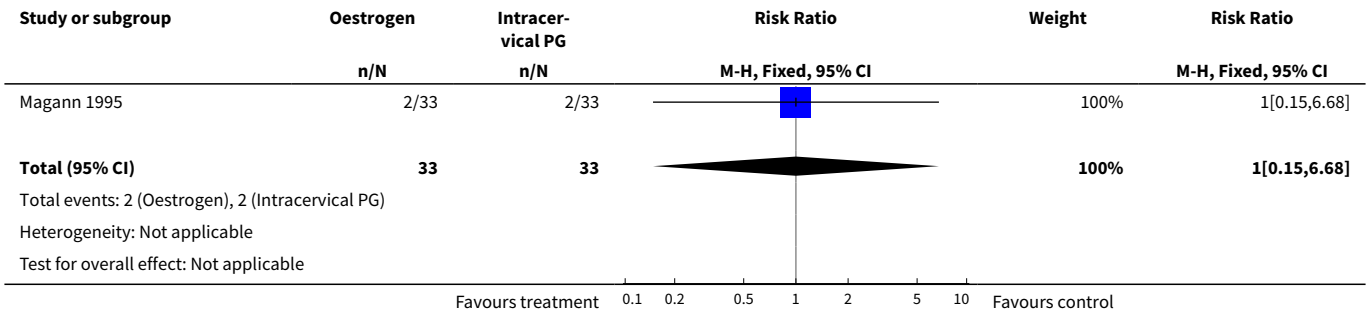
Comparison 21. Oestrogen versus oxytocin alone: all women, unfavourable cervix

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Caesarean section	1	66	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.64, 1.42]
11 Instrumental vaginal delivery	1	66	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.15, 6.68]

Analysis 21.3. Comparison 21 Oestrogen versus oxytocin alone: all women, unfavourable cervix, Outcome 3 Caesarean section.



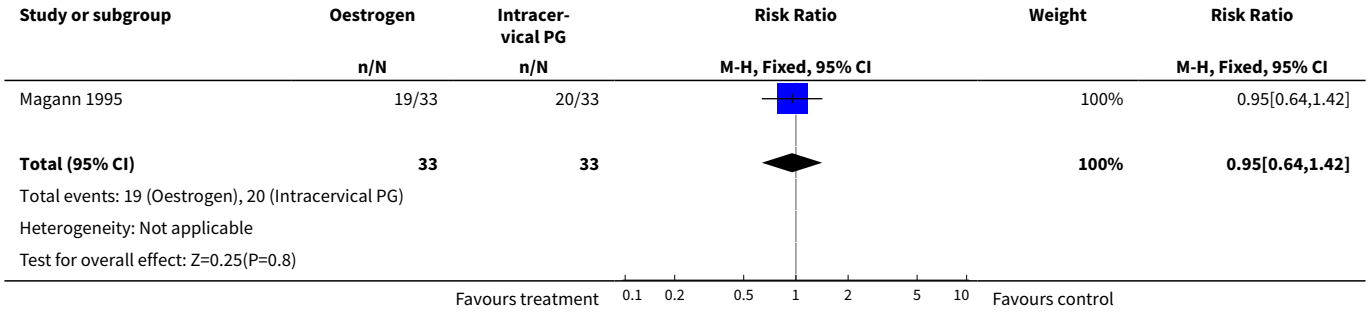
Analysis 21.11. Comparison 21 Oestrogen versus oxytocin alone: all women, unfavourable cervix, Outcome 11 Instrumental vaginal delivery.



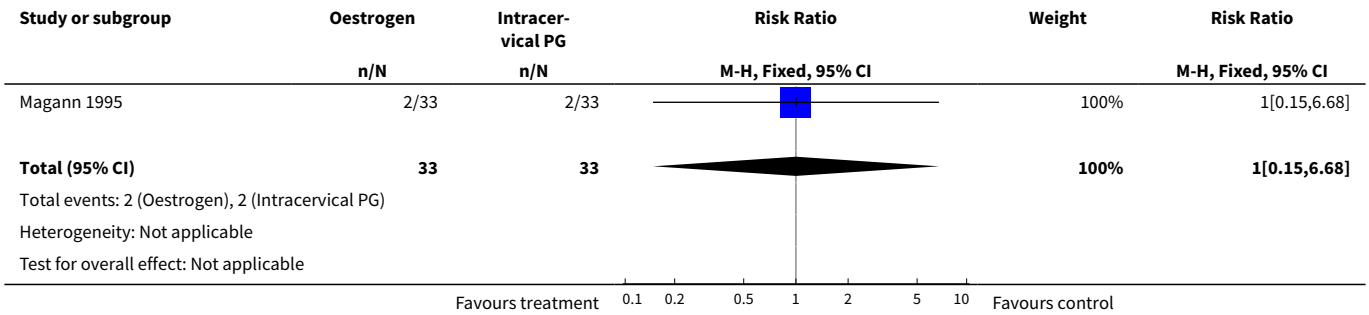
Comparison 22. Oestrogen versus oxytocin alone: all women, intact membranes, unfavourable cervix

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Caesarean section	1	66	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.64, 1.42]
11 Instrumental vaginal delivery	1	66	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.15, 6.68]

Analysis 22.3. Comparison 22 Oestrogen versus oxytocin alone: all women, intact membranes, unfavourable cervix, Outcome 3 Caesarean section.



Analysis 22.11. Comparison 22 Oestrogen versus oxytocin alone: all women, intact membranes, unfavourable cervix, Outcome 11 Instrumental vaginal delivery.

