National Institute for Health and Care Excellence

Final

Inducing labour

[B] Methods for the induction of labour

NICE guideline NG207

Evidence review underpinning recommendations 1.3.4 to 1.3.10 in the NICE guideline

November 2021

Final

This evidence review was developed by the National Guideline Alliance which is a part of the Royal College of Obstetricians and Gynaecologists

Disclaimer

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

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Contents

Methods for induction of labour

Review question

What are the benefits and harms of pharmacological and mechanical methods in induction of labour?

Introduction

Induction of labour is a common procedure, with approximately a third of all women in the UK undergoing induction, and there are a variety of pharmacological and mechanical methods available. The choice of method depends on the condition of the woman's cervix (assessed using a vaginal examination, and categorised using a Bishop score), whether the membranes have ruptured, and taking into consideration a woman's preferences. The choice also depends on the efficacy and possible adverse effects for the woman and her baby associated with each method, and the likelihood that additional interventions (such as caesarean birth) may be required if the induction is not successful.

The aim of this review is to identify the benefits and harms of different pharmacological and mechanical methods to induce labour.

Summary of the protocol

Please see Table 1 for a summary of the Population, Intervention, Comparison and Outcome (PICO) characteristics of this review.

Table 1: Summary of the protocol (PICO table)

Population	Pregnant women offered induction of labour for any indication **Inclusion/exclusion criteria:** • include women in the third trimester (≥28 weeks + 0 days) • include women with viable fetus only • exclude trials where all women had a previous caesarean birth • exclude trials where all women had ruptured membranes
Intervention	• Any method used for induction of labour **<u>Pharmacological methods</u>** • Prostaglandins: a) Vaginal and intracervical administration - Dinoprostone (PGE_2) vaginal tablets (lactose based) - Dinoprostone (PGE_2) vaginal pessaries normal release (sometimes referred to as suppositories, manufactured using various base materials including wax and glycerine) - Dinoprostone (PGE_2) vaginal pessaries sustained or slow release (10-12mg pessaries in a delivery system, can be removed when the cervix is adequately softened and dilated) - Dinoprostone (PGE_2) gel (introduced via vaginal applicator) - Dinoprostone (PGE_2) for intracervical administration - PGF_2 gel b) Extra-amniotic administration c) Intravenous administration

	d) Oral administration • Misoprostol - vaginal misoprostol (dose < 50 microgram) - vaginal misoprostol (dose ≥ 50 microgram) - oral misoprostol tablet (dose < 50 microgram) - oral misoprostol tablet (dose ≥ 50 microgram) - titrated (low-dose) oral misoprostol solution - sustained-release misoprostol insert (vaginal delivery system) - buccal/sublingual misoprostol • Oxytocin - IV oxytocin alone - IV oxytocin with amniotomy • Nitric oxide donors • Mifepristone • Oestrogens • Corticosteroids • Relaxin • Hyaluronidase **Mechanical methods** • Foley catheters • Osmotic cervical dilators (also known as laminaria or dilapan) • Double balloon or Cook's catheter • Amniotomy
Comparison	• No treatment • Placebo • Any intervention (in the above list) compared to any other intervention
Outcomes	**Critical:** • No vaginal birth within 24 hours • Uterine hyperstimulation with fetal heart rate changes • Caesarean birth **Important:** • Serious neonatal morbidity or perinatal death • Serious maternal morbidity or death • Maternal satisfaction • Instrumental birth • NICU admission • Use of epidural

IV: intravenous; NICU: neonatal intensive care unit; PGE: prostaglandin E; PGF: prostaglandin F;
Note: the only licensed medications for induction of labour in the United Kingdom are misoprostol 25 microgram tablets and dinoprostone (PGE_2) vaginal tablets, vaginal gel, sustained release vaginal delivery system, IV infusion and extra-amniotic solution.
Note: the international nonpropietary name (INN) for prostaglandin E_2 (PGE_2) is dinoprostone. The data extraction and analysis for this review was carried out using the term PGE_2, but the discussion sections have been amended to use the INN

For further details, see the review protocol in appendix A.

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Please see the methods chapter for further details. Methods specific to this review question are described in the review protocol in appendix A, and are summarised below.

In 2016, a network meta-analysis (NMA) was published, which considered the efficacy and safety of all methods of induction of labour (pharmacological, mechanical and complementary/alternative methods) (Alfirevic 2016). This evidence review therefore used data from the published NMA, and searches were carried out to ensure that more recent evidence was also incorporated.

Some data included in the original NMA were excluded from this analysis. The reasons for these exclusions are given in the excluded studies list (appendix K), but were predominantly studies that included women with a previous caesarean birth or women with ruptured membranes. The protocol for this evidence review stated that women with a previous caesarean birth or ruptured membranes should be excluded, unless they comprised less than a third of the total study population.

Where possible, all data were obtained from the published NMA – this included study characteristics and outcome data. Where data were missing in the original NMA (including data for the outcome 'use of epidural', and full risk of bias assessment using the Cochrane risk of bias tool), relevant Cochrane reviews were consulted. Data were then obtained from the relevant Cochrane review if possible. If the study had not been included in a Cochrane review then the full text of the article was obtained to enable full data extraction. New data that were added to the trials included in the original NMA were checked by two reviewers.

In addition to adding data that were not included in the original NMA, full text was obtained for all new studies that had been identified by the literature search and which met the protocol criteria. Data extraction from these additional studies was carried out independently by two reviewers.

The protocol specified outcome of "serious neonatal morbidity or perinatal death" was identified as being reported sporadically and inconsistently between different trials by the authors of the existing NMA report. No agreed definition of "serious perinatal morbidity" was identified, and therefore the report authors instead extracted data only on perinatal mortality for this outcome. This approach was therefore also adopted for this evidence review – all data reported for this outcome relate specifically to perinatal death, not serious morbidity.

It was found that admission to neonatal care units or neonatal intensive care units (NICU) were reported variably in the evidence, and thus the decision was taken to classify all neonatal admissions as admission to NICU, although in some cases this admission may have been to a lower intensity care setting.

Further details of the methods used to conduct the NMA are given in appendix N.

Declarations of interest were recorded according to NICE's 2014 conflicts of interest policy until 31 March 2018. From 1 April 2018, declarations of interest were recorded according to NICE's 2018 conflicts of interest policy. Those interests declared until April 2018 were reclassified according to NICE's 2018 conflicts of interest policy (see Register of Interests).

Clinical evidence

Included studies

A total of 564 randomised controlled trials (RCTs) were included in this evidence review. The majority of these studies were identified from the published NMA (n=467). A further 97 studies were identified by the updated literature search.

See the literature search strategy in appendix B and study selection flow chart in appendix C.

Excluded studies

Studies not included in this review with reasons for their exclusions are provided in appendix K.

Summary of studies included in the evidence review

Not all studies provided data for every outcome included in this evidence review, therefore a narrative summary is presented below, which considers the overall evidence, and the studies that provided evidence for specific outcomes.

The majority of studies (n=519) were two arm trials, directly comparing two different interventions. 40 studies were three arm trials, 4 studies were four arm trials and a single study compared five different interventions.

Trials were predominantly conducted in women with a singleton pregnancy (n=428 trials). Thirteen trials included a mixed population of women with both singleton and multi-fetal pregnancies. A single trial was conducted exclusively in women with a multi-fetal pregnancy. The remaining studies (n=122 trials) did not explicitly state whether participants had a single or multi-fetal pregnancy.

The majority of studies were conducted in women with a gestational age of >37 weeks (n=299 studies). Eighty-five trials were conducted specifically in women with a gestation of >40 weeks. One hundred twenty-five studies included a mixed population of women (some of whom had a pregnancy at <37 weeks' gestation) and 55 studies did not explicitly state the gestational age of the participants.

Most studies (n=418) included both nulliparous and multiparous women. A minority of trials included either nulliparous (n=88) or multiparous (n=10) women, and the remainder did not state the parity of participants (n=48).

A small number of studies included some women with a previous caesarean birth (n=32 trials) or ruptured membranes (n=63 trials). The proportion of women with a previous caesarean birth or ruptured membranes was confirmed to be less than a third for each of these studies, in accordance with the protocol for this review.

See the full evidence tables in appendix D (which is provided as a separate document, supplement 3) and the forest plots in appendix E.

Quality assessment of studies included in the evidence review

See the clinical evidence profiles in appendix F (which is provided as a separate document, supplement 4).

For the results of the threshold analysis that assesses the impact of potential bias in studies and quantify how much the evidence in an analysis could change before the recommendation would be expected to change, see appendix Q.

Clinical evidence profile for outcomes included in the network meta-analysis

NMA was used to synthesise evidence for the following outcomes (both for the whole population of women and for those with a Bishop score ≤6):

- No vaginal birth within 24 hours
- Hyperstimulation with fetal heart rate changes
- Caesarean birth
- Instrumental birth
- Admission to NICU
- Epidural.

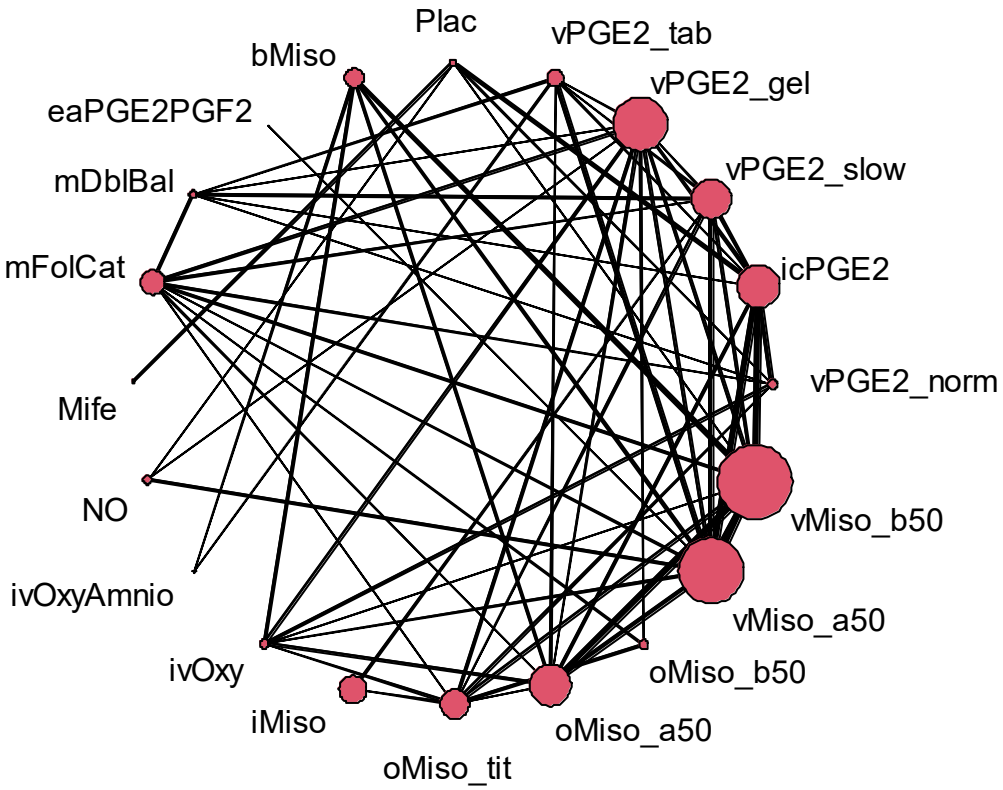
No vaginal birth within 24 hours

141 studies, comparing a total of 20 different interventions in 29,056 women, were included in this analysis. Of these, the majority were conducted specifically in women with a singleton pregnancy (n=127), and women with a Bishop score ≤6 (n=115). 22 studies were conducted exclusively with nulliparous women. 13 trials included women with a previous caesarean birth, but these women comprised less than a third of the study population in these trials.

420 studies were excluded as they reported no data for this outcome. One study (Prasad 1989) was excluded due to reporting 100% events in each arm (all women participating in the study did not achieve vaginal birth within 24 hours). One study was excluded as it included an irrelevant comparison that was not necessary to produce a connected network (Sadi 2016). One study was excluded due to the study protocol affecting the outcome (women receiving no intervention all had caesarean birth) (Frass 2011).

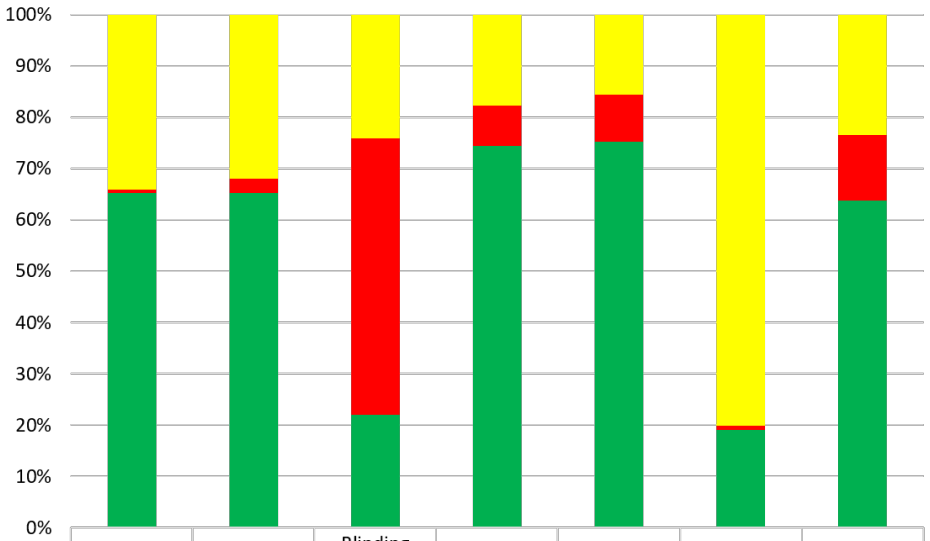
The network plot for this outcome is shown below.

Figure 1: Network for vaginal birth not achieved within 24 hours



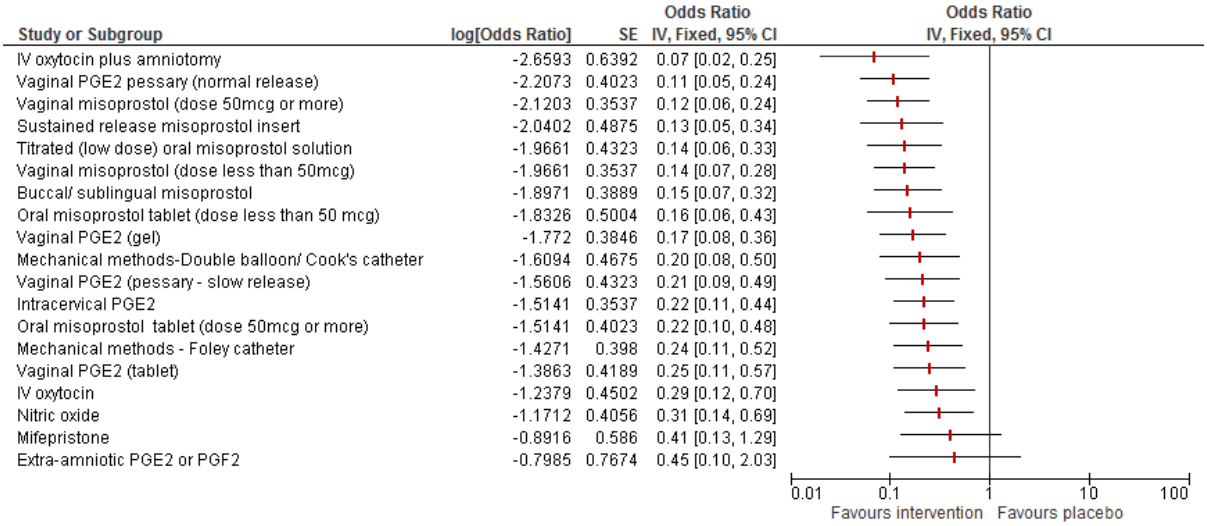
Treatment codes are as follows (in alphabetical order): bMiso: buccal/sublingual misoprostol; eaPGE$_2$PGF$_2$: extra-amniotic prostaglandin; icPEG$_2$: intracervical PGE$_2$; iMiso: misoprostol vaginal insert; ivOxy: iv oxytocin; ivOxyAmino: iv oxytocin plus amniotomy; mDBlBal: double balloon catheter; mFolCat: Foley catheter; Mife: mifepristone; NO: nitric oxide; oMiso_a50: oral misoprostol ≥50mcg; oMiso_b50: oral misoprostol <50mcg; oMiso_tit: titrated low dose oral misoprostol; Plac: placebo; vMiso_a50: vaginal misoprostol ≥50mcgl vMiso_b50: vaginal misoprostol <50mcg; vPEG$_2$_gel: vaginal PGE$_2$ gel; vPGE$_2$_norm: vaginal PGE$_2$ normal release pessary; vPGE$_2$_slow: vaginal PGE$_2$ slow release pessary; vPEG$_2$_tab: vaginal PGE$_2$ tablet. The size of the nodes is proportional to the number of women in the network randomised to a particular intervention. The thickness of the connecting lines is proportional to the number of studies directly comparing 2 interventions.

Figure 2: Vaginal birth not achieved within 24 hours: risk of bias assessment



	Random sequence generation	Allocation concealment	Blinding participants and personnel	Blinding outcome assessors	Incomplete outcome data	Selective reporting	Other bias
Unclear risk (number of studies)	48	45	34	25	22	113	33
High risk (number of studies)	1	4	76	11	13	1	18
Low risk (number of studies)	92	92	31	105	106	27	90

Figure 3: Forest plot showing NMA derived OR for vaginal birth not achieved within 24 hours for all interventions compared to placebo



OR <1 favours the stated intervention, OR >1 favours placebo

Please note: The exact figures for the 95% confidence intervals (CIs) shown in the forest plots are not identical to those given below as the 95% credible intervals (CrIs) in the table below, due to differences in calculation methods and rounding. This applies to the data for all outcomes.

Table 2: OR and 95% CrI for vaginal birth not achieved within 24 hours for all interventions compared to placebo

Intervention	NMA OR (95% CrI)	NMA direct evidence only OR (95% CrI)	Number of studies providing direct evidence
IV oxytocin plus amniotomy	0.07 (0.02, 0.26)	-	
Vaginal PGE_2 pessary (normal release)	0.11 (0.05, 0.25)	0.37 (0.05, 2.57)	1
Vaginal misoprostol ≥50mcg	0.12 (0.06, 0.24)	-	
Misoprostol vaginal insert	0.13 (0.05, 0.32)	-	
Titrated oral (low dose) misoprostol	0.14 (0.06, 0.30)	-	
Vaginal misoprostol <50mcg	0.14 (0.07, 0.27)	0.21 (0.05, 0.82)	1
Buccal/sublingual misoprostol	0.15 (0.07, 0.31)	-	
Oral misoprostol <50mcg	0.16 (0.06, 0.39)	-	
Vaginal PGE_2 gel	0.17 (0.08, 0.34)	-	
Vaginal PGE_2 pessary (slow release)	0.21 (0.09, 0.43)	-	
Double balloon or Cook's catheter	0.20 (0.08, 0.46)	-	
Oral misoprostol ≥50mcg	0.22 (0.10, 0.45)	-	
Intracervical PGE_2	0.22 (0.11, 0.43)	0.06 (0.02, 0.17)	5
Foley catheter	0.24 (0.11, 0.52)	-	
Vaginal PGE_2 tablet	0.25 (0.11, 0.55)	-	
IV oxytocin	0.29 (0.12, 0.66)	-	
Nitric oxide donor	0.31 (0.14, 0.66)	0.91 (0.30, 2.78)	1
Mifepristone	0.41 (0.13, 1.26)	0.42 (0.13, 1.23)	2
Extra-amniotic prostaglandins	0.45 (0.10, 1.88)	-	

Results from overall NMA and using only direct evidence from unrelated mean effect model.
An OR >1 favours placebo (fewer vaginal births in 24 hours were not achieved for placebo arm), and OR <1 favours the active intervention (fewer vaginal births in 24 hours were not achieved in the intervention arm).

The evidence demonstrated a clear increase in the chance of vaginal birth within 24 hours for almost all active treatments, when compared to placebo. The exceptions to this were mifepristone and extra-amniotic prostaglandins – although the point estimate still favoured these interventions, the 95% CrI crossed 1.