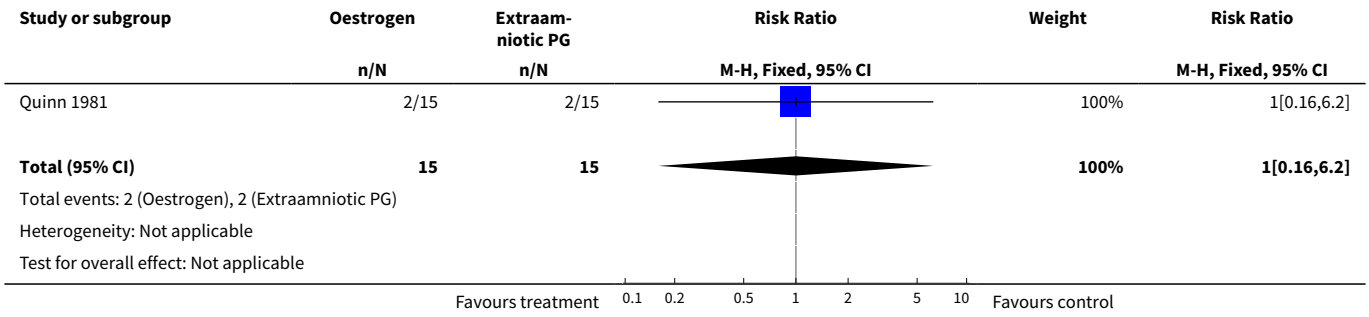


Comparison 25. Oestrogen versus extraamniotic prostaglandins: all women

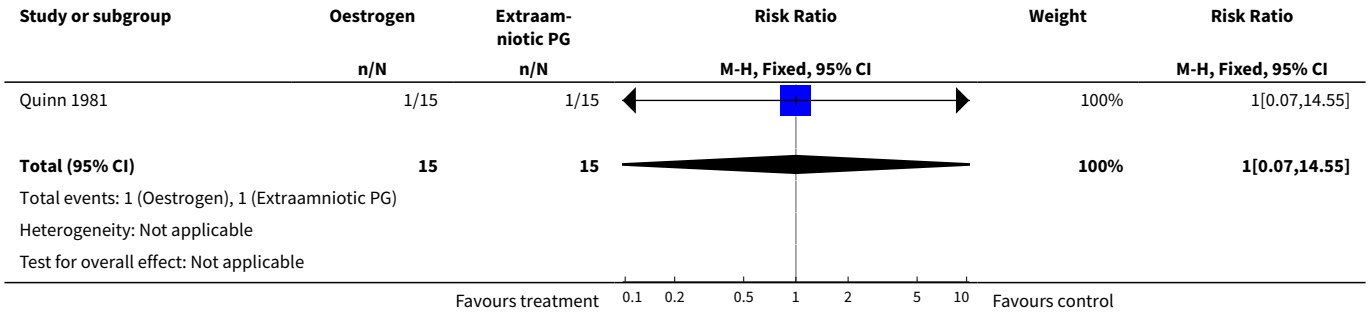
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Uterine hyperstimulation with FHR changes	1	30	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.16, 6.20]
3 Caesarean section	1	30	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.07, 14.55]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4 Serious neonatal morbidity or perinatal death	1	30	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 7.58]
8 Uterine hyperstimulation without FHR changes	1	30	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 7.58]
11 Instrumental vaginal delivery	1	30	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.42, 2.40]
16 Perinatal death	1	30	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 7.58]

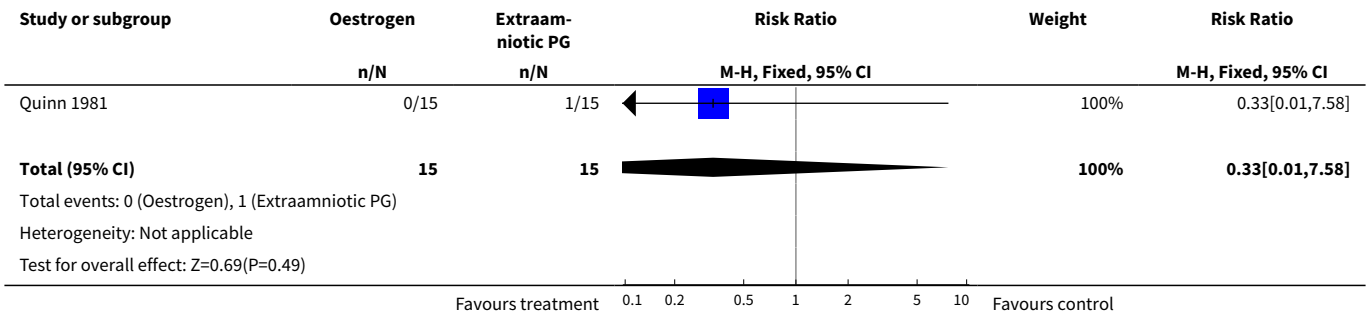
Analysis 25.2. Comparison 25 Oestrogen versus extraamniotic prostaglandins: all women, Outcome 2 Uterine hyperstimulation with FHR changes.



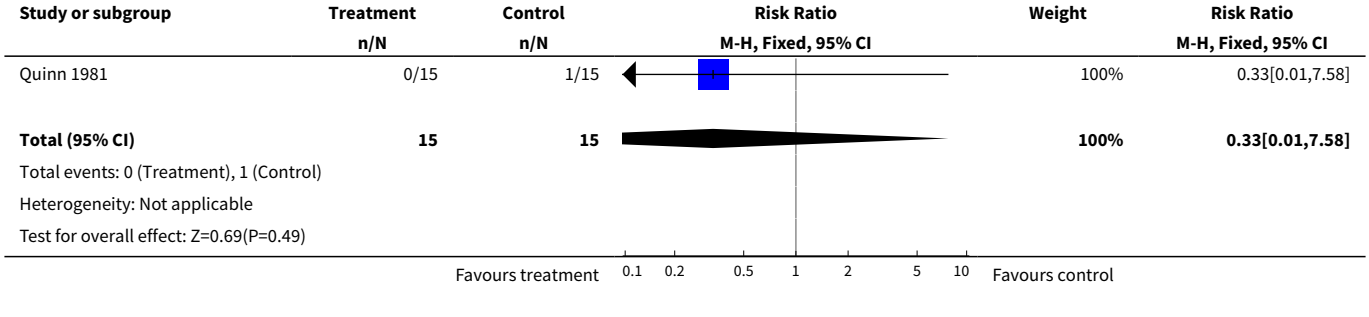
Analysis 25.3. Comparison 25 Oestrogen versus extraamniotic prostaglandins: all women, Outcome 3 Caesarean section.