Table 3: Median treatment ranks and probability of being the best treatment for all interventions, for vaginal birth not achieved within 24 hours

Intervention	Median (95% CrI) treatment rank	Probability of being best
IV oxytocin plus amniotomy	1 (1, 12)	70%
Vaginal PGE_2 pessary (normal release)	3 (1, 9)	13%

Intervention	Median (95% CrI) treatment rank	Probability of being best
Vaginal misoprostol ≥50mcg	4 (1, 7)	3%
Misoprostol vaginal insert	4 (1, 14)	10%
Vaginal misoprostol <50mcg	6 (3, 9)	0%
Titrated oral (low dose) misoprostol	6 (2, 11)	1%
Buccal/sublingual misoprostol	7 (2, 12)	1%
Oral misoprostol <50mcg	8 (2, 16)	2%
Vaginal PGE_2 gel	9 (5, 13)	0%
Double balloon or Cook's catheter	11 (4, 17)	0%
Vaginal PGE_2 pessary (slow release)	11 (7, 16)	0%
Oral misoprostol ≥50mcg	13 (8, 17)	0%
Intracervical PGE_2	13 (9, 16)	0%
Foley catheter	14 (9, 18)	0%
Vaginal PGE_2 tablet	15 (9, 18)	0%
IV oxytocin	16 (9, 19)	0%
Nitric oxide donor	17 (9, 19)	0%
Extra-amniotic prostaglandins	18 (5, 20)	0%
Mifepristone	18 (3, 20)	1%
Placebo	20 (19, 20)	0%

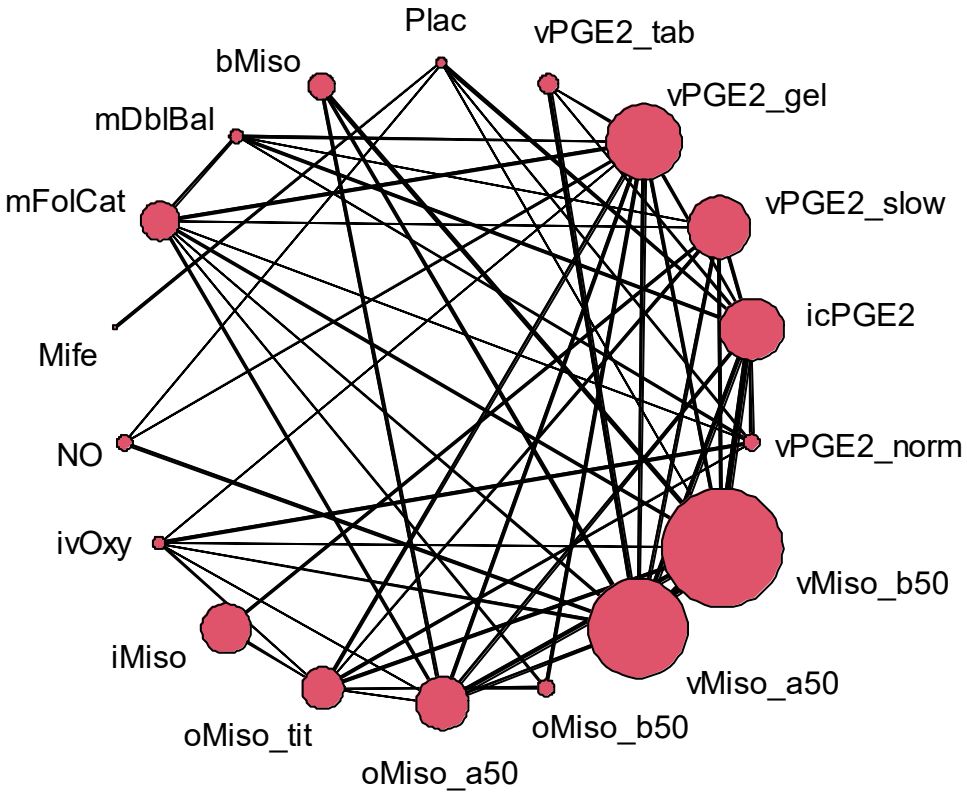
The results are broadly consistent with the data from the odds ratios (ORs), suggesting that intravenous oxytocin plus amniotomy is likely to be the most effective intervention (to promote vaginal birth within 24 hours). Normal release PGE_2 pessary and a variety of preparations of misoprostol (vaginal misoprostol ≥50mcg, misoprostol insert, low dose oral misoprostol <50mcg, buccal/sublingual misoprostol and titrated low dose misoprostol) were also shown to rank highly among the interventions.

The majority of studies contributing to this outcome were at low risk of bias across most domains although a large proportion of studies were at unclear risk of bias for selective reporting and a high risk of bias due to blinding of participants and personnel. For this essentially objective outcome the committee did not consider the lack of blinding to be particularly impactful. There was also some evidence of inconsistency between the direct and indirect effect estimates (see appendix P for more detail). The committee noted these limitations in the quality of the evidence supporting the NMA when making recommendations.

Subgroup analysis for women with a Bishop Score ≤6

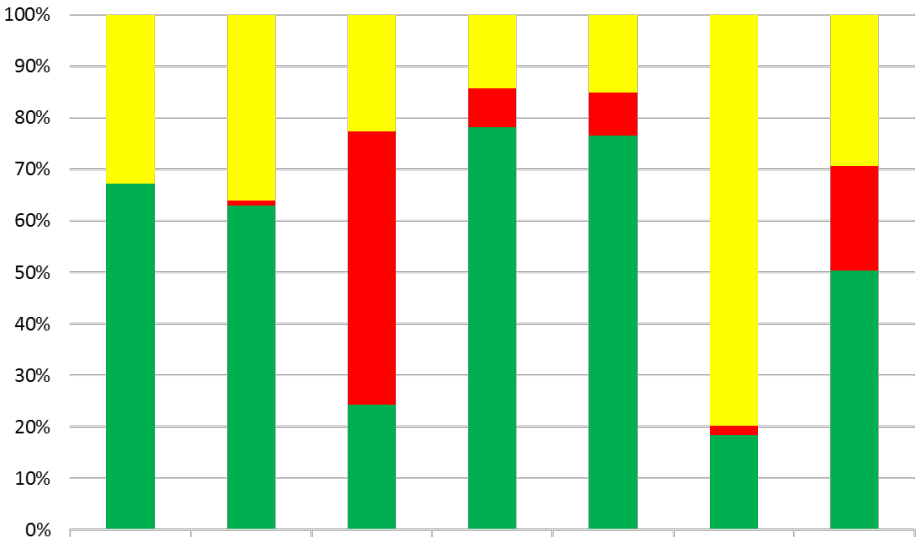
After excluding studies that reported no data, 115 studies, comparing a total of 18 different interventions in 24,242 women were included in this analysis. The network plot for this outcome is shown below.

Figure 4: Network for vaginal birth not achieved within 24 hours: subgroup analysis for women with Bishop score ≤6



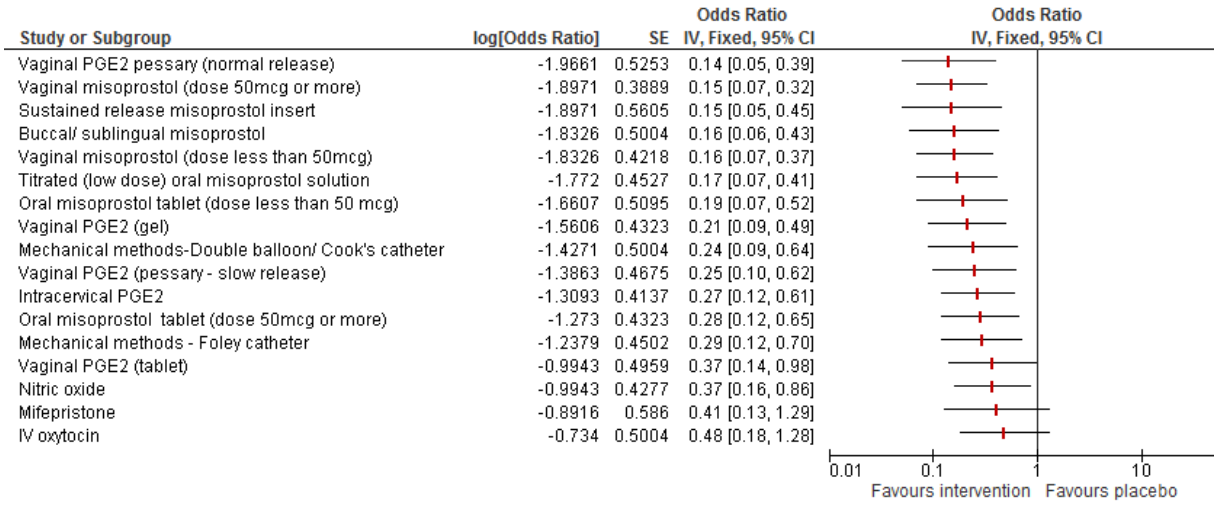
Treatment codes are as follows (in alphabetical order): bMiso: buccal/sublingual misoprostol; eaPGE$_2$PGF$_2$: extra-amniotic prostaglandin; icPGE$_2$: intracervical PGE2; iMiso: misoprostol vaginal insert; ivOxy: iv oxytocin; ivOxyAmino: iv oxytocin plus amniotomy; mDBlBal: double balloon catheter; mFolCat: Foley catheter; Mife: mifepristone; NO: nitric oxide; oMiso_a50: oral misoprostol ≥50mcg; oMiso_b50: oral misoprostol <50mcg; oMiso_tit: titrated low dose oral misoprostol; Plac: placebo; vMiso_a50: vaginal misoprostol ≥50mcgl vMiso_b50: vaginal misoprostol <50mcg; vPGE$_2$_gel: vaginal PGE$_2$ gel; vPGE$_2$_norm: vaginal PGE$_2$ normal release pessary; vPGE$_2$_slow: vaginal PGE$_2$ slow release pessary; vPGE$_2$_tab: vaginal PGE$_2$ tablet. The size of the nodes is proportional to the number of women in the network randomised to a particular intervention. The thickness of the connecting lines is proportional to the number of studies directly comparing 2 interventions.

Figure 5: Vaginal birth not achieved within 24 hours (subgroup analysis for women with Bishop score ≤6): risk of bias assessment



	Random sequence generation	Allocation concealment	Blinding participants and personnel	Blinding outcome assessors	Incomplete outcome data	Selective reporting	Other bias
Unclear risk (number of studies)	39	43	27	17	18	95	35
High risk (number of studies)	0	1	63	9	10	2	24
Low risk (number of studies)	80	75	29	93	91	22	60

Figure 6: Forest plot showing NMA derived OR for vaginal birth not achieved within 24 hours for all interventions compared to placebo: subgroup analysis for women with Bishop score ≤6



OR <1 favours the stated intervention, OR >1 favours placebo

Table 4: OR and 95% CrI for vaginal birth not achieved within 24 hours for all interventions compared to placebo: subgroup analysis for women with Bishop score ≤6

Intervention	NMA OR (95% CrI)	NMA direct evidence only OR (95% CrI)	Number of studies providing direct evidence
Vaginal PGE_2 pessary (normal release)	0.14 (0.05, 0.33)	0.35 (0.05, 2.62)	1
Vaginal misoprostol ≥50mcg	0.15 (0.07, 0.32)	-	
Misoprostol vaginal insert	0.15 (0.05, 0.43)	-	
Buccal/sublingual misoprostol	0.16 (0.06, 0.38)	-	
Vaginal misoprostol <50mcg	0.16 (0.07, 0.35)	0.22 (0.05, 0.86)	1
Titrated oral (low dose) misoprostol	0.17 (0.07, 0.41)	-	
Oral misoprostol <50mcg	0.19 (0.07, 0.52)	-	
Vaginal PGE_2 gel	0.21 (0.09, 0.48)	-	
Double balloon or Cook's catheter	0.24 (0.09, 0.62)	-	
Vaginal PGE_2 pessary (slow release)	0.25 (0.10, 0.57)	-	
Intracervical PGE_2	0.27 (0.12, 0.58)	0.06 (0.01, 0.20)	3
Oral misoprostol ≥50mcg	0.28 (0.12, 0.62)	-	
Foley catheter	0.29 (0.12, 0.67)	-	
Vaginal PGE_2 tablet	0.37 (0.14, 0.90)	-	
Nitric oxide donor	0.37 (0.16, 0.84)	0.91 (0.29, 2.90)	1
Mifepristone	0.41 (0.13, 1.29)	0.42 (0.13, 1.35)	2
IV oxytocin	0.48 (0.18, 1.23)	-	

Results from overall NMA and only using only direct evidence from unrelated mean effect model. An OR >1 favours placebo (fewer vaginal births in 24 hours were not achieved for placebo arm), and OR <1 favours the active intervention (fewer vaginal births in 24 hours were not achieved in the intervention arm).

Intravenous oxytocin plus amniotomy was not included in the network for women with a Bishop Score ≤6, but the remaining interventions were ranked similarly to the full analysis above, with a variety of misoprostol preparations showing good efficacy, alongside some preparations of vaginal PGE_2 (normal release pessary, vaginal PGE_2 gel). Mifepristone and intravenous oxytocin were not clearly demonstrated to be better than placebo at promoting vaginal birth within 24 hours for this subgroup.

Table 5: Median treatment ranks and probability of being the best treatment for all interventions, for vaginal birth not achieved within 24 hours: subgroup analysis for women with Bishop score ≤6

Intervention	Median (95% CrI) treatment rank	Probability of being best
Vaginal PGE_2 pessary (normal release)	2 (1, 9)	34%
Vaginal misoprostol ≥50mcg	3 (1, 7)	10%
Misoprostol vaginal insert	3 (1, 13)	27%

Intervention	Median (95% CrI) treatment rank	Probability of being best
Buccal/sublingual misoprostol	4 (1, 10)	12%
Vaginal misoprostol <50mcg	5 (2, 8)	2%
Titrated oral (low dose) misoprostol	5 (1, 10)	4%
Oral misoprostol <50mcg	7 (1, 13)	7%
Vaginal PGE_2 gel	8 (4, 13)	0%
Vaginal PGE_2 pessary (slow release)	10 (5, 15)	0%
Double balloon or Cook's catheter	10 (2, 16)	1%
Intracervical PGE_2	11 (7, 15)	0%
Oral misoprostol ≥50mcg	12 (7, 15)	0%
Foley catheter	12 (7, 16)	0%
Vaginal PGE_2 tablet	15 (8, 17)	0%
Nitric oxide donor	15 (8, 17)	0%
IV oxytocin	16 (11, 18)	0%
Mifepristone	16 (1, 18)	4%
Placebo	18 (17, 18)	0%

In accordance with the best point estimates of ORs, normal release vaginal PGE_2 pessary appeared to be the highest ranked intervention. A variety of other misoprostol preparations also ranked highly, along with vaginal PGE_2 gel.

Subgroup analysis for women with a Bishop score >6

Fewer studies reported on this outcome for this subgroup of women, therefore the data are presented as pairwise comparisons, rather than with NMA – see the relevant forest plots and GRADE tables (appendix E and F).

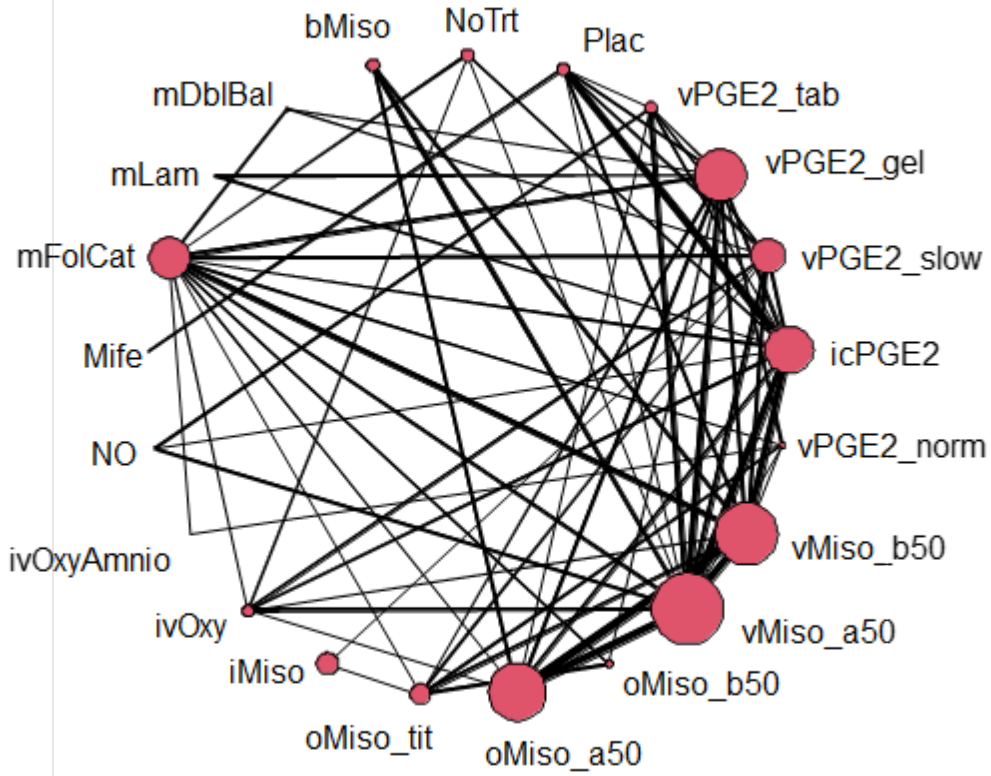
Hyperstimulation with fetal heart rate changes

172 studies, comparing a total of 21 different interventions in 36,849 women were included in this analysis. Most studies (143) included both nulliparous and multiparous women. 19 studies were exclusively in nulliparous women. 41 studies included some women with ruptured membranes, but these comprised less than a third of the total study population. 15 studies included some women with a previous caesarean birth (less than a third of the study population). The majority of studies (143) were specifically carried out in a population of women with a Bishop score ≤6. 55 studies were conducted in women with term or preterm infants, 92 studies were in pregnancies >37 weeks, and 14 were specifically post term (>40 weeks' gestation). 150 studies were conducted in women with a singleton pregnancy, 7 also included some women with multi-fetal pregnancies.

333 studies were excluded as they reported no data for this outcome. 58 studies were excluded as they reported no events in either arm of the study. 1 study was excluded as it reported on an irrelevant comparison that was not necessary to produce a connected network (Sadi 2016).

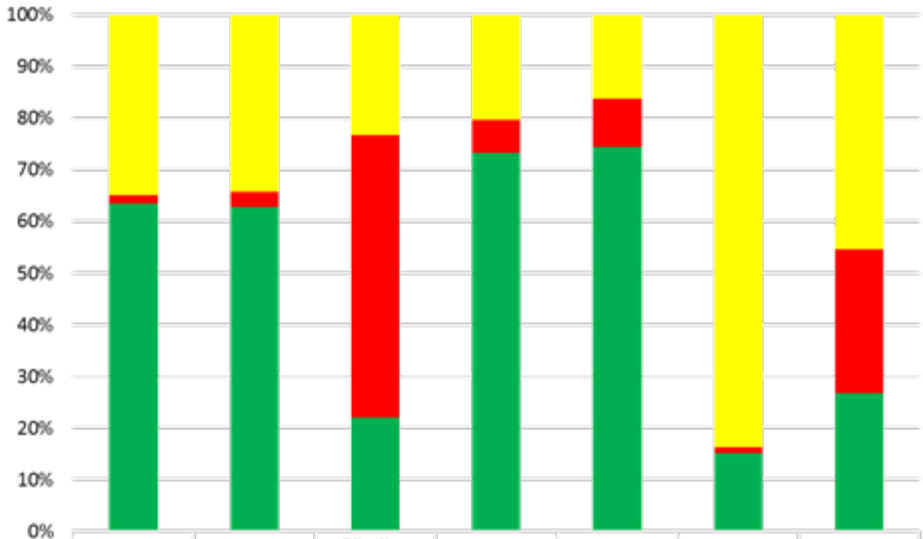
The network plot for this outcome is shown below.

Figure 7: Network for hyperstimulation with fetal heart rate changes



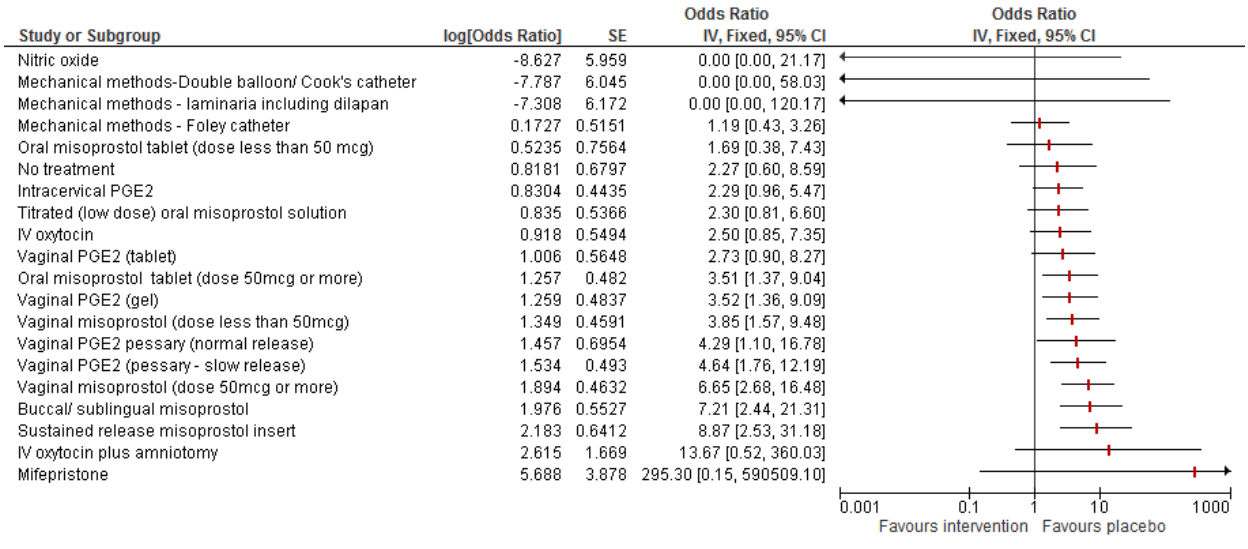
Treatment codes are as follows (in alphabetical order): bMiso: buccal/sublingual misoprostol; icPGE$_2$: intracervical PGE$_2$; iMiso: misoprostol vaginal insert; ivOxy: iv oxytocin; ivOxyAmino: iv oxytocin plus amniotomy; mDblBal: Double balloon or Cook's catheter; mFolCat: Foley catheter; Mife: mifepristone; mLam: Osmotic cervical dilators; NO: nitric oxide; NoTrt: No intervention; oMiso_a50: oral misoprostol ≥50mcg; oMiso_b50: oral misoprostol <50mcg; oMiso_tit: Titrated oral (low dose) misoprostol; Plac: placebo; vMiso_a50: vaginal misoprostol ≥50mcgl vMiso_b50: vaginal misoprostol <50mcg; vPGE$_2$_gel: vaginal PGE$_2$ gel; vPGE$_2$_norm: Vaginal PGE$_2$ pessary (normal release); vPGE$_2$_slow: Vaginal PGE$_2$ pessary (slow release); vPGE$_2$_tab: vaginal PGE$_2$ tablet. The size of the nodes is proportional to the number of women in the network randomised to a particular intervention. The thickness of the connecting lines is proportional to the number of studies directly comparing 2 interventions.