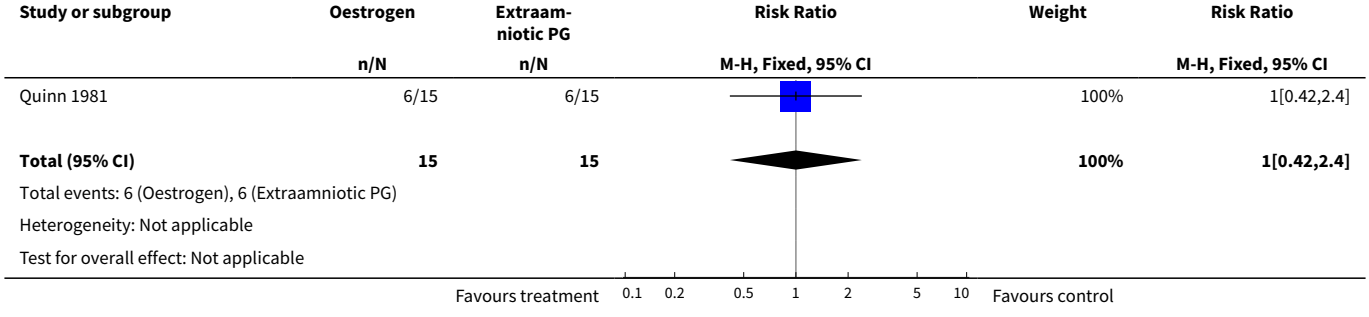
Analysis 25.4. Comparison 25 Oestrogen versus extraamniotic prostaglandins: all women, Outcome 4 Serious neonatal morbidity or perinatal death.



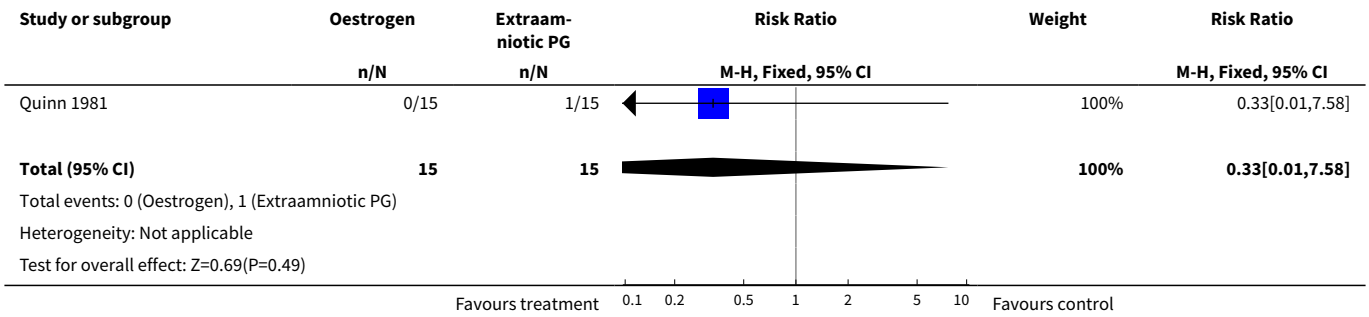
Analysis 25.8. Comparison 25 Oestrogen versus extraamniotic prostaglandins: all women, Outcome 8 Uterine hyperstimulation without FHR changes.



Analysis 25.11. Comparison 25 Oestrogen versus extraamniotic prostaglandins: all women, Outcome 11 Instrumental vaginal delivery.



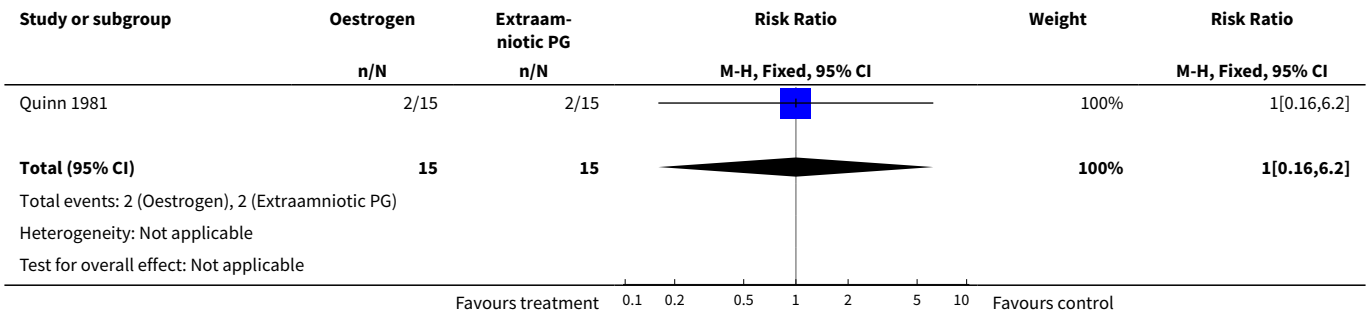
Analysis 25.16. Comparison 25 Oestrogen versus extraamniotic prostaglandins: all women, Outcome 16 Perinatal death.



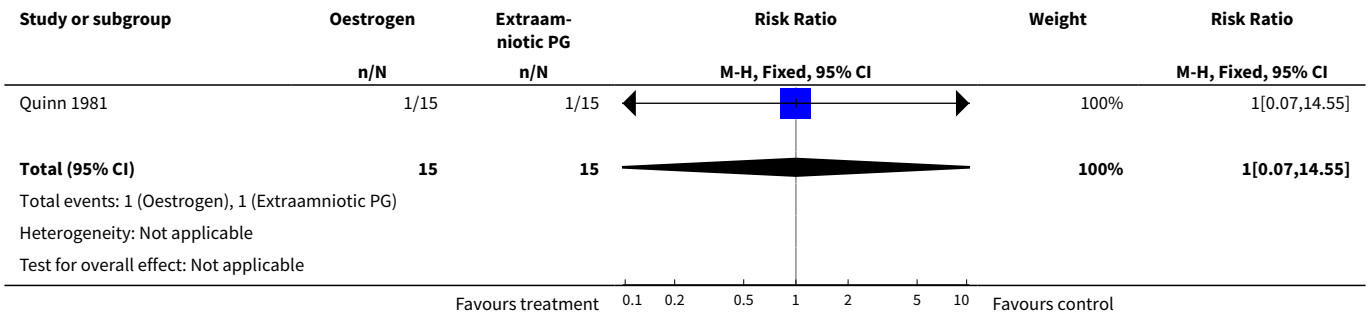
Comparison 26. Oestrogen versus extraamniotic prostaglandins: all women, unfavourable cervix

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Uterine hyperstimulation with FHR changes	1	30	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.16, 6.20]
3 Caesarean section	1	30	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.07, 14.55]
4 Serious neonatal morbidity or perinatal death	1	30	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 7.58]
8 Uterine hyperstimulation without FHR changes	1	30	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 7.58]
11 Instrumental vaginal delivery	1	30	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.42, 2.40]
16 Perinatal death	1	30	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 7.58]

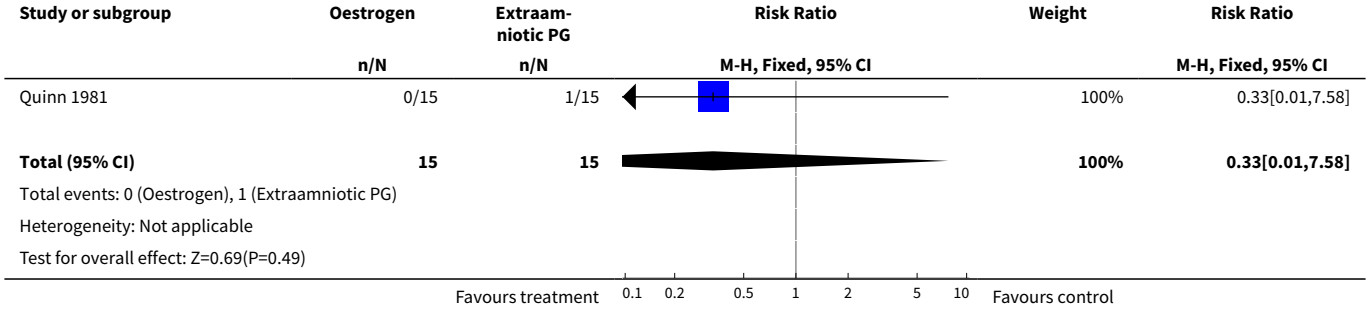
Analysis 26.2. Comparison 26 Oestrogen versus extraamniotic prostaglandins: all women, unfavourable cervix, Outcome 2 Uterine hyperstimulation with FHR changes.



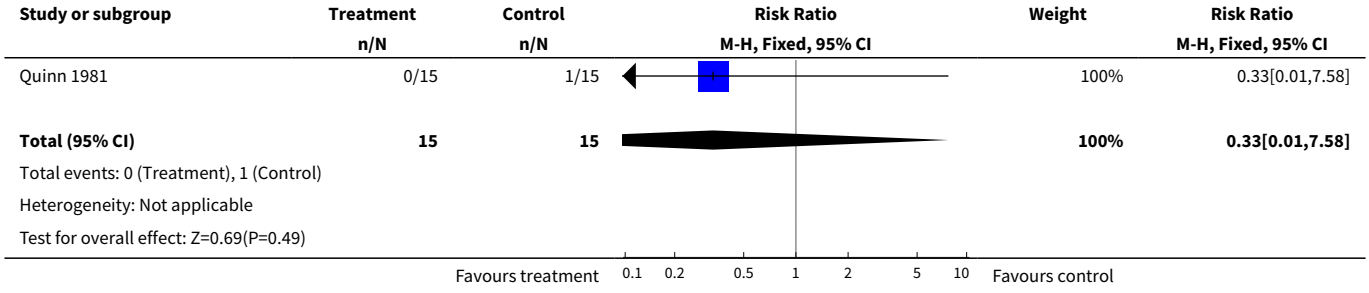
Analysis 26.3. Comparison 26 Oestrogen versus extraamniotic prostaglandins: all women, unfavourable cervix, Outcome 3 Caesarean section.



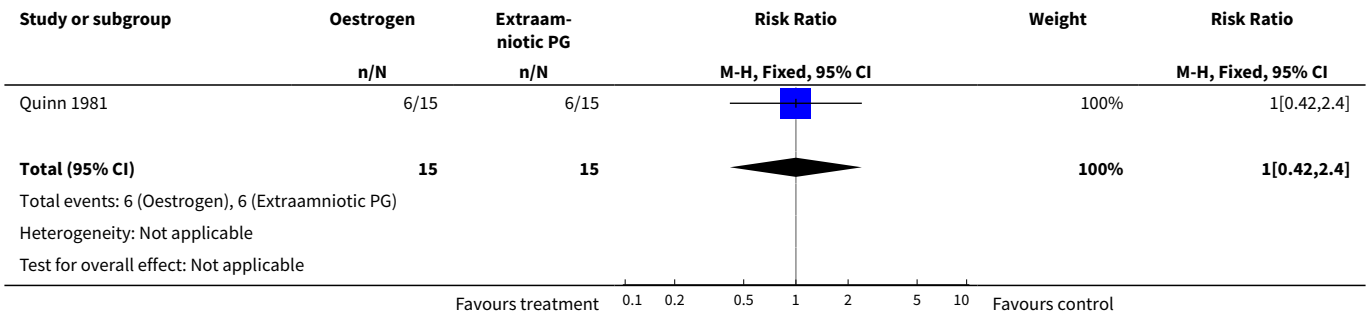
Analysis 26.4. Comparison 26 Oestrogen versus extraamniotic prostaglandins: all women, unfavourable cervix, Outcome 4 Serious neonatal morbidity or perinatal death.