Figure 8: Uterine hyperstimulation with fetal heart rate changes: risk of bias assessment



	Random sequence generation	Allocation concealment	Blinding participants and personnel	Blinding outcome assessors	Incomplete outcome data	Selective reporting	Other bias
Unclear risk (number of studies)	60	59	40	35	28	144	78
High risk (number of studies)	3	5	94	11	16	2	48
Low risk (number of studies)	109	108	38	126	128	26	46

Figure 9: Forest plot showing NMA derived OR for hyperstimulation with fetal heart rate changes for all interventions compared to placebo



OR <1 favours the stated intervention, OR >1 favours placebo.

The very wide confidence intervals for some interventions reflect that data was sparse for some interventions and also the fact that the network included a relatively large number of studies with zero events in one or more of the trial arms. For example, no hyperstimulation events were observed in trial arms of double balloon catheters, nitric oxide donors or

osmotic cervical dilators. It was therefore not possible to estimate an OR from the NMA for these comparisons, but the interpretation of this is that double balloon catheters, nitric oxide donors and osmotic cervical dilators do not appear to lead to hyperstimulation with fetal heart changes relative to placebo.

For the majority of the other interventions, the point estimate for the OR indicated an increase in the occurrence of hyperstimulation with fetal heart rate changes, as compared to placebo. However, for some interventions the 95% CrI crossed 1, showing uncertainty in the effect. A number of interventions were shown to significantly increase the risk of hyperstimulation with fetal heart rate changes, as compared to placebo. These include certain preparations of misoprostol: buccal/sublingual misoprostol, misoprostol vaginal insert, high dose oral misoprostol ≥50mcg, low (<50mcg) or high (>50mcg) dose vaginal misoprostol. It also includes slow release vaginal PGE_2 pessary, normal release vaginal PGE_2 pessary, vaginal PGE_2 gel and intracervical PGE_2.

Table 6: OR and 95% CrI for hyperstimulation with fetal heart rate changes for all interventions compared to placebo

Intervention	NMA OR (95% CrI)	NMA direct evidence only OR (95% CrI)	Number of studies contributing direct evidence
Double balloon or Cook's catheter	0.00 (0.00, 0.44)	-	
Nitric oxide donor	0.00 (0.00, 0.25)	-	
Osmotic cervical dilators	0.00 (0.00, 0.80)	-	
Foley catheter	1.18 (0.44, 3.28)	-	
Oral misoprostol <50mcg	1.68 (0.39, 7.47)	-	
No intervention	2.25 (0.60, 8.72)	-	
Intracervical PGE_2	2.27 (1.00, 5.62)	1.70 (0.57, 5.51)	11
Titrated oral (low dose) misoprostol	2.30 (0.83, 6.79)	-	
IV oxytocin	2.48 (0.87, 7.46)	-	
Vaginal PGE_2 tablet	2.72 (0.93, 8.30)	0.00 (0.00, 2.21)	1
Vaginal PGE_2 gel	3.50 (1.41, 9.40)	36.74 (0.60, 93901)	2
Oral misoprostol ≥50mcg	3.50 (1.42, 9.30)	-	
Vaginal PGE_2 pessary (normal release)	3.69 (1.84, 12.42)	-	
Vaginal misoprostol <50mcg	3.82 (1.63, 9.75)	1.47 (0.23, 9.70)	2
Vaginal PGE_2 pessary (slow release)	4.60 (1.53, 9.15)	117.10 (5.34, 71682)	3
Misoprostol vaginal insert	6.24 (2.78, 16.88)	-	
Vaginal misoprostol ≥50mcg	6.59 (2.60, 13.96)	156.49 (0.75, 5956538)	1
Buccal/sublingual misoprostol	7.17 (2.52, 21.85)	-	
IV oxytocin plus amniotomy	13.43 (0.66, 463.00)	-	

Intervention	NMA OR (95% CrI)	NMA direct evidence only OR (95% CrI)	Number of studies contributing direct evidence
Mifepristone	282.90 (1.75, 8331000)	217.24 (1.69, 4501855)	1

Results from overall NMA and using only direct evidence from unrelated mean effect model. An OR >1 favours placebo (fewer women developed hyperstimulation with fetal heart rate changes in the placebo arm), and OR <1 favours the active intervention (fewer women developed hyperstimulation with fetal heart rate changes in the intervention arm).

Table 7: Median treatment ranks and probability of being the best treatment for all interventions, for hyperstimulation with fetal heart rate changes

Intervention	Median (95% CrI) treatment rank	Probability of being best
Double balloon or Cook's catheter	2 (1, 3)	34%
Nitric oxide donor	2 (1, 3)	34%
Osmotic cervical dilators	2 (1, 3)	32%
Placebo	4 (4, 9)	0%
Foley catheter	5 (4, 8)	0%
Oral misoprostol <50mcg	7 (4, 16)	0%
No intervention	9 (4, 17)	0%
Intracervical PGE_2	9 (6, 12)	0%
Titrated oral (low dose) misoprostol	9 (5, 14)	0%
IV oxytocin	9 (5, 16)	0%
Vaginal PGE_2 tablet	10 (6, 16)	0%
Vaginal PGE_2 gel	13 (9, 17)	0%
Oral misoprostol ≥50mcg	13 (9, 17)	0%
Vaginal misoprostol <50mcg	14 (10, 17)	0%
Vaginal PGE_2 pessary (slow release)	15 (9, 19)	0%
Vaginal PGE_2 pessary (normal release)	15 (10, 19)	0%
Vaginal misoprostol ≥50mcg	18 (16, 20)	0%
Buccal/sublingual misoprostol	18 (14, 20)	0%
Misoprostol vaginal insert	19 (13, 21)	0%
IV oxytocin plus amniotomy	20 (4, 21)	0%
Mifepristone	21 (7, 21)	0%

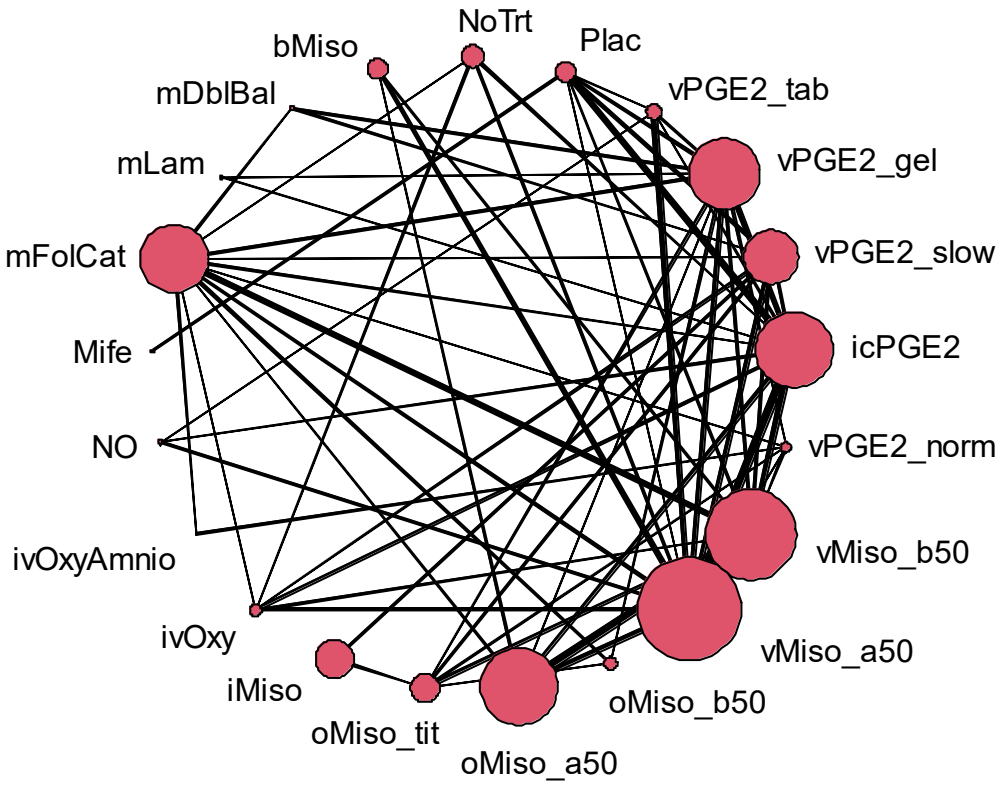
Nitric oxide and two classes of mechanical methods (osmotic cervical dilators and double balloon or Cook catheters) were similarly effective and appeared to rank highly at minimising the risk of hyperstimulation with fetal heart rate changes.

The majority of studies contributing to this outcome were at low risk of bias across most domains although a large proportion of studies were at unclear risk of bias for selective reporting and a high risk of bias due to blinding. There was also some evidence of inconsistency between the direct and indirect effect estimates (see appendix P for more detail). The committee noted these limitations in the quality of the evidence supporting the NMA when making recommendations.

Subgroup analysis for women with a Bishop score ≤6

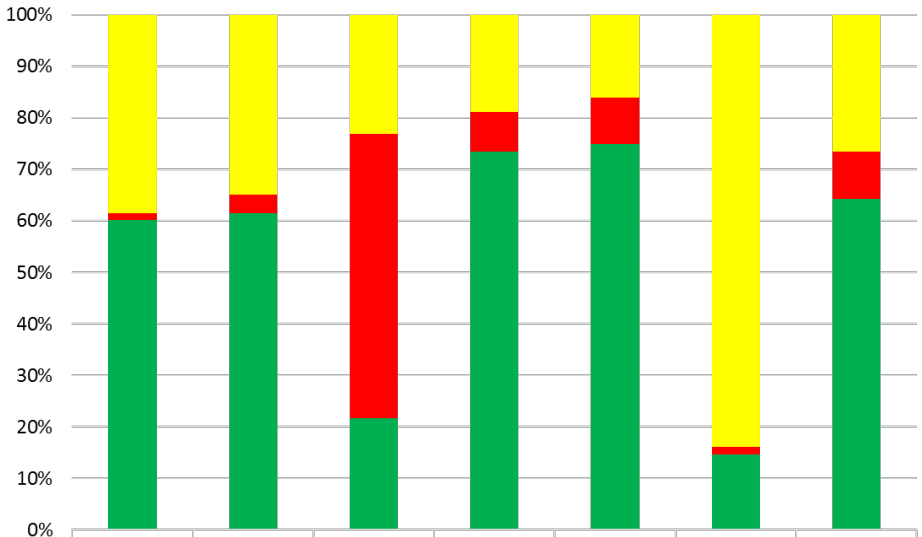
After excluding studies that reported no data, 143 studies, comparing a total of 21 different interventions in 31,556 women were included in this analysis. The network plot for this outcome is shown below.

Figure 10: Network for hyperstimulation with fetal heart rate changes: subgroup analysis for women with Bishop score ≤6



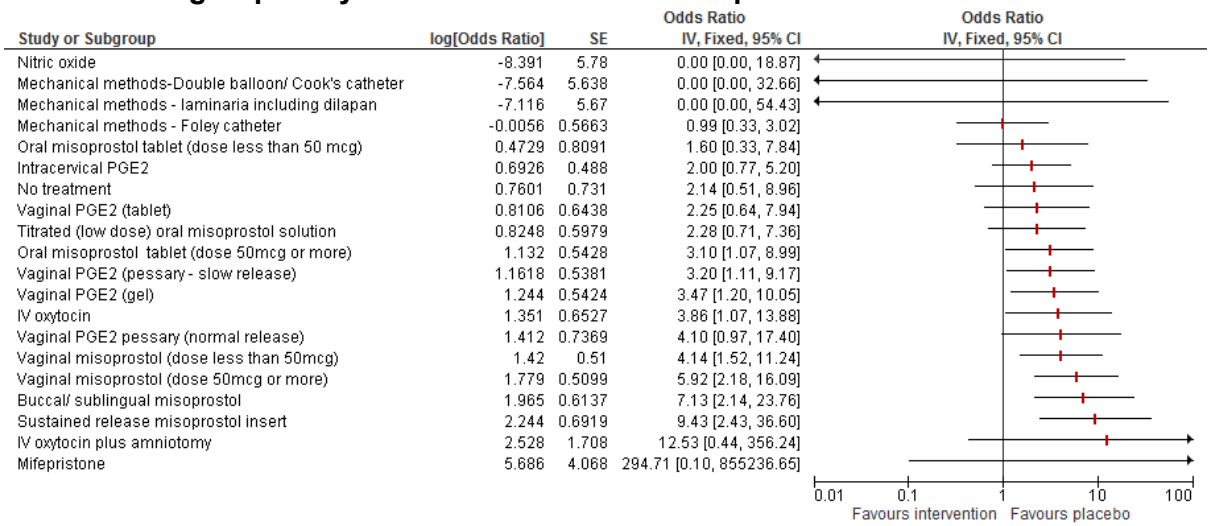
Treatment codes are as follows (in alphabetical order): bMiso: buccal/sublingual misoprostol; icPGE$_2$: intracervical PGE$_2$; iMiso: misoprostol vaginal insert; ivOxy: iv oxytocin; ivOxyAmino: iv oxytocin plus amniotomy; mDblBal: Double balloon or Cook's catheter; mFolCat: Foley catheter; Mife: mifepristone; mLam: Osmotic cervical dilators; NO: nitric oxide; NoTrt: No intervention; oMiso_a50: oral misoprostol ≥50mcg; oMiso_b50: oral misoprostol <50mcg; oMiso_tit: Titrated oral (low dose) misoprostol; Plac: placebo; vMiso_a50: vaginal misoprostol ≥50mcgl vMiso_b50: vaginal misoprostol <50mcg; vPGE$_2$_gel: vaginal PGE$_2$ gel; vPGE$_2$_norm: Vaginal PGE$_2$ pessary (normal release); vPGE$_2$_slow: Vaginal PGE$_2$ pessary (slow release); vPGE$_2$_tab: vaginal PGE$_2$ tablet. The size of the nodes is proportional to the number of women in the network randomised to a particular intervention. The thickness of the connecting lines is proportional to the number of studies directly comparing 2 interventions.

Figure 11: Uterine hyperstimulation with fetal heart rate changes (subgroup analysis for women with Bishop score ≤6): risk of bias assessment



	Random sequence generation	Allocation concealment	Blinding participants and personnel	Blinding outcome assessors	Incomplete outcome data	Selective reporting	Other bias
Unclear risk (number of studies)	55	50	33	27	23	120	38
High risk (number of studies)	2	5	79	11	13	2	13
Low risk (number of studies)	86	88	31	105	107	21	92

Figure 12: OR for hyperstimulation for all interventions compared to placebo: subgroup analysis for women with a Bishop score ≤6



OR < 1 favours the stated intervention, OR >1 favours placebo

Table 8: OR and 95% CrI for hyperstimulation with fetal heart rate changes for all interventions compared to placebo: subgroup analysis for women with Bishop score ≤6

Intervention	NMA OR (95% CrI)	NMA direct evidence only OR (95% CrI)	Number of studies contributing direct evidence
Double balloon or Cook's catheter	0.00 (0.00, 0.48)	-	
Nitric oxide donor	0.00 (0.00, 0.21)	-	
Osmotic cervical dilators	0.00 (0.00, 0.76)	-	
Foley catheter	0.99 (0.33, 3.04)	-	
Oral misoprostol <50mcg	1.54 (0.32, 7.60)	-	
Titrated oral (low dose) misoprostol	1.96 (0.65, 8.12)	-	
Intracervical PGE_2	2.00 (0.79, 5.38)	1.70 (0.57, 5.51)	8
Vaginal PGE_2 tablet	2.22 (0.59, 6.03)	0.00 (0.00, 2.21)	1
No intervention	2.15 (0.54, 9.02)	-	
Oral misoprostol ≥50mcg	3.09 (1.10, 9.19)	-	
Vaginal PGE_2 gel	3.45 (1.24, 10.53)	36.74 (0.60, 93901)	2
IV oxytocin	3.86 (1.12, 14.09)	-	
Vaginal PGE_2 pessary (normal release)	4.06 (0.97, 17.85)	-	
Vaginal misoprostol <50mcg	4.12 (1.57, 11.60)	1.47 (0.23, 9.70)	1
Vaginal PGE_2 pessary (slow release)	4.98 (1.82, 15.01)	117.10 (5.34, 71682)	3
Vaginal misoprostol ≥50mcg	5.92 (2.26, 16.81)	156.49 (0.75, 5956538)	1
Buccal/sublingual misoprostol	7.07 (2.22, 24.45)	-	
Misoprostol vaginal insert	9.36 (2.52, 38.54)	-	
IV oxytocin plus amniotomy	12.62 (0.58, 469)	-	
Mifepristone	323 (1.78, 8753000)	217.24 (1.69, 4501855)	1

Results from overall NMA and using only direct evidence from unrelated mean effect model. An OR >1 favours placebo (fewer women developed hyperstimulation with fetal heart rate changes in the placebo arm), and OR <1 favours the active intervention (fewer women developed hyperstimulation with fetal heart rate changes in the intervention arm).

Again, double balloon catheters, nitric oxide donors and osmotic cervical dilators were shown to significantly reduce the chance of hyperstimulation as compared to placebo, although due to the fact there were no events, the OR could not be estimated. As with the whole population results, a number of interventions were shown to significantly increase the chance of hyperstimulation – these included misoprostol preparations (high dose oral or vaginal misoprostol ≥50mcg, low dose vaginal misoprostol <50mcg, buccal/sublingual

misoprostol and misoprostol vaginal insert), vaginal PGE_2 gel, slow release vaginal PGE_2 pessary and IV oxytocin.

Table 9: Median treatment ranks and probability of being the best treatment for all interventions, for hyperstimulation with fetal heart rate changes: subgroup analysis for women with a Bishop score ≤6

Intervention	Median (95% CrI) treatment rank	Probability of being best
Nitric oxide donor	2 (1, 3)	39%
Double balloon or Cook's catheter	2 (1, 3)	32%
Osmotic cervical dilators	2 (1, 4)	30%
Foley catheter	5 (4, 7)	0%
Placebo	5 (4, 10)	0%
Oral misoprostol <50mcg	7 (4, 16)	0%
Intracervical PGE_2	8 (6, 12)	0%
No intervention	9 (4, 17)	0%
Titrated oral (low dose) misoprostol	9 (5, 14)	0%
vaginal PGE_2 tablet	9 (5, 16)	0%
Oral misoprostol ≥50mcg	12 (7, 16)	0%
Vaginal PGE_2 gel	12 (9, 17)	0%
Vaginal PGE_2 pessary (normal release)	14 (6, 20)	0%
IV oxytocin	14 (7, 19)	0%
Vaginal misoprostol <50mcg	14 (11, 17)	0%
Vaginal PGE_2 pessary (slow release)	16 (11, 19)	0%
Vaginal misoprostol ≥50mcg	17 (14, 20)	0%
Buccal/sublingual misoprostol	18 (13, 20)	0%
Misoprostol vaginal insert	19 (13, 21)	0%
IV oxytocin plus amniotomy	20 (4, 21)	0%
Mifepristone	21 (7, 21)	0%

The interventions which appeared to be ranked highly include nitric oxide donors, double balloon and Foley catheters and osmotic cervical dilators.

Subgroup analysis for women with a Bishop score >6

Fewer studies reported on this outcome for this subgroup of women, therefore the data are presented as pairwise comparisons, rather than with NMA – see the relevant forest plots and GRADE tables (appendix E and F).

Caesarean birth

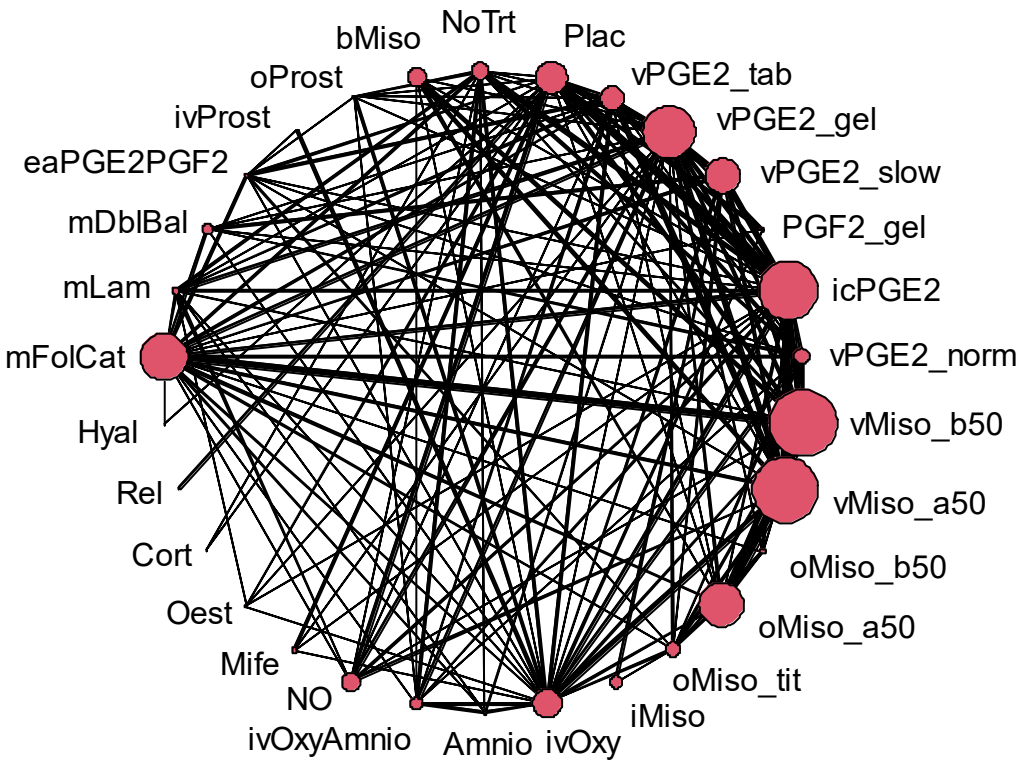
485 studies, comparing a total of 29 different interventions in 81,995 women were included in this analysis.