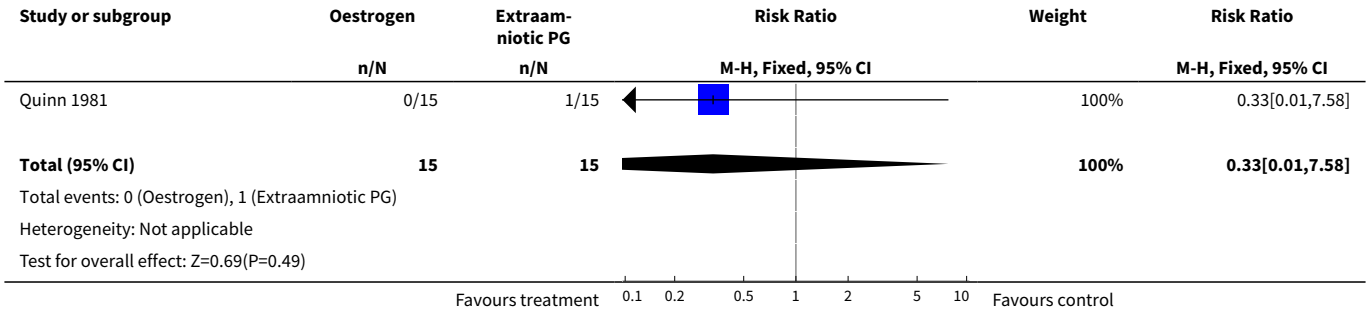
Analysis 26.8. Comparison 26 Oestrogen versus extraamniotic prostaglandins: all women, unfavourable cervix, Outcome 8 Uterine hyperstimulation without FHR changes.



Analysis 26.11. Comparison 26 Oestrogen versus extraamniotic prostaglandins: all women, unfavourable cervix, Outcome 11 Instrumental vaginal delivery.



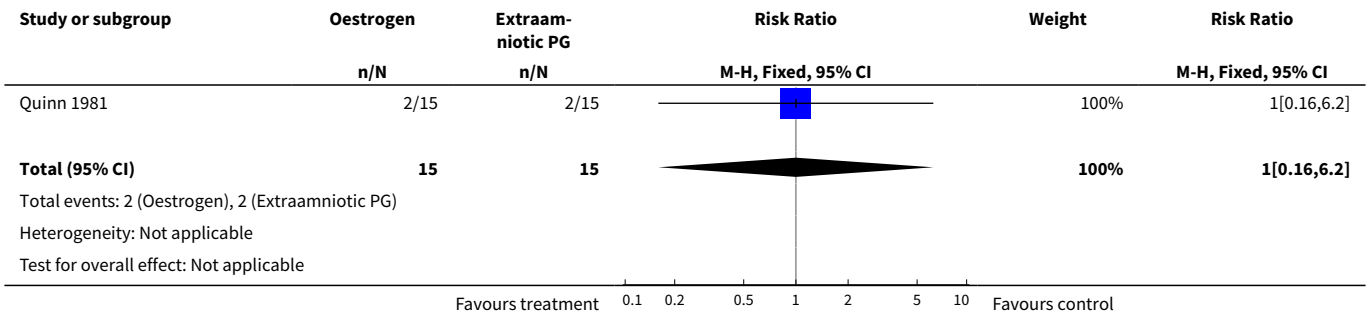
Analysis 26.16. Comparison 26 Oestrogen versus extraamniotic prostaglandins: all women, unfavourable cervix, Outcome 16 Perinatal death.



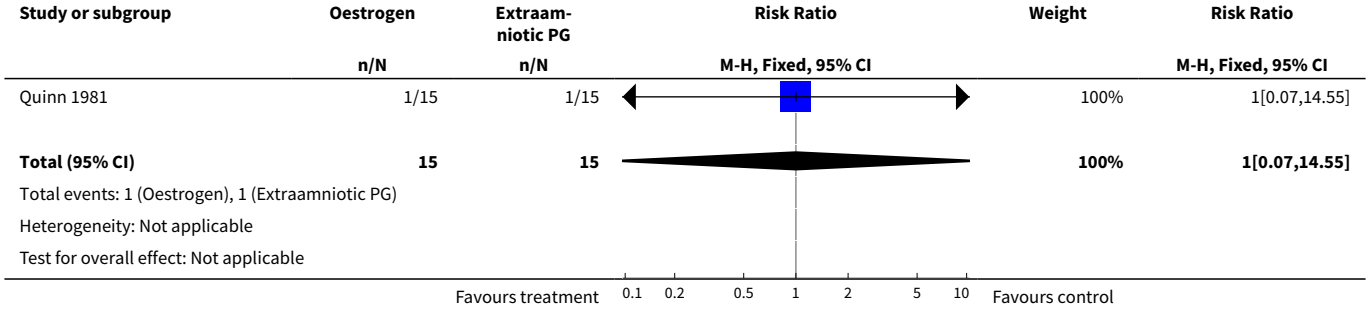
Comparison 27. Oestrogen versus extraamniotic prostaglandins: all primiparae

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
2 Uterine hyperstimulation with FHR changes	1	30	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.16, 6.20]
3 Caesarean section	1	30	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.07, 14.55]
4 Serious neonatal morbidity or perinatal death	1	30	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 7.58]
8 Uterine hyperstimulation with-out FHR changes	1	30	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 7.58]
11 Instrumental vaginal delivery	1	30	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.42, 2.40]
16 Perinatal death	1	30	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 7.58]

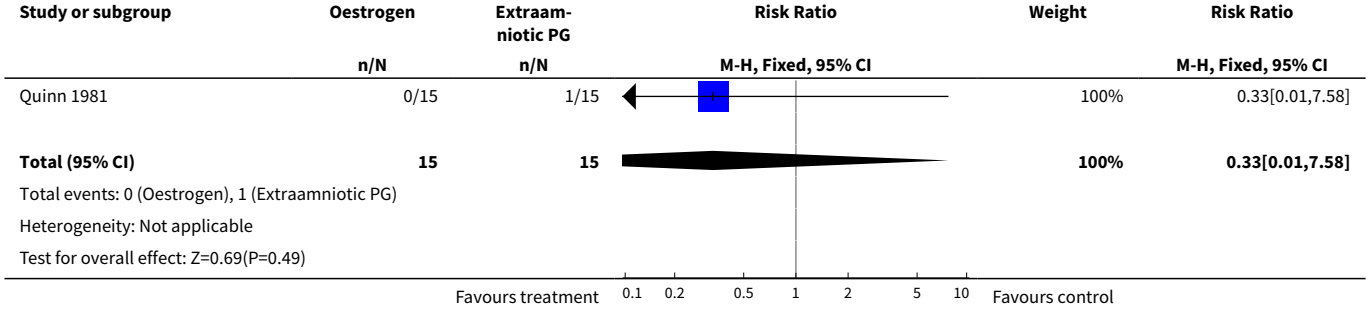
Analysis 27.2. Comparison 27 Oestrogen versus extraamniotic prostaglandins: all primiparae, Outcome 2 Uterine hyperstimulation with FHR changes.



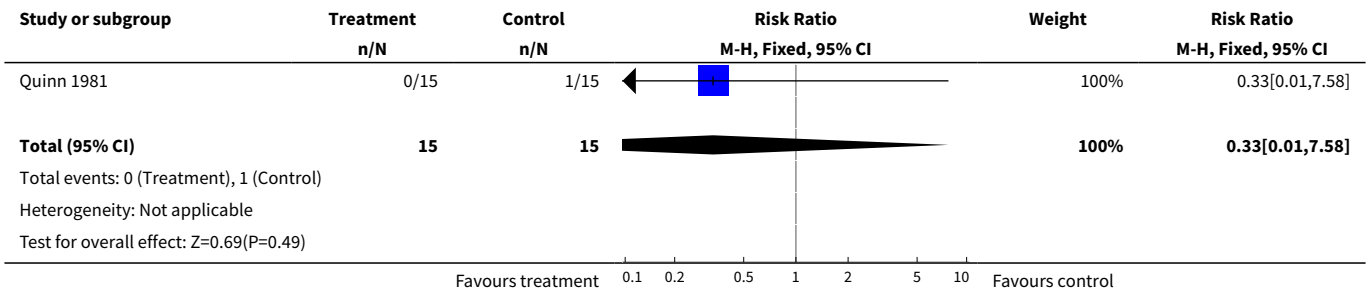
Analysis 27.3. Comparison 27 Oestrogen versus extraamniotic prostaglandins: all primiparae, Outcome 3 Caesarean section.



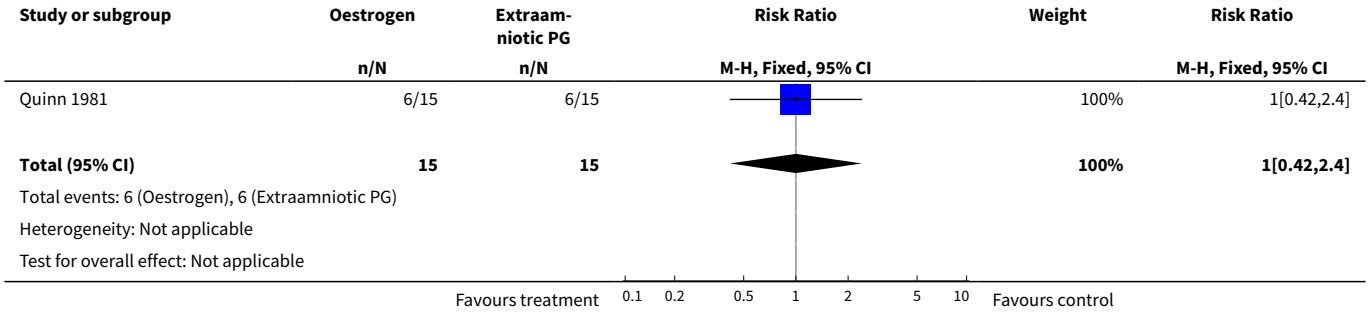
Analysis 27.4. Comparison 27 Oestrogen versus extraamniotic prostaglandins: all primiparae, Outcome 4 Serious neonatal morbidity or perinatal death.



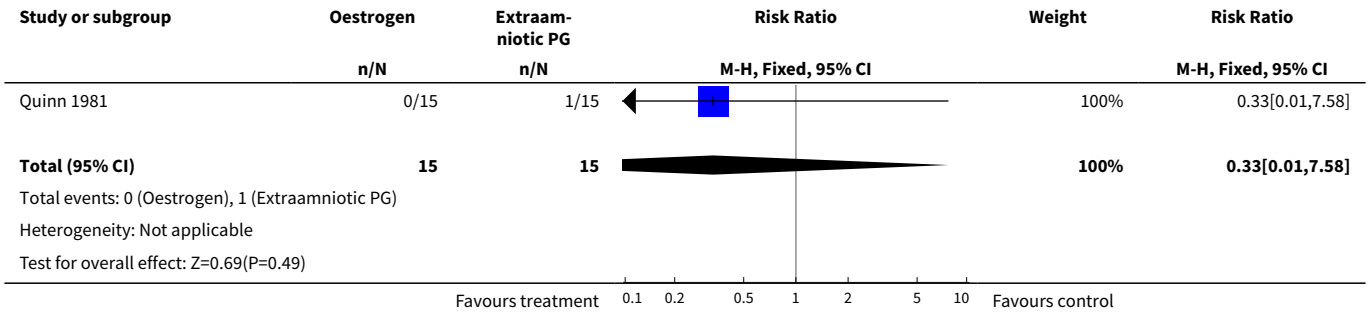
Analysis 27.8. Comparison 27 Oestrogen versus extraamniotic prostaglandins: all primiparae, Outcome 8 Uterine hyperstimulation without FHR changes.



Analysis 27.11. Comparison 27 Oestrogen versus extraamniotic prostaglandins: all primiparae, Outcome 11 Instrumental vaginal delivery.



Analysis 27.16. Comparison 27 Oestrogen versus extraamniotic prostaglandins: all primiparae, Outcome 16 Perinatal death.