375 trials were conducted specifically in women with a singleton pregnancy. 1 trial was conducted in women with multi-fetal pregnancy, and 13 trials included women with singleton and multi-fetal pregnancies. The majority of trials (259) included women with pregnancies at or greater than 37 weeks' gestation (defined as at term or post-term pregnancies). 63 trials included only women with pregnancies at or greater than 40 weeks' gestation. 118 trials included a mixed population, which included some women with preterm gestations (<37 weeks). 363 studies were conducted specifically in women with a Bishop score ≤6. 31 trials included women with a previous caesarean birth, but these women comprised less than a third of the study population in these trials. 62 trials included some women with ruptured membranes, but again these comprised fewer than a third of the study population in these trials.

26 studies were excluded as they reported no data for this outcome. 47 studies were excluded as they included an irrelevant comparison (such as membrane sweeping or acupuncture versus placebo), that was not necessary to produce a connected network. Two studies reported zero events in both arms (Greer 1990, Ulmsten 1982). Two studies were excluded as participants underwent automatic caesarean birth after 24 hours (Frass 2011, Gelisen 2005). One study was removed due to its inclusion criteria (Silva-Cruz 1988) and one study was removed due to the quality of the trial (Atad 1996).

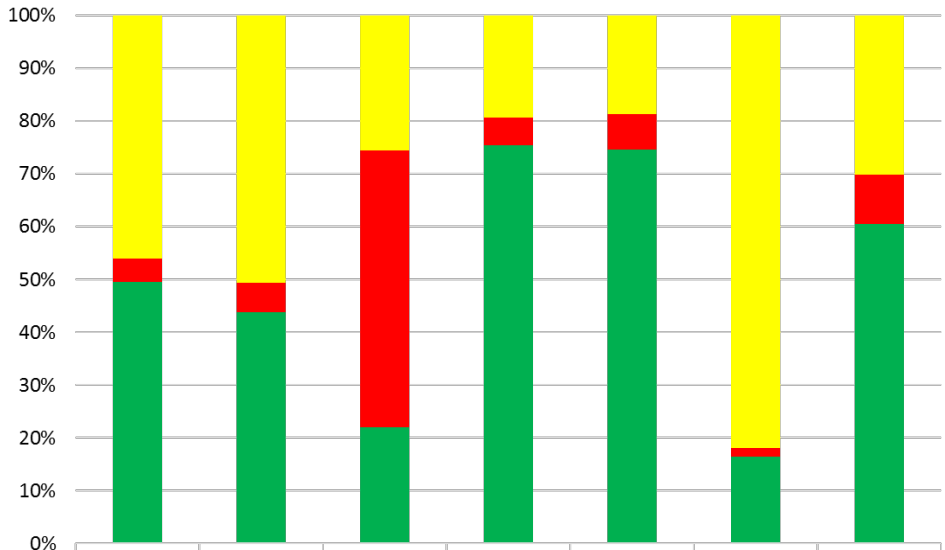
The network plot for this outcome is shown below.

Figure 13: Network for caesarean birth



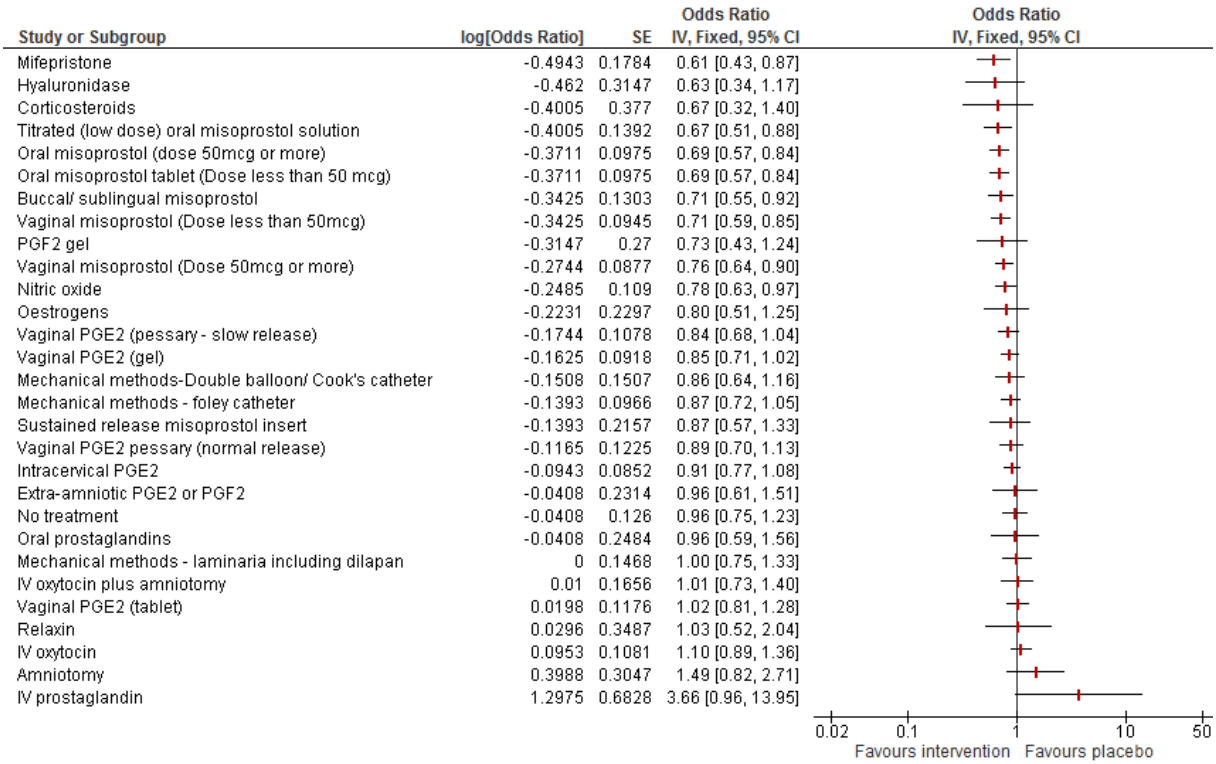
Treatment codes are as follows (in alphabetical order): Amnio: Amniotomy; bMiso: Buccal/sublingual misoprostol; Cort: Corticosteroids; eaPGE$_2$PGF$_2$: Extra-amniotic prostaglandins; Hyal: Hyaluronidase; icPGE$_2$: Intracervical PGE$_2$; iMiso: Misoprostol vaginal insert; ivOxy: IV oxytocin; ivOxyAmino: IV oxytocin plus amniotomy; ivProst: IV prostaglandins; mDblBal: Double balloon or Cook's catheter; mFolCat: Foley catheter; Mife: Mifepristone; mLam: Osmotic cervical dilators; NO: Nitric oxide; NoTrt: No intervention; Oest: Oestrogens; oMiso_a50: Oral misoprostol ≥50mcg; oMiso_b50: Oral misoprostol <50mcg; oMiso_tit: Titrated oral (low dose) misoprostol; oProst: Oral prostaglandins; PGF$_2$_gel: PGF$_2$ gel; Plac: placebo; Rel: Relaxin; vMiso_a50: Vaginal misoprostol ≥50mcg; vMiso_b50: Vaginal misoprostol <50mcg; vPGE$_2$ gel: Vaginal PGE$_2$_gel; vPGE$_2$_norm: Vaginal PGE$_2$ pessary (normal release); vPGE$_2$_slow: Vaginal PGE$_2$ pessary (slow release); vPGE$_2$_tab: vaginal PGE$_2$ tablet. The size of the nodes is proportional to the number of women in the network randomised to a particular intervention. The thickness of the connecting lines is proportional to the number of studies directly comparing 2 interventions.

Figure 14: Caesarean birth: risk of bias assessment



	Random sequence generation	Allocation concealment	Blinding participants and personnel	Blinding outcome assessors	Incomplete outcome data	Selective reporting	Other bias
Unclear risk (number of studies)	223	246	124	94	91	397	146
High risk (number of studies)	22	27	254	25	32	8	46
Low risk (number of studies)	240	212	107	366	362	80	293

Figure 15: Forest plot showing NMA derived OR for caesarean birth for all interventions compared to placebo



OR <1 favours the stated intervention, OR >1 favours placebo

Table 10: OR and 95% CrI for caesarean birth for all interventions compared to placebo

Intervention	NMA OR (95% CrI)	NMA direct evidence only OR (95% CrI)	Number of studies contributing direct evidence
Mifepristone	0.61 (0.43, 0.87)	0.68 (0.45, 1.02)	7
Hyaluronidase	0.63 (0.34, 1.16)	0.22 (0.09, 0.52)	1
Corticosteroids	0.67 (0.32, 1.39)	0.84 (0.38, 1.83)	2
Titrated oral (low dose) misoprostol	0.67 (0.51, 0.88)	-	
Oral misoprostol ≥50mcg	0.69 (0.57, 0.85)	0.36 (0.13, 0.96)	1
Oral misoprostol <50mcg	0.69 (0.47, 1.01)	-	
Buccal/sublingual misoprostol	0.71 (0.55, 0.91)	-	
Vaginal misoprostol <50mcg	0.71 (0.59, 0.84)	0.74 (0.46, 1.18)	5
PGF_2 gel	0.73 (0.43, 1.26)	0.62 (0.29, 1.34)	4
Vaginal misoprostol ≥50mcg	0.76 (0.64, 0.91)	0.59 (0.19, 1.79)	2
Nitric oxide donor	0.78 (0.63, 0.95)	0.94 (0.71, 1.24)	10

Intervention	NMA OR (95% CrI)	NMA direct evidence only OR (95% CrI)	Number of studies contributing direct evidence
Oestrogens	0.80 (0.51, 1.26)	1.07 (0.54, 2.14)	3
Vaginal PGE_2 pessary (slow release)	0.84 (0.68, 1.03)	0.56 (0.24, 1.29)	2
Foley catheter	0.87 (0.72, 1.06)	-	
Misoprostol vaginal insert	0.87 (0.57, 1.34)	-	
Vaginal PGE_2 gel	0.85 (0.75, 1.01)	0.94 (0.62, 1.43)	10
Double balloon or Cook's catheter	0.86 (0.64, 1.15)	-	
Vaginal PGE_2 pessary (normal release)	0.89 (0.70, 1.14)	0.85 (0.48, 1.49)	5
Intracervical PGE_2	0.91 (0.77, 1.08)	0.83 (0.63, 1.09)	19
Extra-amniotic prostaglandins	0.96 (0.61, 1.48)	0.39 (0.06, 1.94)	2
No intervention	0.96 (0.75, 1.22)	-	
Oral prostaglandins	0.96 (0.59, 1.56)	0.39 (0.01, 5.87)	1
Osmotic cervical dilators	1.00 (0.75, 1.35)	1.26 (0.39, 4.13)	2
IV oxytocin plus amniotomy	1.01 (0.73, 1.39)	-	
Vaginal PGE_2 tablet	1.02 (0.81, 1.27)	2.27 (0.48, 13.20)	2
Relaxin	1.03 (0.52, 2.07)	1.03 (0.52, 2.07)	5
IV oxytocin	1.10 (0.89, 1.35)	-	
Amniotomy	1.49 (0.82, 2.66)	-	
IV prostaglandins	3.66 (0.96, 17.76)	-	

Results from overall NMA and using only direct evidence from unrelated mean effect model. An OR >1 favours placebo (fewer women required caesarean birth for placebo arm), and OR <1 favours the active intervention (fewer women required caesarean birth in the intervention arm).

A small number of interventions showed apparent benefit at reducing the rate of caesarean birth as compared with placebo – these were mifepristone, titrated oral (low dose) misoprostol, oral or vaginal high dose misoprostol (>50mcg), vaginal low dose misoprostol (<50mcg), buccal/sublingual misoprostol, and nitric oxide donors. No intervention was definitively found to significantly increase the rate of caesarean birth (as compared to placebo). However, the point estimates for certain interventions (particularly amniotomy and IV prostaglandin) suggested that these treatments may result in an increased caesarean birth rate as compared to placebo.

Table 11: Median treatment ranks and probability of being the best treatment for all interventions, for caesarean birth

Intervention	Median (95% CrI) treatment rank	Probability of being best
Mifepristone	3 (1, 17)	20%
Hyaluronidase	4 (1, 27)	25%
Titrated oral (low dose) misoprostol	5 (1, 14)	4%
Corticosteroids	5 (1, 28)	24%
Oral misoprostol ≥50mcg	6 (2, 12)	1%

Intervention	Median (95% CrI) treatment rank	Probability of being best
Oral misoprostol <50mcg	6 (1, 22)	7%
Buccal/sublingual misoprostol	7 (2, 16)	1%
Vaginal misoprostol <50mcg	7 (3, 12)	0%
PGF_2 gel	8 (1, 28)	9%
Vaginal misoprostol ≥50mcg	10 (5, 15)	0%
Nitric oxide donor	11 (4, 20)	0%
Oestrogens	12 (1, 28)	3%
Vaginal PGE_2 pessary (slow release)	14 (7, 22)	0%
Vaginal PGE_2 gel	15 (9, 21)	0%
Foley catheter	16 (10, 23)	0%
Misoprostol vaginal insert	16 (2, 28)	1%
Double balloon or Cook's catheter	16 (5, 26)	0%
Vaginal PGE_2 pessary (normal release)	17 (8, 26)	0%
Intracervical PGE_2	19 (13, 24)	0%
Extra-amniotic prostaglandins	21 (4, 29)	0%
No intervention	21 (11, 27)	0%
Oral prostaglandins	21 (3, 29)	1%
Placebo	23 (16, 27)	0%
IV oxytocin plus amniotomy	23 (10, 28)	0%
Osmotic cervical dilators	23 (11, 28)	0%
Vaginal PGE_2 tablet	23 (16, 28)	0%
Relaxin	24 (2, 29)	2%
IV oxytocin	26 (20, 29)	0%
Amniotomy	29 (15, 30)	0%
IV prostaglandins	30 (22, 30)	0%

There was considerable uncertainty in the treatment rankings for many interventions, shown by the wide 95% CrIs for several treatments (including hyaluronidase, corticosteroids, PGF_2 gel, oestrogens, misoprostol vaginal insert, relaxin).

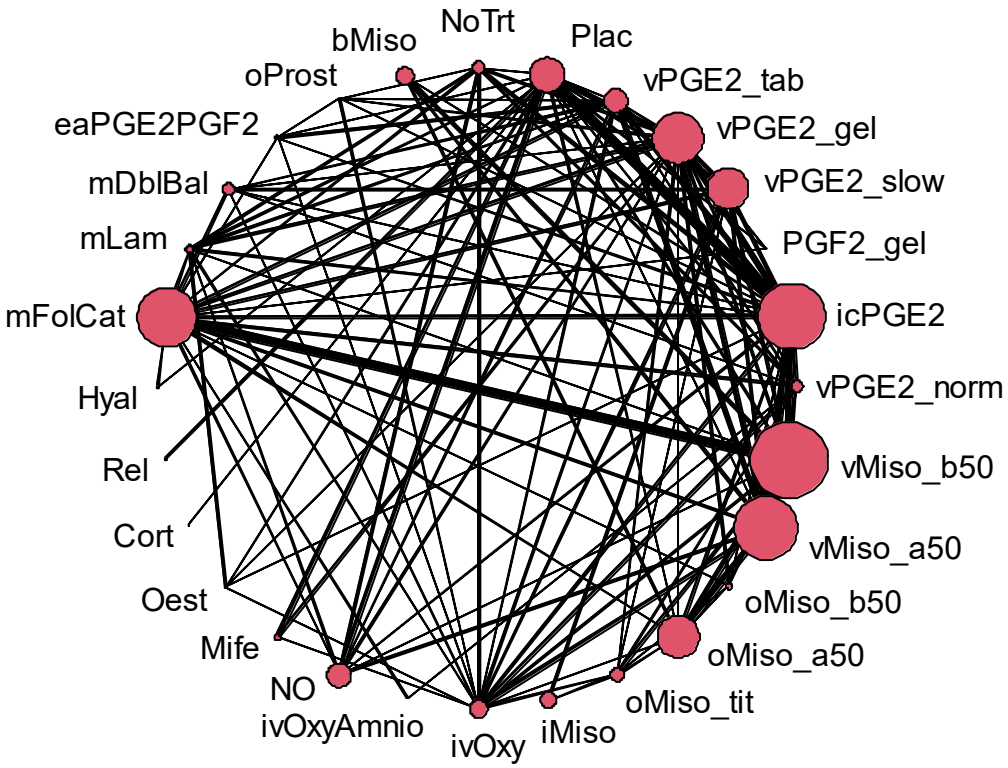
The majority of studies contributing to this outcome were at low risk of bias for incomplete outcome data, a large proportion of studies were at unclear risk of bias for selective reporting and a high risk of bias due to blinding of participants and personnel (although a low risk of bias for outcome assessors). While whether or not a caesarean birth occurs is an objective outcome, it is plausible that personnel's awareness of what treatments have predated a decision about caeserean birth may be influential. Approximately half of the studies contributing to this outcome were at unclear risk of bias for random sequence generation and allocation concealment. There was also some evidence of inconsistency between the direct and indirect effect estimates (see appendix P for more detail). The committee noted

these limitations in the quality of the evidence supporting the NMA when making recommendations.

Subgroup analysis for women with a Bishop score ≤6

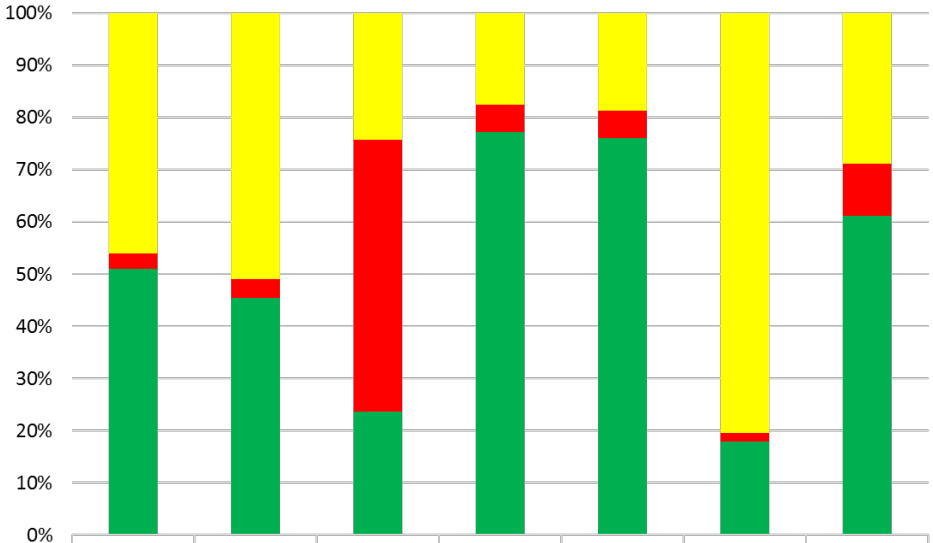
After excluding studies that reported no data, 363 studies, comparing a total of 28 different interventions in 63,034 women were included in this analysis. The network plot for this outcome is shown below.

Figure 16: Network for caesarean birth: subgroup analysis for women with Bishop score ≤6



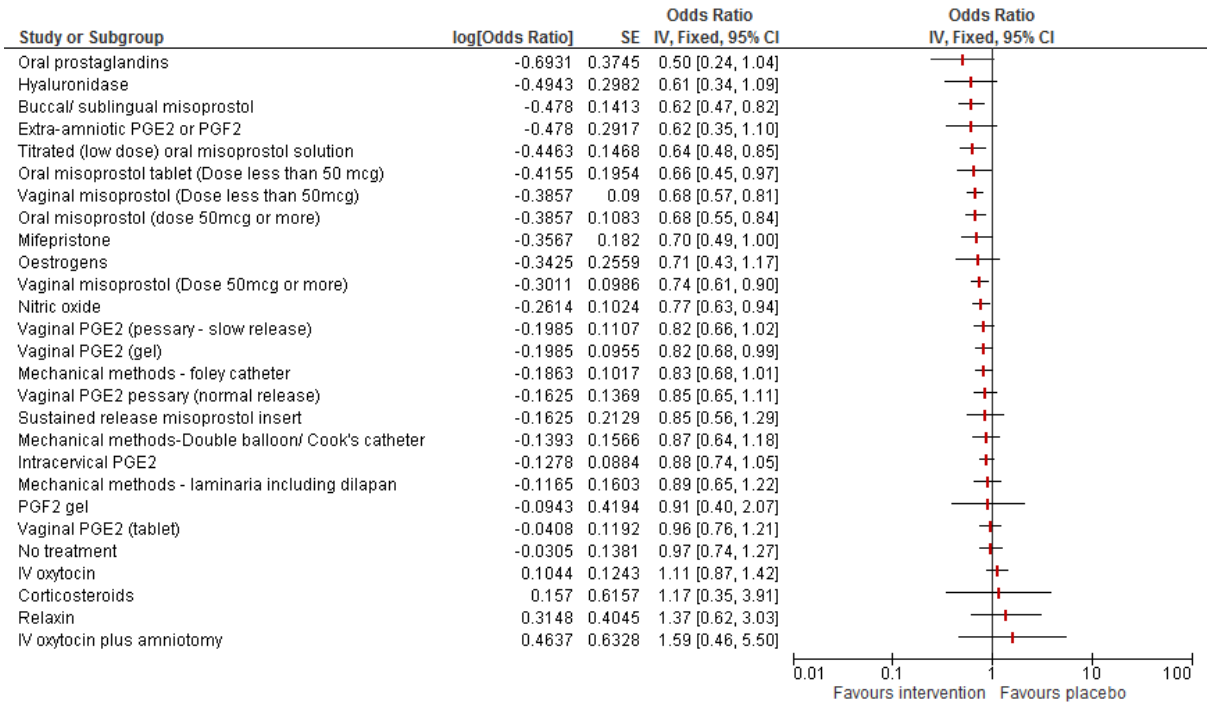
Treatment codes are as follows (in alphabetical order): Amnio: Amniotomy; bMiso: Buccal/sublingual misoprostol; Cort: Corticosteroids; eaPGE$_2$PGF$_2$: Extra-amniotic prostaglandins; Hyal: Hyaluronidase; icPGE$_2$: Intracervical PGE$_2$; iMiso: Misoprostol vaginal insert; ivOxy: IV oxytocin; ivOxyAmino: IV oxytocin plus amniotomy; ivProst: IV prostaglandins; mDblBal: Double balloon or Cook's catheter; mFolcat: Foley catheter; Mife: Mifepristone; mLam: Osmotic cervical dilators; NO: Nitric oxide; NoTrt: No intervention; Oest: Oestrogens; oMiso_a50: Oral misoprostol ≥50mcg; oMiso_b50: Oral misoprostol <50mcg; oMiso_tit: Titrated oral (low dose) misoprostol; oPost: Oral prostaglandins; PGF$_2$_gel: PGF$_2$ gel; Plac: placebo; Rel: Relaxin; vMiso_a50: Vaginal misoprostol ≥50mcg; vMiso_b50: Vaginal misoprostol <50mcg; vPGE$_2$ gel: Vaginal PGE$_2$_gel; vPGE$_2$_norm: Vaginal PGE$_2$ pessary (normal release); vPGE$_2$_slow: Vaginal PGE$_2$ pessary (slow release); vPGE$_2$_tab: vaginal PGE$_2$ tablet. The size of the nodes is proportional to the number of women in the network randomised to a particular intervention The thickness of the connecting lines is proportional to the number of studies directly comparing 2 interventions.

Figure 17: Caesarean birth (subgroup analysis for women with Bishop score ≤6): risk of bias assessment



	Random sequence generation	Allocation concealment	Blinding participants and personnel	Blinding outcome assessors	Incomplete outcome data	Selective reporting	Other bias
Unclear risk (number of studies)	167	185	88	64	68	292	105
High risk (number of studies)	11	13	189	19	19	6	36
Low risk (number of studies)	185	165	86	280	276	65	222

Figure 18: Forest plot showing NMA derived OR for caesarean birth for all interventions compared to placebo: subgroup analysis for women with a Bishop score ≤6



Study or Subgroup	log[Odds Ratio]	SE	Odds Ratio IV, Fixed, 95% CI
Oral prostaglandins	-0.6931	0.3745	0.50 [0.24, 1.04]
Hyaluronidase	-0.4943	0.2982	0.61 [0.34, 1.09]
Buccal/ sublingual misoprostol	-0.478	0.1413	0.62 [0.47, 0.82]
Extra-amniotic PGE2 or PGF2	-0.478	0.2917	0.62 [0.35, 1.10]
Titrated (low dose) oral misoprostol solution	-0.4463	0.1468	0.64 [0.48, 0.85]
Oral misoprostol tablet (Dose less than 50 mcg)	-0.4155	0.1954	0.66 [0.45, 0.97]
Vaginal misoprostol (Dose less than 50mcg)	-0.3857	0.09	0.68 [0.57, 0.81]
Oral misoprostol (dose 50mcg or more)	-0.3857	0.1083	0.68 [0.55, 0.84]
Mifepristone	-0.3567	0.182	0.70 [0.49, 1.00]
Oestrogens	-0.3425	0.2559	0.71 [0.43, 1.17]
Vaginal misoprostol (Dose 50mcg or more)	-0.3011	0.0986	0.74 [0.61, 0.90]
Nitric oxide	-0.2614	0.1024	0.77 [0.63, 0.94]
Vaginal PGE2 (pessary - slow release)	-0.1985	0.1107	0.82 [0.66, 1.02]
Vaginal PGE2 (gel)	-0.1985	0.0955	0.82 [0.68, 0.99]
Mechanical methods - foley catheter	-0.1863	0.1017	0.83 [0.68, 1.01]
Vaginal PGE2 pessary (normal release)	-0.1625	0.1369	0.85 [0.65, 1.11]
Sustained release misoprostol insert	-0.1625	0.2129	0.85 [0.56, 1.29]
Mechanical methods-Double balloon/ Cook's catheter	-0.1393	0.1566	0.87 [0.64, 1.18]
Intracervical PGE2	-0.1278	0.0884	0.88 [0.74, 1.05]
Mechanical methods - laminaria including dilapan	-0.1165	0.1603	0.89 [0.65, 1.22]
PGF2 gel	-0.0943	0.4194	0.91 [0.40, 2.07]
Vaginal PGE2 (tablet)	-0.0408	0.1192	0.96 [0.76, 1.21]
No treatment	-0.0305	0.1381	0.97 [0.74, 1.27]
IV oxytocin	0.1044	0.1243	1.11 [0.87, 1.42]
Corticosteroids	0.157	0.6157	1.17 [0.35, 3.91]
Relaxin	0.3148	0.4045	1.37 [0.62, 3.03]
IV oxytocin plus amniotomy	0.4637	0.6328	1.59 [0.46, 5.50]

OR <1 favours the stated intervention, OR >1 favours placebo

Table 12: OR and 95% CrI for caesarean birth for all interventions compared to placebo: subgroup analysis for women with Bishop score ≤6

Intervention	NMA OR (95% CrI)	NMA direct evidence only OR (95% CrI)	Number of studies contributing direct evidence
Oral prostaglandin	0.50 (0.24, 1.04)	-	
Hyaluronidase	0.61 (0.34, 1.10)	0.22 (0.09, 0.51)	1
Buccal/sublingual misoprostol	0.62 (0.47, 0.81)	-	
Extra-amniotic prostaglandin	0.62 (0.35, 1.07)	0.39 (0.07, 1.95)	2
Titrated oral (low dose) misoprostol	0.64 (0.48, 0.86)	-	
Oral misoprostol <50mcg	0.66 (0.45, 0.96)	-	
Oral misoprostol ≥50mcg	0.68 (0.55, 0.84)	0.37 (0.14, 0.95)	1
Vaginal misoprostol <50mcg	0.68 (0.57, 0.82)	0.69 (0.42, 1.14)	4
Mifepristone	0.70 (0.49, 1.01)	0.68 (0.46, 1.01)	2
Oestrogens	0.71 (0.43, 1.15)	1.04 (0.47, 2.25)	2
Vaginal misoprostol ≥50mcg	0.74 (0.61, 0.90)	0.62 (0.16, 2.31)	1
Nitic oxide donor	0.77 (0.63, 0.94)	0.94 (0.72, 1.23)	10
Vaginal PGE_2 pessary (slow release)	0.82 (0.66, 1.02)	0.56 (0.25, 1.27)	2
Vaginal PGE_2 gel	0.82 (0.68, 0.99)	0.86 (0.55, 1.34)	8
Foley catheter	0.83 (0.68, 1.01)	-	
Misoprostol vaginal insert	0.85 (0.56, 1.27)	-	
Vaginal PGE_2 pessary (normal release)	0.85 (0.65, 1.12)	1.11 (0.49, 2.54)	2
Double balloon or Cook's catheter	0.87 (0.64, 1.17)	-	
Intracervical PGE_2	0.88 (0.74, 1.05)	0.83 (0.63, 1.11)	16
Osmotic cervical dilators	0.89 (0.65, 1.22)	1.27 (0.40, 4.13)	2
PGF_2 gel	0.91 (0.40, 2.03)	0.64 (0.07 4.00)	1
Vaginal PGE_2 tablet	0.96 (0.76, 1.23)	-	
No intervention	0.97 (0.74, 1.28)	-	
IV oxytocin	1.11 (0.87, 1.41)	-	
Corticosteroids	1.17 (0.35, 3.92)	1.16 (0.36, 3.94)	1
Relaxin	1.37 (0.62, 3.10)	1.36 (0.61, 3.15)	3
IV oxytocin plus amniotomy	1.59 (0.46, 5.28)	-	

Results from overall NMA and using only direct evidence from unrelated mean effect model. An OR >1 favours placebo (fewer women underwent caesarean birth in the placebo arm), and OR <1 favours the active intervention (fewer women underwent caesarean birth in the intervention arm).

Several interventions were shown to be of benefit over placebo to reduce the rate of caesarean birth. These were: various forms of misoprostol (buccal, titrated oral, low/high dose oral, low/high dose vaginal) vaginal PGE_2 gel and nitric oxide donors. A number of interventions (slow release vaginal PGE_2 pessary, mifepristone, Foley catheter, extra-amniotic prostaglandin and oral prostaglandin) appeared to be of similar effectiveness to placebo at reducing the chance of caesarean birth.

Table 13: Median treatment ranks and probability of being the best treatment for all interventions, for caesarean birth: subgroup analysis for women with Bishop score ≤6

Intervention	Median (95% CrI) treatment rank	Probability of being best
Oral prostaglandin	2 (1, 23)	42%
Buccal/sublingual misoprostol	5 (1, 12)	3%
Extra-amniotic prostaglandins	5 (1, 24)	13%
Hyaluronidase	5 (1, 25)	16%
Titrated oral (low dose) misoprostol	6 (2, 15)	2%
Oral misoprostol ≥50mcg	7 (3, 14)	0%
Oral misoprostol <50mcg	7 (1, 21)	3%
Mifepristone	8 (1, 23)	3%
Vaginal misoprostol <50mcg	8 (4, 12)	0%
Oestrogens	9 (1, 25)	4%
Vaginal misoprostol ≥50mcg	11 (6, 16)	0%
Nitric oxide donor	12 (5, 21)	0%
Vaginal PGE_2 pessary (slow release)	15 (8, 22)	0%
Vaginal PGE_2 gel	15 (10, 21)	0%
Foley catheter	16 (10, 21)	0%
Misoprostol vaginal insert	17 (4, 26)	0%
Vaginal PGE_2 pessary (normal release)	17 (7, 25)	0%
Double balloon or Cook's catheter	18 (7, 25)	0%
Intracervical PGE_2	19 (13, 23)	0%
Osmotic cervical dilators	19 (7, 26)	0%
PGF_2 gel	20 (1, 28)	4%
Vaginal PGE_2 tablet	22 (14, 26)	0%
No intervention	22 (12, 27)	0%
Placebo	23 (17, 26)	0%
IV oxytocin	25 (20, 27)	0%
Corticosteroids	26 (1, 28)	6%
Relaxin	27 (5, 28)	0%
IV oxytocin plus amniotomy	27 (2, 28)	2%

As with the full data, there is considerable uncertainty in the rankings for many of the interventions.

Subgroup analysis for women with a Bishop score >6

Fewer studies reported on this outcome for this subgroup of women, therefore the data are presented as pairwise comparisons, rather than with NMA – see the relevant forest plots and GRADE tables (appendix E and F).

Instrumental birth

243 studies, comparing a total of 28 different interventions in 42,671 women were included in this analysis.

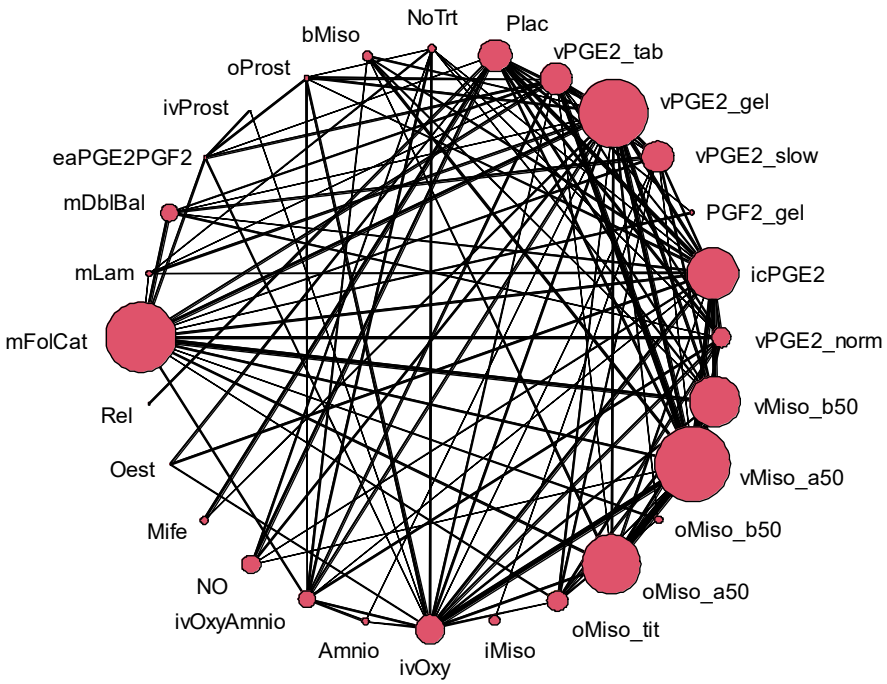
41 studies were conducted in nulliparous women, 8 studies were exclusively in multiparous women, and 188 included a mixed population (6 studies did not comment on parity in the demographics/inclusion criteria). The majority of studies (171) were conducted in women with a Bishop score of ≤6. 14 studies only included women with a Bishop score >6. 46 studies included women with any Bishop score, and 12 did not report the cervical status. Most studies (134) included women at 37 weeks of gestation or greater. 30 studies specifically included women with a gestational age of 40 weeks or more. 59 studies included a mixed population, which may have included some women at <37 week's gestation, and 20 studies did not state the gestational age of participants. The vast majority of studies (200) were in women with a singleton pregnancy. 8 studies included some women with multi-fetal pregnancy, but none were conducted exclusively in women with multiple gestations. 35 studies did not report whether participants had a singleton or multi-fetal pregnancy.

182 studies specifically excluded women with a previous caesarean birth. 16 studies included some women with a previous caesarean birth, but these comprised less than a third of the total study population. The remaining 45 studies did not comment on whether women with a previous caesarean birth were excluded. 132 studies specifically included women with intact membranes, 46 studies also included some women with ruptured membranes, but again these comprised less than a third of the total population in the study. The remaining 65 studies did not comment on membrane status.

296 studies were excluded as they reported no data for this outcome. 23 studies were excluded as they included an irrelevant comparison that was not necessary to produce a connected network. 1 study was excluded as it reported no events in either arm (Aalami-Harandi 2013). 1 study was excluded for its inclusion criteria (Silva-Cruz 1988).

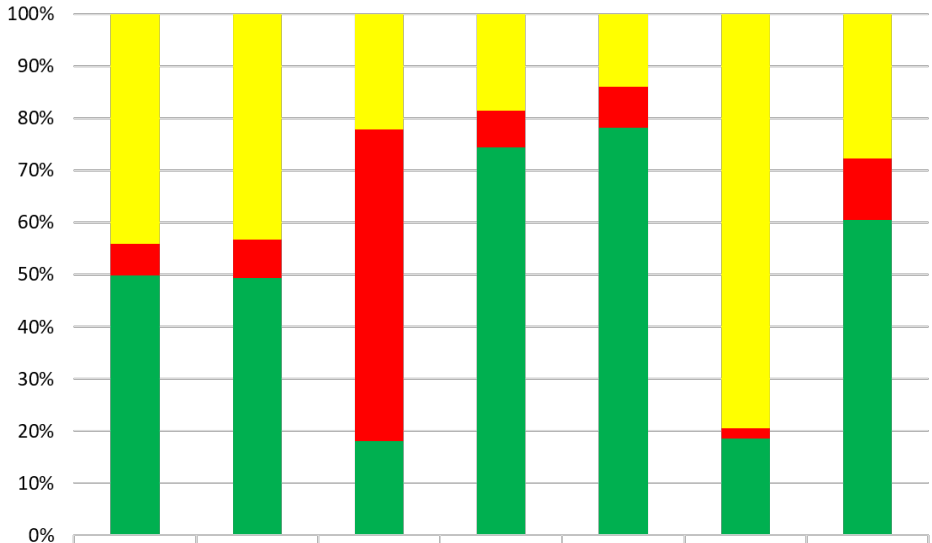
The network plot for this outcome is shown below.

Figure 19: Network for instrumental birth



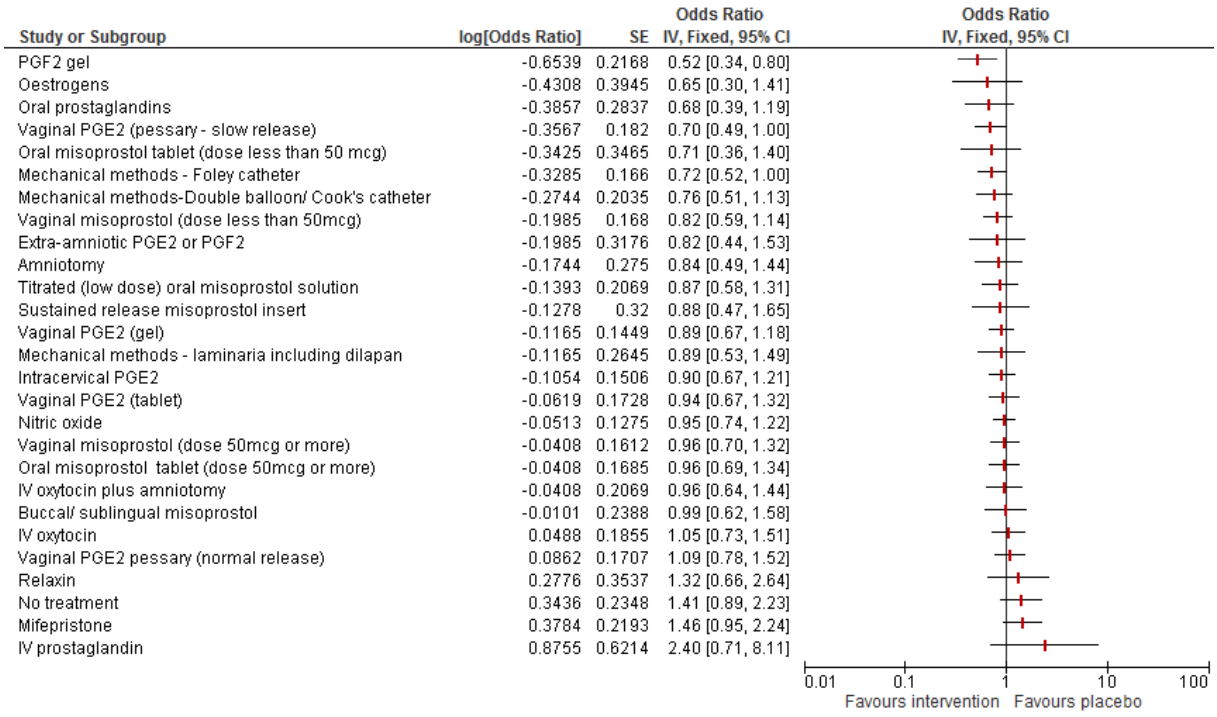
Treatment codes are as follows (in alphabetical order): Amnio: Amniotomy; bMiso: Buccal/sublingual misoprostol; eaPGE$_2$PGF$_2$: Extra-amniotic prostaglandins; icPGE$_2$: Intracervical PGE$_2$; iMiso: Misoprostol vaginal insert; ivOxy: IV oxytocin; ivOxyAmino: IV oxytocin plus amniotomy; ivProst: IV prostaglandins; mDblBal: Double balloon or Cook's catheter; mFolCat: Foley catheter; Mife: Mifepristone; mLam: Osmotic cervical dilators; NO: Nitric oxide; NoTrt: No intervention; Oest: Oestrogens; oMiso_a50: Oral misoprostol ≥50mcg; oMiso_b50: Oral misoprostol <50mcg; oMiso_tit: Titrated oral (low dose) misoprostol; oProst: Oral prostaglandins; PGF$_2$_gel: PGF$_2$ gel; Plac: placebo; Rel: Relaxin; vMiso_a50: Vaginal misoprostol ≥50mcg; vMiso_b50: Vaginal misoprostol <50mcg; vPGE$_2$ gel: Vaginal PGE$_2$_gel; vPGE$_2$_norm: Vaginal PGE$_2$ pessary (normal release); vPGE$_2$_slow: Vaginal PGE$_2$ pessary (slow release); vPGE$_2$_tab: vaginal PGE$_2$ tablet. The size of the nodes is proportional to the number of women in the network randomised to a particular intervention. The thickness of the connecting lines is proportional to the number of studies directly comparing 2 interventions.