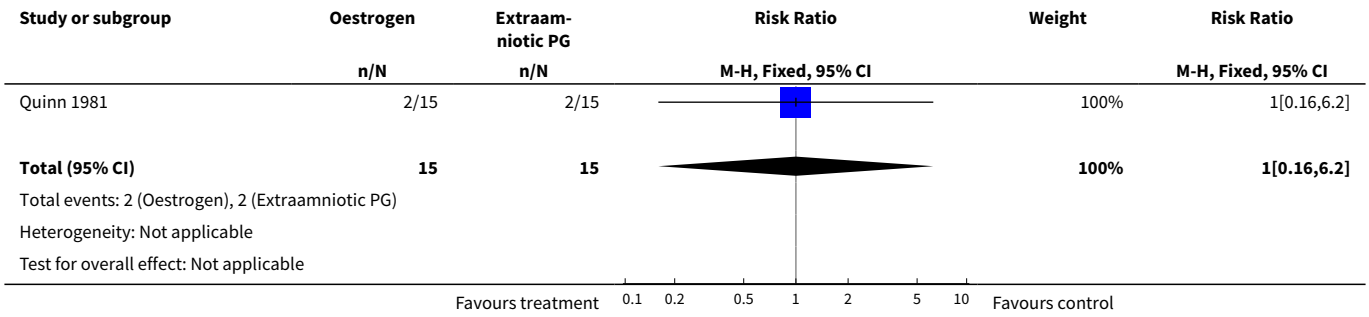


Comparison 28. Oestrogen versus extraamniotic prostaglandins: all primiparae, unfavourable cervix

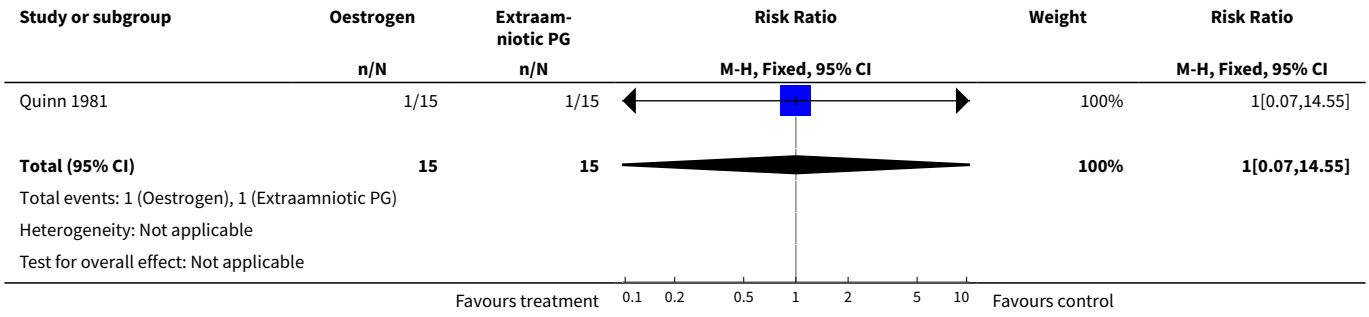
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
2 Uterine hyperstimulation with FHR changes	1	30	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.16, 6.20]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Caesarean section	1	30	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.07, 14.55]
4 Serious neonatal morbidity or perinatal death	1	30	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 7.58]
8 Uterine hyperstimulation without FHR changes	1	30	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 7.58]
11 Instrumental vaginal delivery	1	30	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.42, 2.40]
16 Perinatal death	1	30	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 7.58]

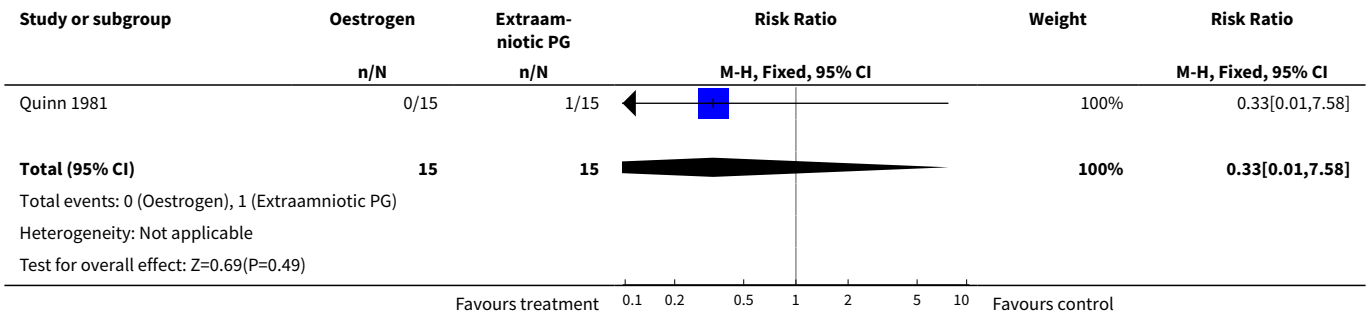
Analysis 28.2. Comparison 28 Oestrogen versus extraamniotic prostaglandins: all primiparae, unfavourable cervix, Outcome 2 Uterine hyperstimulation with FHR changes.



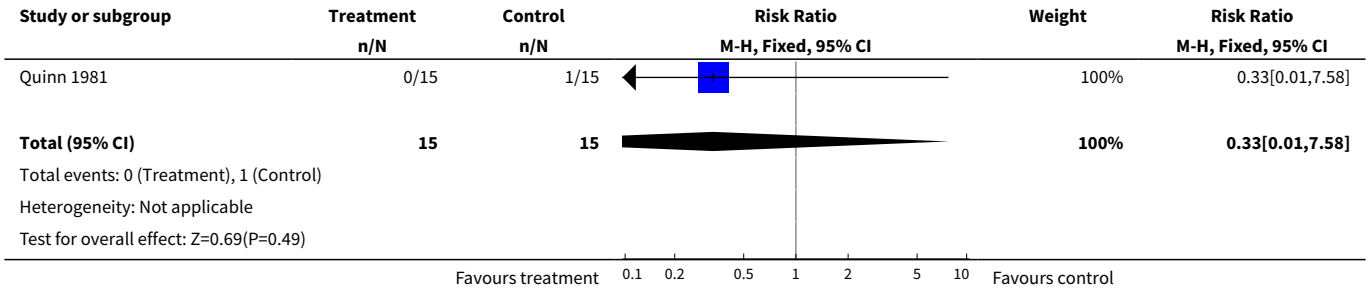
Analysis 28.3. Comparison 28 Oestrogen versus extraamniotic prostaglandins: all primiparae, unfavourable cervix, Outcome 3 Caesarean section.



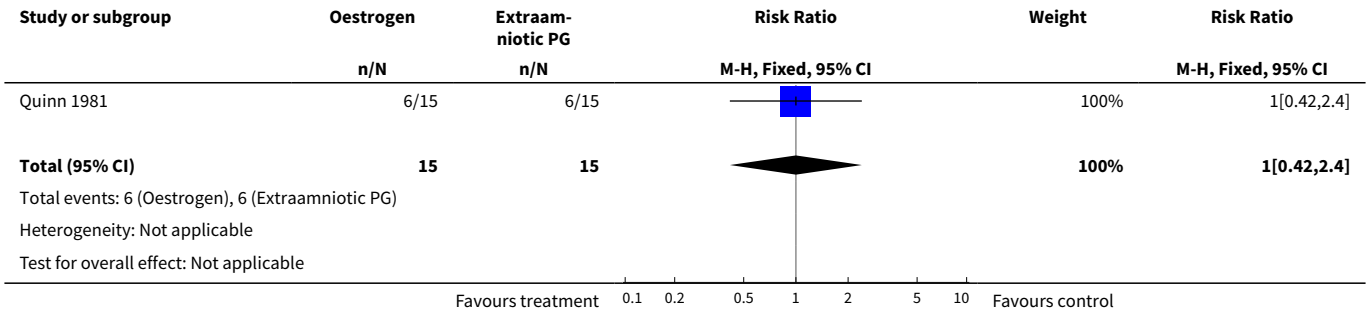
Analysis 28.4. Comparison 28 Oestrogen versus extraamniotic prostaglandins: all primiparae, unfavourable cervix, Outcome 4 Serious neonatal morbidity or perinatal death.



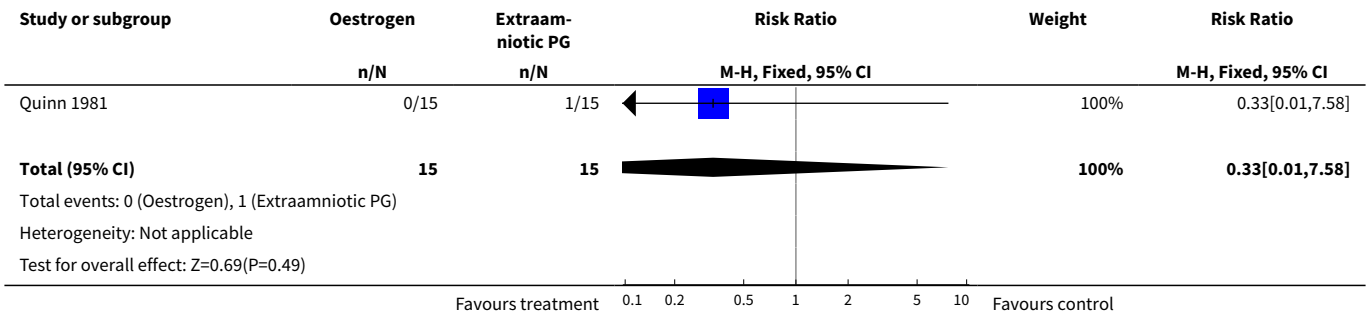
Analysis 28.8. Comparison 28 Oestrogen versus extraamniotic prostaglandins: all primiparae, unfavourable cervix, Outcome 8 Uterine hyperstimulation without FHR changes.



Analysis 28.11. Comparison 28 Oestrogen versus extraamniotic prostaglandins: all primiparae, unfavourable cervix, Outcome 11 Instrumental vaginal delivery.



Analysis 28.16. Comparison 28 Oestrogen versus extraamniotic prostaglandins: all primiparae, unfavourable cervix, Outcome 16 Perinatal death.



ADDITIONAL TABLES

Table 1. Methodological quality of trials

Methodological item	Adequate	Inadequate
Generation of random sequence	Computer generated sequence, random number tables, lot drawing, coin tossing, shuffling cards, throwing dice.	Case number, date of birth, date of admission, alternation.
Concealment of allocation	Central randomisation, coded drug boxes, sequentially sealed opaque envelopes.	Open allocation sequence, any procedure based on inadequate generation.

WHAT'S NEW

Date	Event	Description
1 July 2008	Amended	Converted to new review format.
17 April 2008	New search has been performed	Four new studies were identified and evaluated for the purpose of this update (Griffin 2003; Larmon 2002; Moran 1994; Thiery 1979). One of these (Larmon 2002) is included in the review; the other three excluded: two because they did not report any of the prespecified outcomes (Griffin 2003; Moran 1994) and one (Thiery 1979) because it was a "complex intervention" - the oestrogen used within the trial was combined with the use of an extra amniotic placed foley catheter. A study awaiting awaiting assessment in the previous review has now been excluded (Luther 1980), again because the trial evaluated a "complex intervention" of intramuscular oestradiol with PGE2.

CONTRIBUTIONS OF AUTHORS

J Thomas, AJ Kelly and J Kavanagh were involved in developing the protocol, data extraction, assessment of the trials and drafting and re-drafting the review.

DECLARATIONS OF INTEREST

None known.

INDEX TERMS

Medical Subject Headings (MeSH)

*Cervical Ripening; *Estrogens; Amnion [*surgery]; Labor, Induced [*methods]; Randomized Controlled Trials as Topic

MeSH check words

Female; Humans; Pregnancy