Figure 20: Instrumental birth: risk of bias assessment



	Random sequence generation	Allocation concealment	Blinding participants and personnel	Blinding outcome assessors	Incomplete outcome data	Selective reporting	Other bias
Unclear risk (number of studies)	107	105	54	45	34	193	66
High risk (number of studies)	15	18	145	17	19	5	28
Low risk (number of studies)	121	120	44	181	190	45	144

Figure 21: Forest plot showing NMA derived OR for instrumental birth for all interventions compared to placebo



OR <1 favours the stated intervention, OR >1 favours placebo.

Table 14: OR and 95% CrI for instrumental birth for all interventions compared to placebo

Intervention	NMA OR (95% CrI)	NMA direct evidence only OR (95% CrI)	Number of studies providing direct evidence
PGF_2 gel	0.52 (0.34, 0.81)	0.51 (0.31, 0.83)	3
Oestrogens	0.65 (0.30, 1.39)	0.66 (0.25, 1.65)	1
Oral prostaglandins	0.68 (0.39, 1.18)	-	
Vaginal PGE_2 pessary (slow release)	0.70 (0.49, 1.00)	0.95 (0.41, 2.25)	2
Oral misoprostol <50mcg	0.71 (0.36, 1.31)	-	
Foley catheter	0.72 (0.52, 0.98)	-	
Double balloon or Cook's catheter	0.76 (0.51, 1.13)	-	
Vaginal misoprostol <50mcg	0.82 (0.59, 1.12)	0.41 (0.09, 1.60)	2
Extra-amniotic prostaglandins	0.82 (0.44, 1.53)	1.32 (0.29, 6.33)	1
Amniotomy	0.84 (0.49, 1.41)	-	
Titrated oral (low dose) misoprostol	0.87 (0.58, 1.30)	-	
Misoprostol vaginal insert	0.88 (0.47, 1.65)	-	
Vaginal PGE_2 gel	0.89 (0.67, 1.20)	0.49 (0.12, 1.72)	2
Osmotic cervical dilators	0.89 (0.53, 1.49)	-	
Intracervical PGE_2	0.90 (0.67, 1.22)	1.02 (0.58, 1.81)	6
Vaginal PGE_2 tablet	0.94 (0.67, 1.33)	-	
Nitric oxide donor	0.95 (0.74, 1.23)	0.95 (0.68, 1.34)	4
Vaginal misoprostol ≥50mcg	0.96 (0.70, 1.29)	1.04 (0.35, 3.10)	2
Oral misoprostol ≥50mcg	0.96 (0.69, 1.31)	-	
IV oxytocin plus amniotomy	0.96 (0.64, 1.42)	-	
Buccal/sublingual misoprostol	0.99 (0.62, 1.56)	-	
IV oxytocin	1.05 (0.73, 1.52)	-	
Vaginal PGE_2 pessary (normal release)	1.09 (0.78, 1.54)	0.93 (0.50, 1.72)	4
Relaxin	1.32 (0.66, 2.75)	1.33 (0.65, 2.80)	3
No intervention	1.41 (0.89, 2.31)	-	
Mifepristone	1.46 (0.95, 2.33)	1.56 (0.97, 2.54)	5
IV prostaglandins	2.40 (0.71, 8.64)	-	

Results from overall NMA and using only direct evidence from unrelated mean effect model. An OR >1 favours placebo (fewer women required instrumental birth for placebo arm), and OR <1 favours the active intervention (fewer women required instrumental birth in the intervention arm).

The only interventions found to decrease the likelihood of instrumental birth were prostaglandin F_2 gel, Foley catheter and slow release vaginal PGE_2 pessary.

Table 15: Median treatment ranks and probability of being the best treatment for all interventions, for instrumental birth

Intervention	Median (95% CrI) treatment rank	Probability of being best
PGF_2 gel	2 (1, 12)	43%
Oestrogens	4 (1, 26)	22%
Oral prostaglandins	5 (1, 22)	10%
Oral misoprostol tablet (<50 mcg)	5 (1, 25)	12%
Vaginal PGE_2 (pessary – slow release)	5 (2, 14)	2%
Foley catheter	6 (2, 11)	0%
Double balloon or Cook's catheter	8 (2, 20)	1%
Vaginal misoprostol (<50 mcg)	10 (4, 18)	0%
Extra-amniotic PGE_2 or PGF_2	10 (1, 26)	4%
Amniotomy	11 (2, 25)	1%
Titrated oral (low dose) misoprostol	12 (3,24)	0%
Vaginal PGE_2 (gel)	13 (8, 20)	0%
Osmotic cervical dilators including dilapan	13 (2, 26)	1%
Sustained release misoprostol insert	13 (1, 27)	3%
Intracervical PGE_2	14 (7, 22)	0%
Vaginal PGE_2 (tablet)	16 (8, 24)	0%
Nitric oxide donor	16 (5, 25)	0%
Vaginal misoprostol (≥50mcg)	17 (10, 23)	0%
Oral misoprostol tablet (≥50mcg)	17 (9, 24)	0%
IV oxytocin plus amniotomy	17 (6, 25)	0%
Buccal/sublingual misoprostol	19 (4, 26)	0%
Placebo	19 (8, 25)	0%
IV oxytocin	21 (10, 26)	0%
Vaginal PGE_2 pessary (normal release)	22 (12, 26)	0%
Relaxin	25 (4, 28)	0%
No treatment	26 (18, 28)	0%
Mifepristone	26 (15, 28)	0%
IV prostaglandin	28 (7, 28)	0%

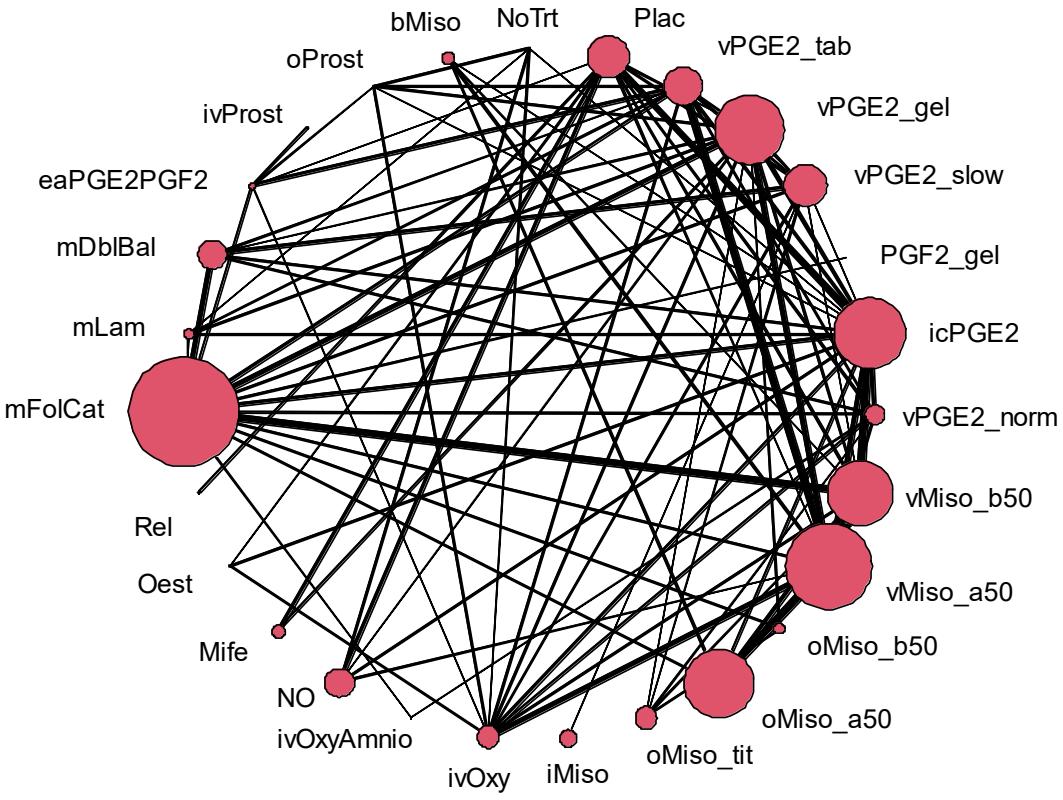
There was considerable uncertainty in the treatment rankings. In keeping with the odds ratios, PGF_2 gel and Foley catheter appeared to rank highly (at reducing the chance of instrumental birth).

The majority of studies contributing to this outcome were at low risk of bias for incomplete outcome data, a large proportion of studies were at unclear risk of bias for selective reporting and a high risk of bias due to blinding of participants and personnel (although a low risk of bias for outcome assessors). While whether or not an instrumental birth occurs is an objective outcome, it is plausible that personnel's awareness of what treatments have predated a decision about birth may be influential. Approximately half of the studies contributing to this outcome were at unclear risk of bias for random sequence generation and allocation concealment. There was also some evidence of inconsistency between the direct and indirect effect estimates (see appendix P for more detail). The committee noted these limitations in the quality of the evidence supporting the NMA when making recommendations.

Subgroup analysis for women with a Bishop score ≤6

After excluding studies that reported no data, 171 studies, comparing a total of 27 different interventions in 37,387 women were included in this analysis. The network plot for this outcome is shown below.

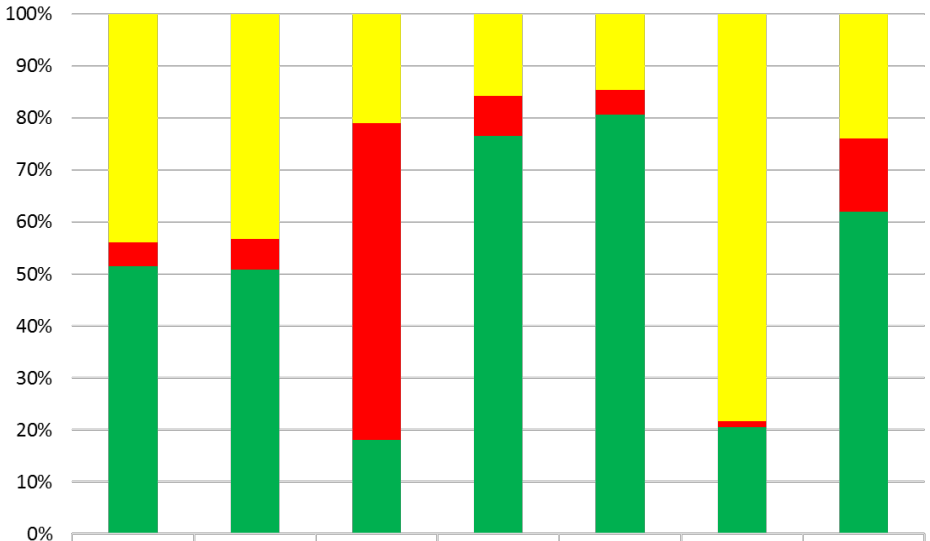
Figure 22: Network for instrumental birth: subgroup analysis for women with Bishop score ≤6



Treatment codes are as follows (in alphabetical order): Amnio: Amniotomy; bMiso: Buccal/sublingual misoprostol; eaPGE$_2$PGF$_2$: Extra-amniotic prostaglandins; icPGE$_2$: Intracervical PGE$_2$; iMiso: Misoprostol vaginal insert; ivOxy: IV oxytocin; ivOxyAmino: IV oxytocin plus amniotomy; ivProst: IV prostaglandins; mDblBal: Double balloon or Cook's catheter; mFolCat: Foley catheter; Mife: Mifepristone; mLam: Osmotic cervical dilators; NO: Nitric oxide; NoTrt: No intervention; Oest: Oestrogens; oMiso_a50: Oral misoprostol ≥50mcg; oMiso_b50: Oral misoprostol <50mcg; oMiso_tit: Titrated oral (low dose) misoprostol; oProst: Oral prostaglandins; PGF$_2$_gel: PGF$_2$ gel; Plac: placebo; Rel: Relaxin; vMiso_a50: Vaginal misoprostol ≥50mcg; vMiso_b50: Vaginal misoprostol <50mcg; vPGE$_2$ gel: Vaginal PGE$_2$_gel; vPGE$_2$_norm: Vaginal PGE$_2$ pessary (normal release); vPGE$_2$_slow: Vaginal PGE$_2$ pessary (slow release); vPGE$_2$_tab: vaginal

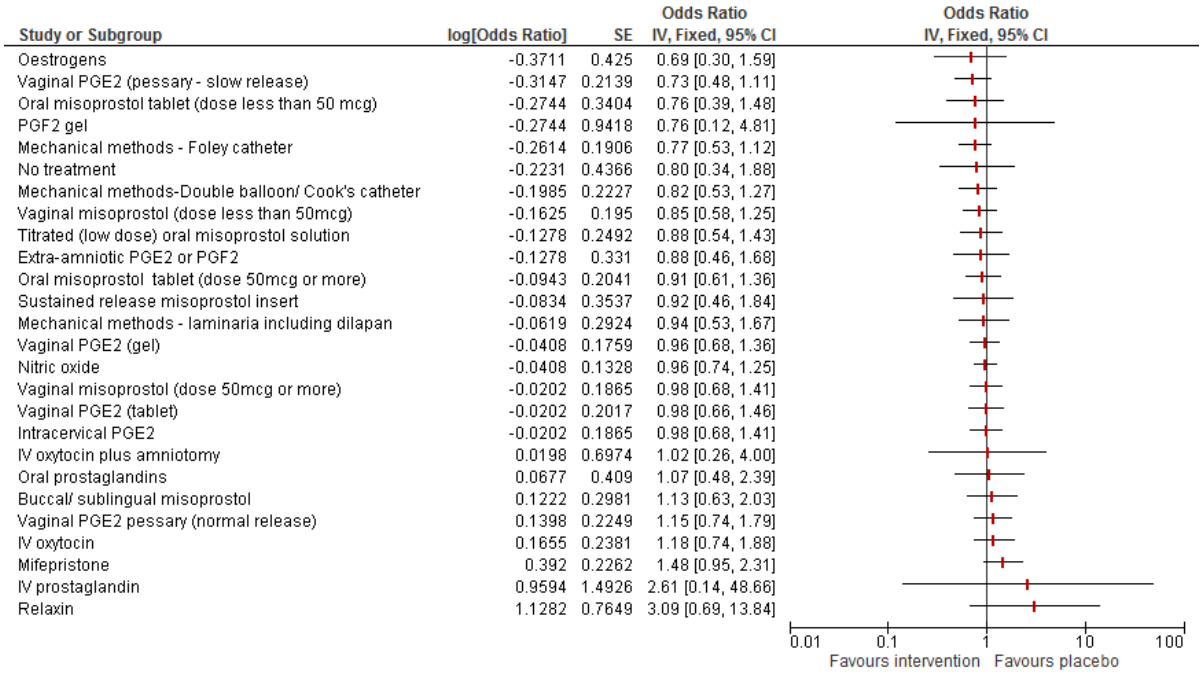
PGE_2 tablet. The size of the nodes is proportional to the number of women in the network randomised to a particular intervention. The thickness of the connecting lines is proportional to the number of studies directly comparing 2 interventions.

Figure 23: Instrumental birth (subgroup analysis for women with Bishop score ≤6): risk of bias assessment



	Random sequence generation	Allocation concealment	Blinding participants and personnel	Blinding outcome assessors	Incomplete outcome data	Selective reporting	Other bias
Unclear risk (number of studies)	75	74	36	27	25	134	41
High risk (number of studies)	8	10	104	13	8	2	24
Low risk (number of studies)	88	87	31	131	138	35	106

Figure 24: Forest plot showing NMA derived OR for instrumental birth for all interventions compared to placebo: subgroup analysis for women with a Bishop score ≤6



OR <1 favours the stated intervention, OR >1 favours placebo

Table 16: OR and 95% CrI for instrumental birth for all interventions compared to placebo: subgroup analysis for women with a Bishop score ≤6

Intervention	NMA OR (95% CrI)	NMA direct evidence only OR (95% CrI)	Number of studies providing direct evidence
Oestrogens	0.69 (0.30, 1.49)	0.65 (0.25, 1.65)	1
Vaginal PGE_2 pessary (slow release)	0.73 (0.48, 1.13)	0.96 (0.41, 2.24)	2
PGF_2 gel	0.76 (0.12, 3.94)	-	
Oral misoprostol <50mcg	0.76 (0.39, 1.53)	-	
Foley catheter	0.77 (0.53, 1.12)	-	
No intervention	0.80 (0.34, 1.67)	-	
Double balloon or Cook's catheter	0.82 (0.53, 1.25)	-	
Vaginal misoprostol <50mcg	0.85 (0.58, 1.23)	0.29 (0.01, 9.83)	1
Extra-amniotic prostaglandins	0.88 (0.46, 1.63)	1.31 (0.28, 6.24)	1
Titrated oral (low dose) misoprostol	0.88 (0.54, 1.46)	-	
Oral misoprostol ≥50mcg	0.91 (0.61, 1.35)	-	
Misoprostol vaginal insert	0.92 (0.46, 1.83)	-	
Osmotic cervical dilators	0.94 (0.53, 1.63)	-	
Vaginal PGE_2 gel	0.96 (0.68, 1.35)	0.43 (0.08, 1.80)	1
Nitric oxide donor	0.96 (0.74, 1.25)	0.95 (0.68, 1.36)	4
Vaginal PGE_2 tablet	0.98 (0.66, 1.47)		
Intracervical PGE_2	0.98 (0.68, 1.39)	1.01 (0.56, 1.78)	6
Vaginal misoprostol ≥50mcg	0.98 (0.68, 1.40)	1.07 (0.34, 3.43)	1
IV oxytocin plus amniotomy	1.02 (0.26, 3.62)	-	
Oral prostaglandins	1.07 (0.48, 2.37)	-	
Buccal/sublingual misoprostol	1.13 (0.63, 1.99)	-	
Vaginal PGE_2 pessary (normal release)	1.15 (0.74, 1.79)	0.72 (0.19, 2.42)	2
IV oxytocin	1.18 (0.74, 1.89)		
Mifepristone	1.48 (0.95, 2.33)	1.57 (0.97, 2.55)	5
IV prostaglandins	2.61 (0.14, 58.17)	-	
Relaxin	3.09 (0.69, 25.74)	3.13 (0.70, 26.29)	1

Results from overall NMA and using only direct evidence from unrelated mean effect model. An OR >1 favours placebo (fewer women required instrumental birth for placebo arm), and OR <1 favours the active intervention (fewer women required instrumental birth in the intervention arm).

For the subgroup analysis, no interventions were shown to significantly reduce the chance of instrumental birth, as compared to placebo.

Table 17: Median treatment ranks and probability of being the best treatment for all interventions, for instrumental birth: subgroup analysis for women with Bishop score ≤6

Intervention	Median (95% CrI) treatment rank	Probability of being best
Oestrogens	4 (1, 24)	17%
Vaginal PGE_2 (pessary – slow release)	5 (1, 17)	4%
PGF_2 gel	6 (1, 27)	29%
Oral misoprostol tablet (<50mcg)	6 (1, 24)	8%
Mechanical methods – Foley catheter	6 (2, 13)	0%
Mechanical methods – Double balloon or Cook's catheter	8 (2, 20)	1%
No treatment	8 (1, 25)	9%
Vaginal misoprostol (<50mcg)	9 (3, 18)	0%
Extra-amniotic PGE_2 or PGF_2	10 (1, 24)	3%
Titrated (low dose) oral misoprostol solution	11 (2, 23)	1%
Oral misoprostol tablet (≥50mcg)	12 (4, 21)	0%
Sustained release misoprostol insert	12 (1, 25)	3%
Mechanical methods – osmotic cervical dilators including dilapan	13 (2, 25)	1%
Nitric oxide donor	14 (4, 23)	0%
Vaginal PGE_2 (gel)	15 (8, 21)	0%
Vaginal misoprostol (≥50mcg)	15 (8, 22)	0%
Intracervical PGE_2	15 (7, 22)	0%
Vaginal PGE_2 (tablet)	15 (6, 23)	0%
Placebo	16 (5, 24)	0%
IV oxytocin plus amniotomy	17 (1, 27)	11%
Oral prostaglandins	19 (2, 26)	2%
Buccal/sublingual misoprostol	20 (4, 26)	0%
Vaginal PGE_2 pessary (normal release)	21 (10, 25)	0%
IV oxytocin	21 (9, 26)	0%
Mifepristone	24 (11, 27)	0%
Relaxin	26 (4, 27)	1%
IV prostaglandin	26 (1, 27)	10%

As with the full data, there is great uncertainty in the rankings for the specific interventions, making it difficult to draw firm conclusions on the efficacy of the different treatments.

Subgroup analysis for women with a Bishop score >6

Fewer studies reported on this outcome for this subgroup of women, therefore the data are presented as pairwise comparisons, rather than with NMA – see the relevant forest plots and GRADE tables (appendix E and F).

NICU admission

186 studies, comparing a total of 25 different interventions in 43,283 women were included in this analysis.

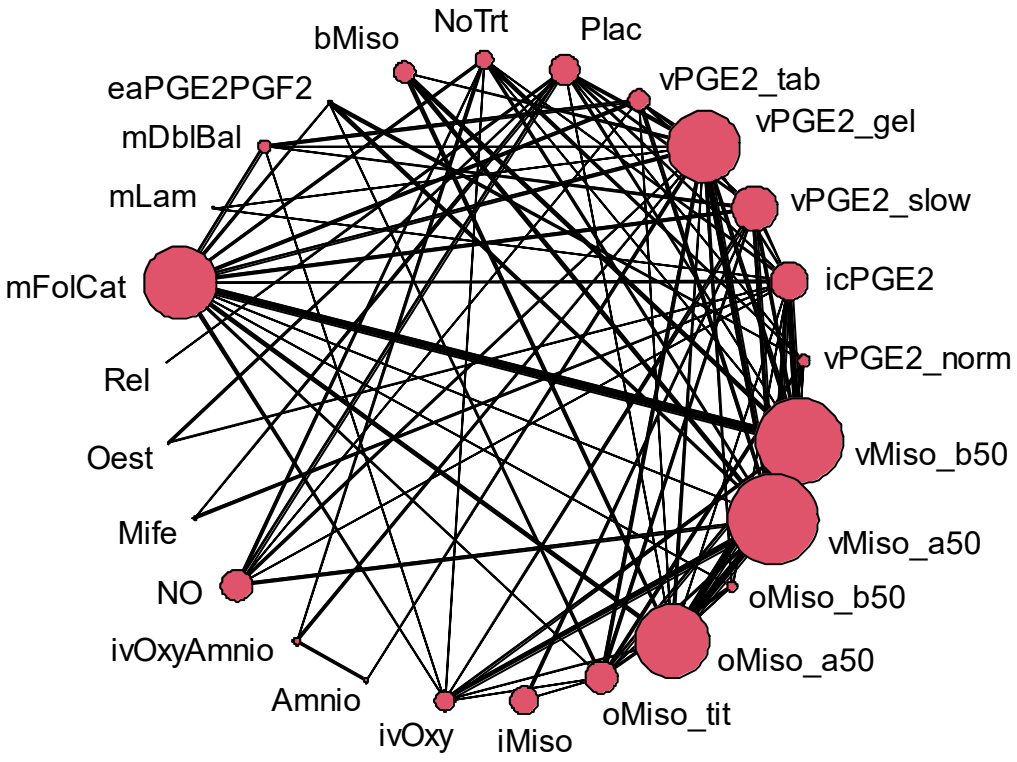
25 studies were exclusively in nulliparous women, and 5 were specifically in multiparous women. 152 included women who were either nulliparous or multiparous. The majority of studies (146) were in women with a Bishop score ≤6, with only 5 studies conducted in women with a Bishop score >6, and 25 studies in a mixed population. Most studies (99) were conducted in women with a gestational age >37 weeks; 49 studies were in a mixed population (including term and preterm infants) and 30 were in women at >40 weeks gestation. 169 studies were conducted in women with a singleton pregnancy, and a further 8 trials included some women with multiple pregnancy.

157 studies only included women with no previous caesarean birth. 14 studies did include some women with previous caesarean birth, but these comprised fewer than a third of the study population. 46 studies included some women with ruptured membranes, but the majority (111) were specifically conducted in women with intact membranes.

339 studies were excluded as they reported no data for this outcome. 20 studies were excluded as they included an irrelevant comparison that was not necessary to produce a connected network. 19 studies were excluded as they reported no events in either treatment arm of the study.

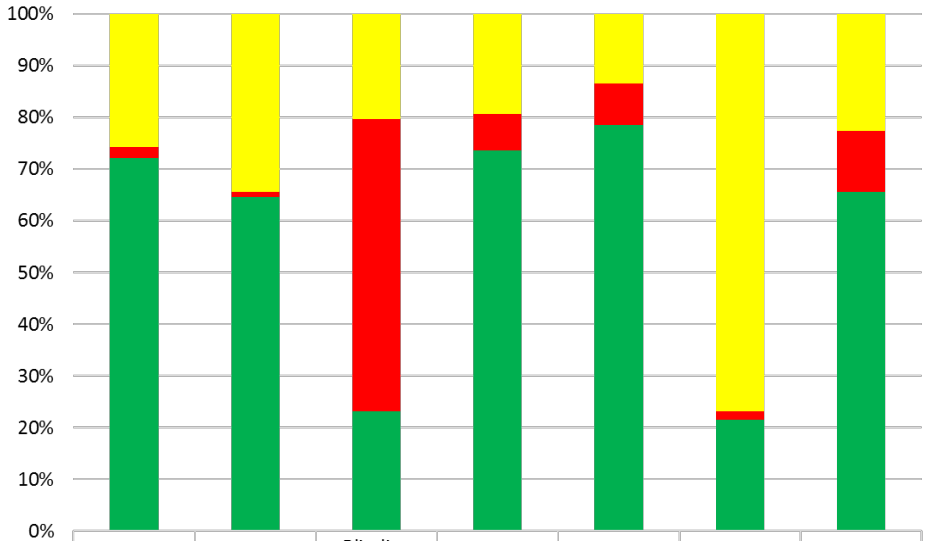
The network plot for this outcome is shown below.

Figure 25: Network for NICU admission



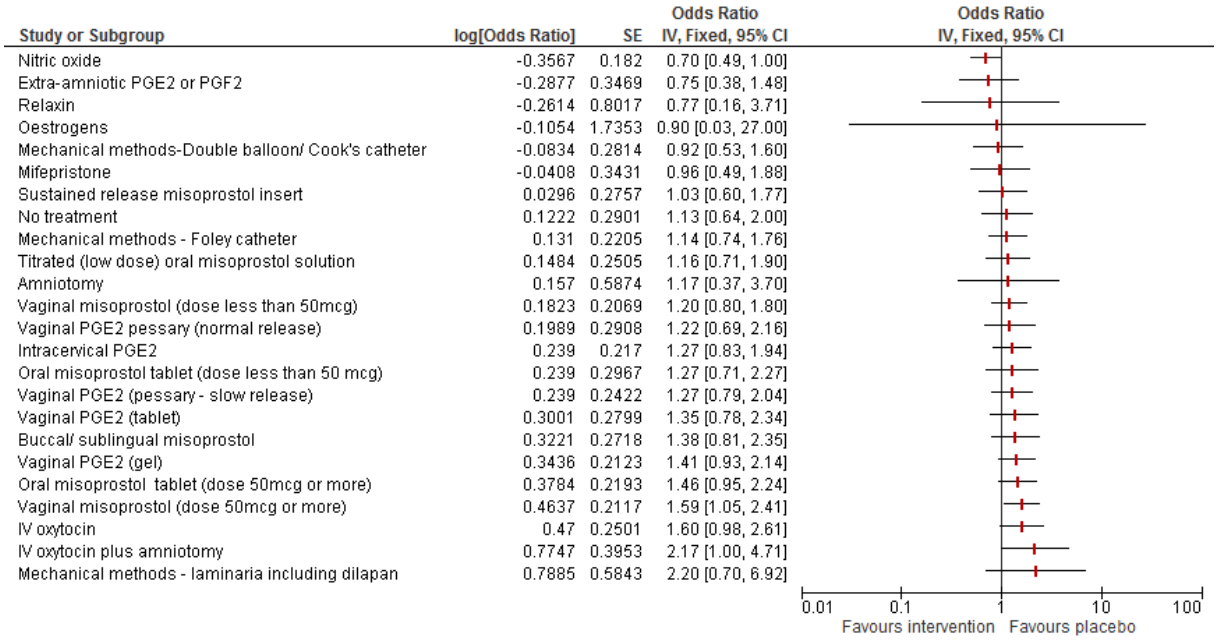
Treatment codes are as follows (in alphabetical order): Amnio: Amniotomy; bMiso: Buccal/sublingual misoprostol; eaPGE$_2$PGF$_2$: Extra-amniotic prostaglandins; icPGE$_2$: Intracervical PGE$_2$; iMiso: Misoprostol vaginal insert; ivOxy: IV oxytocin; ivOxyAmino: IV oxytocin plus amniotomy; mDblBal: Double balloon or Cook's catheter; mFolCat: Foley catheter; Mife: Mifepristone; mLam: Osmotic cervical dilators; NO: Nitric oxide; NoTrt: No intervention; Oest: Oestrogens; oMiso_a50: Oral misoprostol ≥50mcg; oMiso_b50: Oral misoprostol <50mcg; oMiso_tit: Titrated oral (low dose) misoprostol; Plac: placebo; Rel: Relaxin; vMiso_a50: Vaginal misoprostol ≥50mcg; vMiso_b50: Vaginal misoprostol <50mcg; vPGE$_2$ gel: Vaginal PGE$_2$_gel; vPGE$_2$_norm: Vaginal PGE$_2$ pessary (normal release); vPGE$_2$_slow: Vaginal PGE$_2$ pessary (slow release); vPGE$_2$_tab: vaginal PGE$_2$ tablet. The size of the nodes is proportional to the number of women in the network randomised to a particular intervention. The thickness of the connecting lines is proportional to the number of studies directly comparing 2 interventions.

Figure 26: NICU admission: risk of bias assessment



	Random sequence generation	Allocation concealment	Blinding participants and personnel	Blinding outcome assessors	Incomplete outcome data	Selective reporting	Other bias
Unclear risk (number of studies)	48	64	38	36	25	143	42
High risk (number of studies)	4	2	105	13	15	3	22
Low risk (number of studies)	134	120	43	137	146	40	122

Figure 27: Forest plot showing NMA derived OR for NICU admission for all interventions compared to placebo



OR <1 favours the stated intervention, OR >1 favours placebo

Table 18: OR and 95% CrI for NICU admission for all interventions compared to placebo

Intervention	NMA OR (95% CrI)	NMA direct evidence only OR (95% CrI)	Number of studies providing direct evidence
Nitric oxide donor	0.70 (0.49, 1.00)	0.87 (0.58, 1.30)	7
Extra-amniotic prostaglandins	0.75 (0.38, 1.43)	-	
Relaxin	0.77 (0.16, 3.73)	0.77 (0.16, 3.66)	1
Oestrogens	0.90 (0.03, 11.97)	0.69 (0.02, 10.30)	1
Double balloon or Cook's catheter	0.92 (0.53, 1.60)	-	
Mifepristone	0.96 (0.49, 1.88)	1.18 (0.54, 2.61)	2
Misoprostol vaginal insert	1.03 (0.60, 1.77)	-	
No intervention	1.13 (0.64, 1.99)	-	
Foley catheter	1.14 (0.74, 1.76)	-	
Titrated oral (low dose) misoprostol	1.16 (0.71, 1.87)	-	
Amniotomy	1.17 (0.37, 3.56)	-	
Vaginal misoprostol <50mcg	1.20 (0.80, 1.80)	0.89 (0.42, 1.84)	4
Vaginal PGE_2 pessary (normal release)	1.22 (0.69, 2.13)	0.46 (0.06, 2.78)	1
Intracervical PGE_2	1.27 (0.83, 1.96)	0.63 (0.07, 4.22)	2
Vaginal PGE_2 pessary (slow release)	1.27 (0.79, 2.03)	4.16 (0.44, 105.85)	1
Oral misoprostol <50mcg	1.27 (0.71, 2.27)	-	
Vaginal PGE_2 tablet	1.35 (0.78, 2.32)	-	
Buccal/sublingual misoprostol	1.38 (0.81, 2.37)	-	
Vaginal PGE_2 gel	1.41 (0.93, 2.14)	0.36 (0.07, 1.39)	3
Oral misoprostol ≥50mcg	1.46 (0.95, 2.23)	0.97 (0.10, 9.11)	1
Vaginal misoprostol ≥50mcg	1.59 (1.05, 2.40)	-	
IV oxytocin	1.60 (0.98, 2.64)	-	
IV oxytocin plus amniotomy	2.17 (1.00, 4.70)	-	
Osmotic cervical dilators	2.20 (0.70, 7.35)	-	

Results from overall NMA and using only direct evidence from unrelated mean effect model. An OR >1 favours placebo (fewer infants required admission to NICU for placebo arm), and OR <1 favours the active intervention (fewer infants required admission to NICU in the intervention arm).

Nitric oxide donors was the only intervention in the NMA results that was shown to be significantly better than placebo at reducing the admission to NICU. However, although there was overlap with the confidence interval from the direct estimates, the direct evidence did not show a statistically significant reduction in NICU admission rates.

For the majority of interventions there was considerable imprecision in the effect estimates, such that the intervention may increase or decrease NICU admission as compared to placebo. The only interventions shown to significantly increase admission to NICU was high dose vaginal misoprostol (≥50mcg) and IV oxytocin plus amniotomy.

Table 19: Median treatment ranks and probability of being the best treatment for all interventions, for NICU admission

Intervention	Median (95% CrI) treatment rank	Probability of being best
Nitric oxide donor	3 (1, 7)	12%
Extra-amniotic prostaglandins	3 (1, 14)	13%
Relaxin	4 (1, 25)	27%
Oestrogens	5 (1, 25)	33%
Double balloon or Cook's catheter	6 (2, 16)	2%
Mifepristone	6 (1, 23)	5%
Placebo	7 (3, 19)	0%
Misoprostol vaginal insert	8 (2, 19)	1%
No intervention	10 (3, 22)	0%
Titrated oral (low dose) misoprostol	11 (4, 20)	0%
Foley catheter	11 (5, 17)	0%
Amniotomy	11 (1, 25)	6%
Vaginal misoprostol <50mcg	12 (7, 18)	0%
Vaginal PGE_2 pessary (normal release)	13 (4, 23)	0%
Intracervical PGE_2	14 (7, 21)	0%
Vaginal PGE_2 pessary (slow release)	14 (7, 22)	0%
Oral misoprostol <50mcg	14 (4, 24)	0%
Vaginal PGE_2 tablet	16 (6, 24)	0%
Buccal/sublingual misoprostol	17 (6, 24)	0%
Vaginal PGE_2 gel	18 (11, 23)	0%
Oral misoprostol ≥50mcg	19 (12, 23)	0%
Vaginal misoprostol ≥50mcg	21 (16, 24)	0%
IV oxytocin	21 (11, 25)	0%
IV oxytocin plus amniotomy	24 (10, 25)	0%
Osmotic cervical dilators	24 (4, 25)	1%

The wide credible intervals for most interventions show considerable uncertainty for the ranking of different treatments. Nitric oxide was ranked highly among the interventions included in the network, being in the top seven interventions in 95% of the runs.

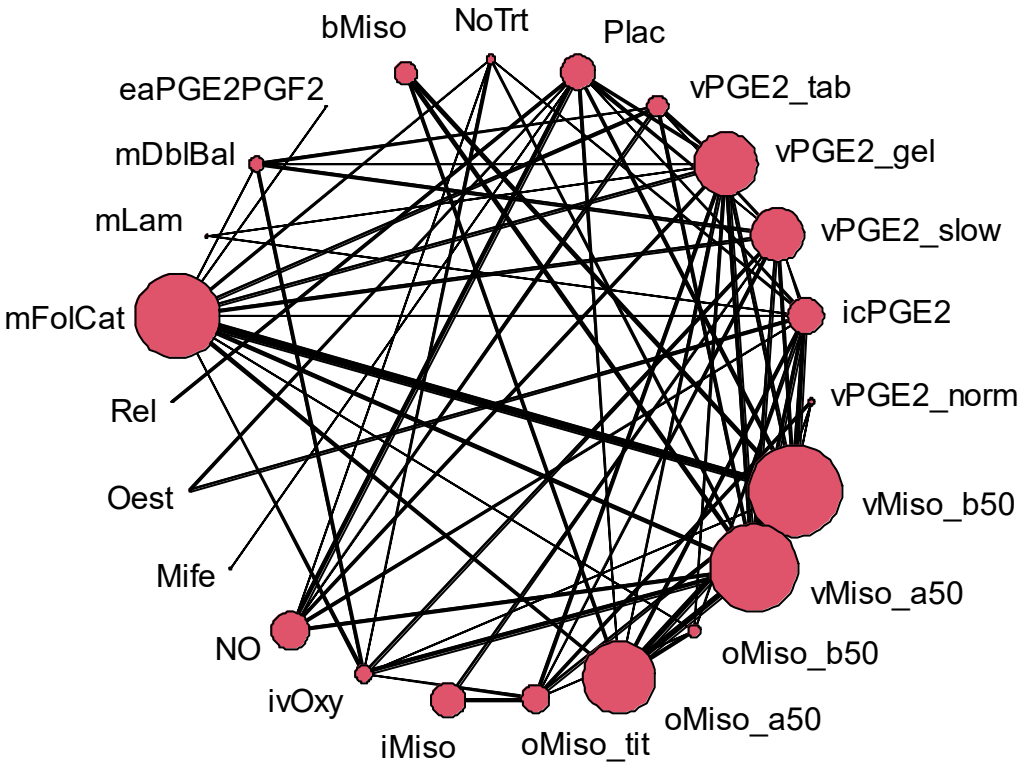
The majority of studies contributing to this outcome were at low risk of bias across most domains although a large proportion of studies were at unclear risk of bias for selective reporting and a high risk of bias due to blinding of participants and personnel. For this essentially objective outcome the committee did not consider the lack of blinding to be

particularly impactful. There was also some evidence of inconsistency between the direct and indirect effect estimates (see appendix P for more detail). The committee noted these limitations in the quality of the evidence supporting the NMA when making recommendations.

Subgroup analysis for women with a Bishop score ≤6

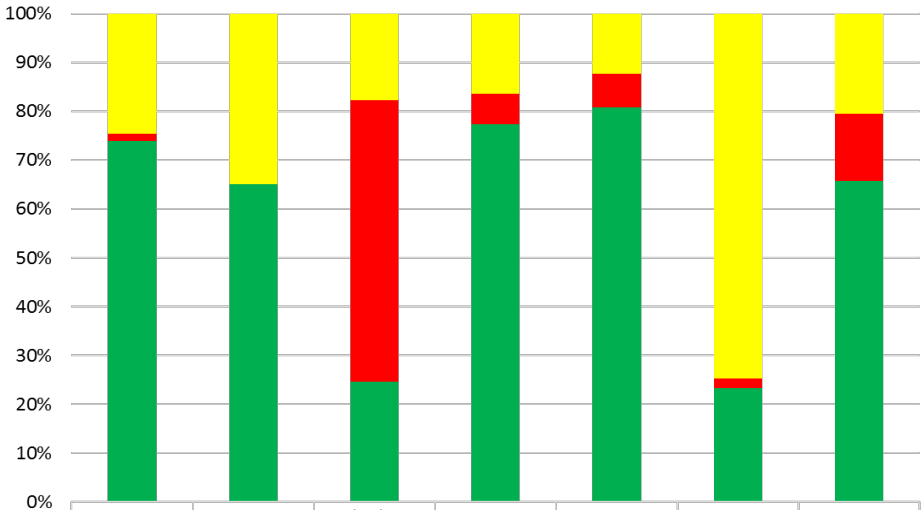
After excluding studies that reported no data, 146 studies, comparing a total of 23 different interventions in 35,361 women were included in this analysis. The network plot for this outcome is shown below.

Figure 28: Network for NICU admission: subgroup analysis for women with Bishop score ≤6



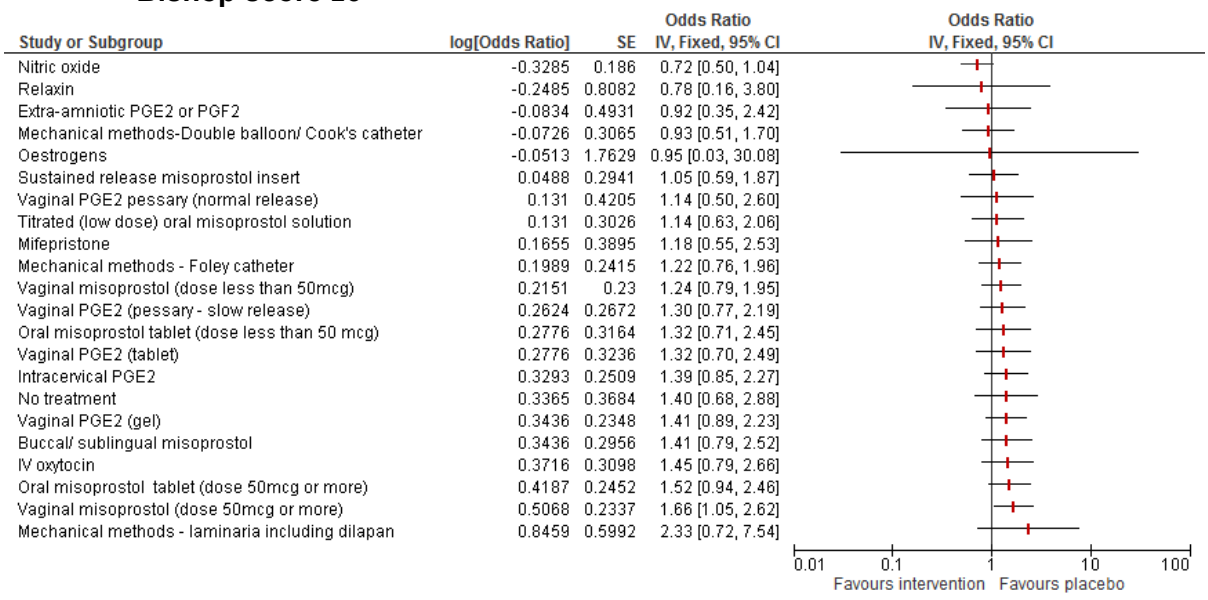
Treatment codes are as follows (in alphabetical order): Amnio: Amniotomy; bMiso: Buccal/sublingual misoprostol; eaPGE$_2$PGF$_2$: Extra-amniotic prostaglandins; icPGE$_2$: Intracervical PGE$_2$; iMiso: Misoprostol vaginal insert; ivOxy: IV oxytocin; ivOxyAmino: IV oxytocin plus amniotomy; mDblBal: Double balloon or Cook's catheter; mFolCat: Foley catheter; Mife: Mifepristone; mLam: Osmotic cervical dilators; NO: Nitric oxide; NoTrt: No intervention; Oest: Oestrogens; oMiso_a50: Oral misoprostol ≥50mcg; oMiso_b50: Oral misoprostol <50mcg; oMiso_tit: Titrated oral (low dose) misoprostol; Plac: placebo; Rel: Relaxin; vMiso_a50: Vaginal misoprostol ≥50mcg; vMiso_b50: Vaginal misoprostol <50mcg; vPGE$_2$ gel: Vaginal PGE$_2$_gel; vPGE$_2$_norm: Vaginal PGE$_2$ pessary (normal release); vPGE$_2$_slow: Vaginal PGE$_2$ pessary (slow release); vPGE$_2$_tab: vaginal PGE$_2$ tablet. The size of the nodes is proportional to the number of women in the network randomised to a particular intervention. The thickness of the connecting lines is proportional to the number of studies directly comparing 2 interventions.

Figure 29: NICU admission (subgroup analysis for women with Bishop score ≤6): risk of bias assessment



	Random sequence generation	Allocation concealment	Blinding participants and personnel	Blinding outcome assessors	Incomplete outcome data	Selective reporting	Other bias
Unclear risk (number of studies)	36	51	26	24	18	109	30
High risk (number of studies)	2	0	84	9	10	3	20
Low risk (number of studies)	108	95	36	113	118	34	96

Figure 30: Forest plot showing NMA derived OR for NICU admission for all interventions compared to placebo: subgroup analysis for women with a Bishop score ≤6



OR <1 favours the stated intervention, OR >1 favours placebo

Table 20: OR and 95% CrI for NICU admission for all interventions compared to placebo: subgroup analysis for women with Bishop score ≤6

Intervention	NMA OR (95% CrI)	NMA direct evidence only OR (95% CrI)	Number of studies contributing direct evidence
Nitric oxide donor	0.72 (0.50, 1.03)	0.87 (0.58, 1.30)	7
Relaxin	0.78 (0.16, 3.73)	0.77 (0.16, 3.70)	1
Extra-amniotic prostaglandins	0.92 (0.35, 2.43)	-	
Double balloon or Cook's catheter	0.93 (0.51, 1.70)	-	
Oestrogens	0.95 (0.03, 12.84)	0.92 (0.03, 28.33)	1
Misoprostol vaginal insert	1.05 (0.59, 1.87)	-	
Titrated oral (low dose) misoprostol	1.14 (0.63, 2.03)	-	
Vaginal PGE_2 pessary (normal release)	1.14 (0.50, 2.61)	-	
Mifepristone	1.18 (0.55, 2.61)	1.18 (0.54, 2.60)	2
Foley catheter	1.22 (0.76, 1.96)	-	
Vaginal misoprostol <50mcg	1.24 (0.79, 1.93)	0.89 (0.42, 1.83)	3
Vaginal PGE_2 pessary (slow release)	1.30 (0.77, 2.16)	4.14 (0.45, 100.69)	1
Vaginal PGE_2 tablet	1.32 (0.70, 2.48)	-	
Oral misoprostol <50mcg	1.32 (0.71, 2.44)	-	
Intracervical PGE_2	1.39 (0.85, 2.27)	0.99 (0.03, 30.88)	1
No intervention	1.40 (0.68, 2.82)	-	
Vaginal PGE_2 gel	1.41 (0.89, 2.24)	0.14 (0.01, 1.05)	1
Buccal/sublingual misoprostol	1.41 (0.79, 2.51)		
IV oxytocin	1.45 (0.79, 2.66)	-	
Oral misoprostol ≥50mcg	1.52 (0.94, 2.45)	0.98 (0.10, 9.18)	1
Vaginal misoprostol ≥50mcg	1.66 (1.05, 1.87)	-	
Osmotic cervical dilators	2.33 (0.72, 7.98)	-	

Results from overall NMA and using only direct evidence from unrelated mean effect model. An OR >1 favours placebo (fewer infants required admission to NICU for placebo arm), and OR <1 favours the active intervention (fewer infants required admission to NICU in the intervention arm).

No intervention was shown to significantly reduce the rate of NICU admission. However, in keeping with the result from the whole population, nitric oxide came close to reaching conventional statistical significance (OR 0.72 [95% CrI 0.50 to 1.03]). High dose vaginal misoprostol was the only intervention found to significantly increase the risk of admission to NICU, as compared to placebo (OR 1.66 [95% CrI 1.05 to 1.87]), although high dose oral misoprostol also came close to achieving statistical significance (OR 1.52 [95% CrI 0.94 to 2.45]).

Table 21: Median treatment ranks and probability of being the best treatment for all interventions, for NICU admission: subgroup analysis for women with a Bishop score ≤6

Intervention	Median (95% CrI) treatment rank	Probability of being best
Nitric oxide donor	3 (1, 7)	15%
Relaxin	3 (1, 23)	28%

Intervention	Median (95% CrI) treatment rank	Probability of being best
Extra-amniotic prostaglandins	5 (1, 22)	11%
Double balloon/Cook's catheter	5 (1, 15)	3%
Oestrogens	5 (1, 23)	33%
Placebo	6 (3, 18)	0%
Sustained release misoprostol vaginal insert	7 (2, 18)	0%
Titrated/low dose oral misoprostol	9 (3, 20)	0%
Vaginal PGE_2 pessary (normal release)	9 (1, 22)	3%
Mifepristone	10 (1, 23)	3%
Vaginal misoprostol tablet (≤50mcg)	11 (6, 17)	0%
Foley catheter	11 (6, 17)	0%
Vaginal PGE_2 pessary (slow release)	13 (6, 21)	0%
Oral misoprostol tablet (≤50mcg)	14 (4, 22)	0%
Vaginal PGE_2 tablet	14 (4, 22)	0%
No treatment	15 (3, 23)	0%
Intracervical PGE_2	15 (7, 21)	0%
Buccal/sublingual misoprostol	16 (5, 22)	0%
Vaginal PGE_2 gel	16 (9, 21)	0%
IV oxytocin	17 (5, 23)	0%
Oral misoprostol tablet (>50mcg)	18 (11, 22)	0%
Vaginal misoprostol tablet (>50mcg)	20 (15, 23)	0%
Osmotic cervical dilators	22 (3, 23)	1%

Subgroup analysis for women with a Bishop score >6

Fewer studies reported on this outcome for this subgroup of women, therefore the data are presented as pairwise comparisons, rather than with NMA – see the relevant forest plots and GRADE tables (appendix E and F).

Use of epidural

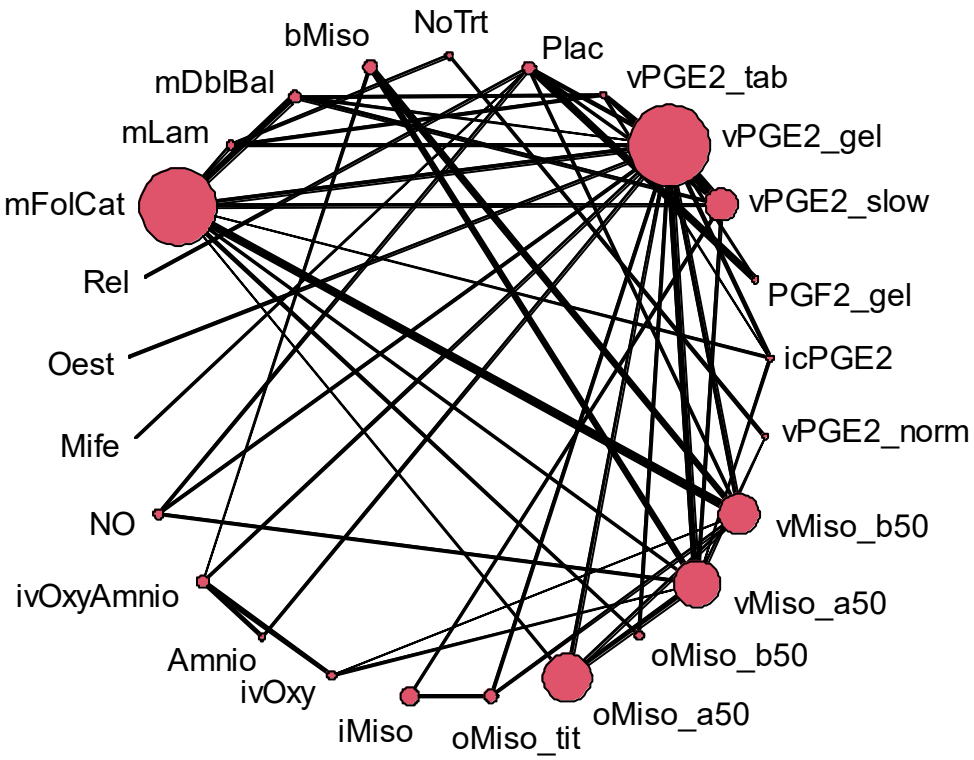
85 studies, comparing a total of 25 different interventions in 20,972 women were included in this analysis. The majority of trials (67) were conducted in singleton pregnancies; 4 trials also included some multi-fetal pregnancies, and 14 did not report whether singletons/multi-fetal pregnancies were included. Most trials (54) were conducted in pregnancies >37 weeks. Of the remaining trials, 23 were conducted in a mixed population (including some pregnancies at <37 weeks), 4 were conducted specifically in pregnancies at >40 weeks, and 4 did not report the gestation at which the trial was conducted. 60 trials were conducted in women with a Bishop score ≤6, 7 were in women with a Bishop score >6, 14 were a mixed population and 4 did not report the cervical status. Most trials (65) included nulliparous and multiparous women. 15 were conducted exclusively in nulliparous women, 2 in multiparous

women, and 3 did not report on parity. 58 trials stated that no women had a previous caesarean birth, 12 did not report this, and 15 reported that some participants (less than a third of the total) had a previous caesarean birth. 49 trials were in women with intact membranes, 17 did not report on membrane status, and 19 included some women (less than a third of the study population) with ruptured membranes.

461 studies were excluded as they reported no data for this outcome. 15 studies were excluded as they included an irrelevant comparison that was not necessary to produce a connected network. 3 studies were excluded as they reported no events or 100% events in either arm (Lo 1994, Craft 1971, Saleh 1975).

The network plot for this outcome is shown below.

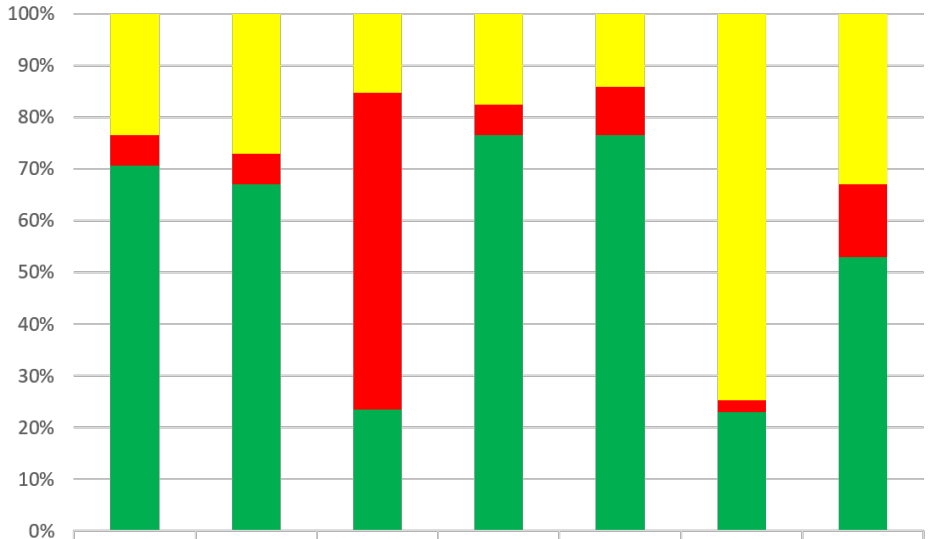
Figure 31: Network for use of epidural



Treatment codes are as follows (in alphabetical order): Amnio: Amniotomy; bMiso: Buccal/sublingual misoprostol; icPGE$_2$: Intracervical PGE$_2$; iMiso: Misoprostol vaginal insert; ivOxy: IV oxytocin; ivOxyAmino: IV oxytocin plus amniotomy; mDblBal: Double balloon or Cook's catheter; mFolCat: Foley catheter; Mife: Mifepristone; mLam: Osmotic cervical dilators; NO: Nitric oxide; NoTrt: No intervention; Oest: Oestrogens; oMiso_a50: Oral misoprostol ≥50mcg; oMiso_b50: Oral misoprostol <50mcg; oMiso_tit: Titrated oral (low dose) misoprostol; PGF$_2$_gel: PGF$_2$ gel; Plac: placebo; Rel: Relaxin; vMiso_a50: Vaginal misoprostol ≥50mcg; vMiso_b50: Vaginal misoprostol <50mcg; vPGE$_2$ gel: Vaginal PGE$_2$_gel; vPGE$_2$_norm: Vaginal PGE$_2$ pessary (normal release); vPGE$_2$_slow: Vaginal PGE$_2$ pessary (slow release); vPGE$_2$_tab: vaginal PGE$_2$ tablet. The size of the nodes is proportional to the number of women

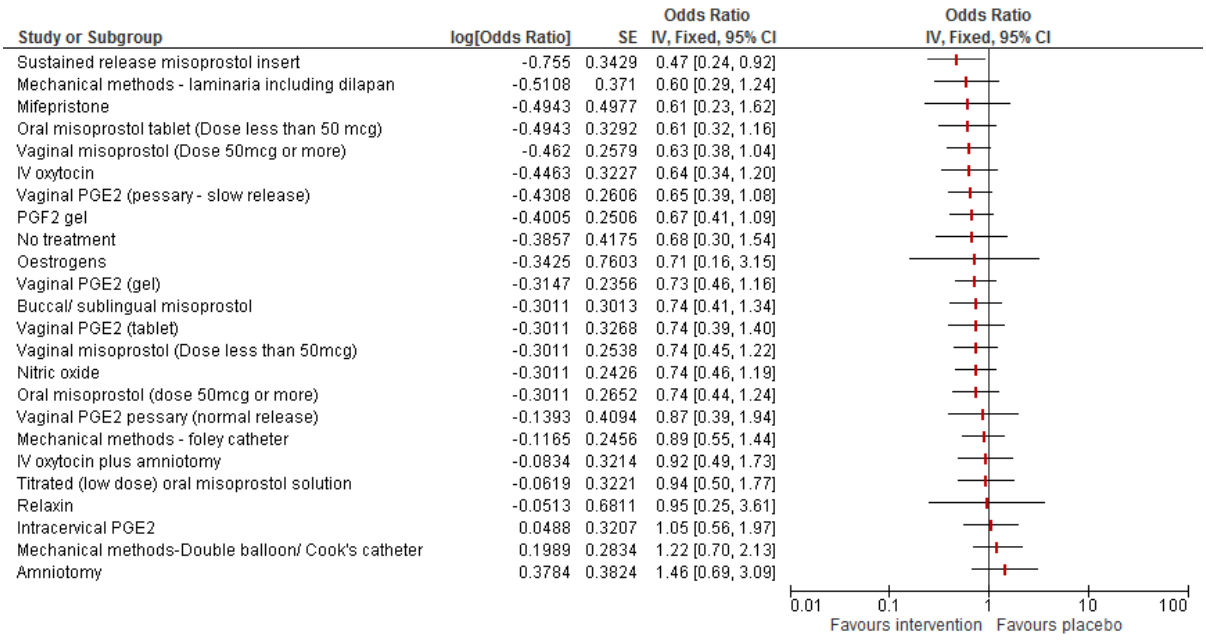
in the network randomised to a particular intervention. The thickness of the connecting lines is proportional to the number of studies directly comparing 2 interventions.

Figure 32: Use of epidural: risk of bias assessment



	Random sequence generation	Allocation concealment	Blinding participants and personnel	Blinding outcome assessors	Incomplete outcome data	Selective reporting	Other bias
Unclear risk (number of studies)	20	23	13	15	12	65	28
High risk (number of studies)	5	5	52	5	8	2	12
Low risk (number of studies)	60	57	20	65	65	20	45

Figure 33: Forest plot showing NMA derived OR for use of epidural for all interventions compared to placebo



OR <1 favours the stated intervention, OR >1 favours placebo.

Table 22: OR and 95% CrI for use of epidural for all interventions compared to placebo

Intervention	NMA OR (95% CrI)	NMA direct evidence only OR (95% CrI)	Number of studies reporting direct evidence
Sustained release misoprostol insert	0.47 (0.24, 0.93)	-	
Osmotic cervical dilators	0.60 (0.30, 1.18)	-	
Mifepristone	0.61 (0.24, 1.54)	0.61 (0.23, 1.54)	1
Oral misoprostol tablet (<50mcg)	0.62 (0.33, 1.14)	-	
Vaginal misoprostol (≥50mcg)	0.63 (0.38, 1.03)	-	
Vaginal PGE_2 pessary (slow release)	0.65 (0.39, 1.09)	1.28 (0.44, 3.81)	1
IV oxytocin	0.65 (0.34, 1.20)	-	
PGF_2 gel	0.67 (0.42, 1.09)	0.64 (0.40, 1.03)	4
No treatment	0.68 (0.31, 1.51)	-	
Oestrogens	0.72 (0.17, 2.99)	-	
Vaginal PGE_2 (tablet)	0.74 (0.40, 1.39)	-	
Vaginal PGE_2 (gel)	0.74 (0.46, 1.16)	-	
Nitric oxide donor	0.74 (0.46, 1.16)	0.84 (0.48, 1.47)	1
Oral misoprostol tablet (≥50mcg)	0.74 (0.44, 1.24)	-	
Buccal/SL misoprostol	0.75 (0.42, 1.36)	-	
Vaginal misoprostol (<50 mcg)	0.75 (0.46, 1.24)	0.91 (0.17, 4.64)	1
Vaginal PGE_2 pessary (normal release)	0.88 (0.39, 1.99)	-	
Foley catheter	0.90 (0.55, 1.46)	-	
IV oxytocin plus amniotomy	0.93 (0.50, 1.71)	-	
Titrated (low dose) oral misoprostol solution	0.95 (0.51, 1.76)	-	
Relaxin	0.96 (0.25, 3.57)	0.96 (0.25, 3.59)	1
Intracervical PGE_2	1.06 (0.57, 1.96)	-	
Double balloon catheter	1.23 (0.70, 2.14)	-	
Amniotomy	1.46 (0.69, 3.12)	-	

Results from overall NMA and using only direct evidence from unrelated mean effect model. An OR >1 favours placebo (fewer women required epidural analgesia in the placebo arm), and OR <1 favours the active intervention (fewer women required epidural analgesia in the intervention arm).

There was evidence that misoprostol vaginal insert reduced the epidural rate as compared with placebo (OR 0.47 [95% CrI 0.24-0.93]). For most interventions, the point estimate for the OR was in favour of active treatment rather than placebo, but the 95% CrI crossed 1, showing uncertainty in the effect estimate.

Table 23: Median treatment ranks and probability of being the best treatment for all interventions, for use of epidural

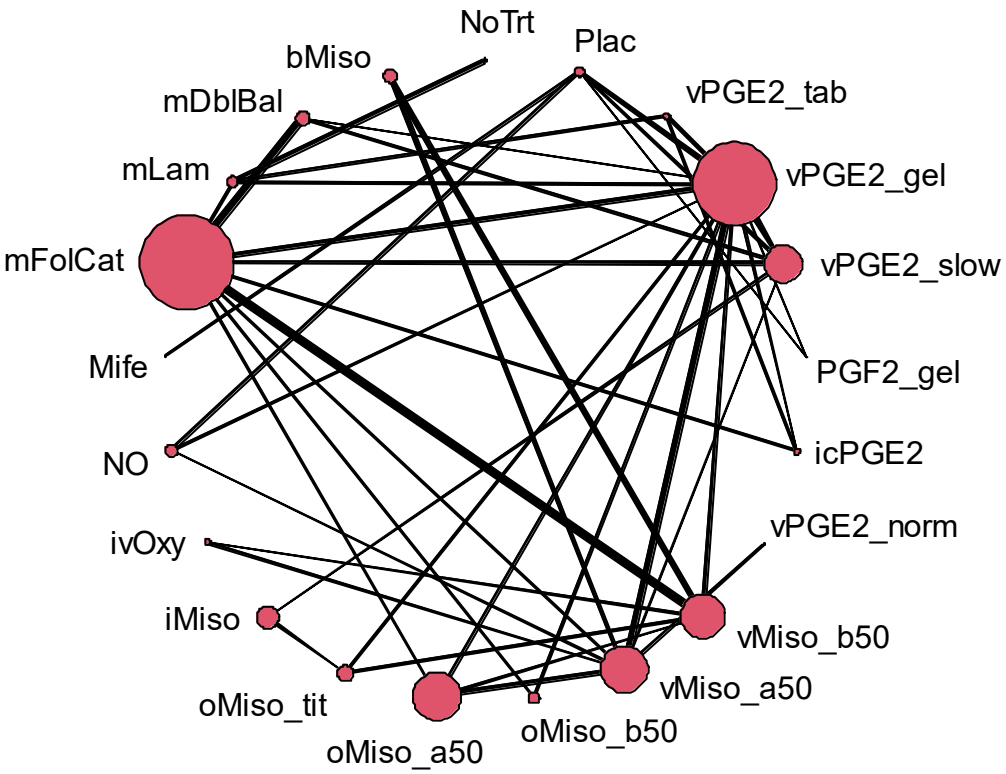
Intervention	Median (95% CrI) treatment rank	Probability of being best
Sustained release misoprostol insert	2 (1, 14)	29%
Osmotic cervical dilators	6 (1, 19)	6%
Oral misoprostol tablet (<50 mcg)	6 (1, 19)	4%
Mifepristone	6 (1, 25)	19%
Vaginal misoprostol (≥50 mcg)	7 (2, 14)	0%
Vaginal PGE_2 pessary (slow release)	8 (3, 17)	0%
IV oxytocin	8 (1, 20)	3%
PGF_2 gel	9 (1, 22)	4%
No treatment	9 (1, 23)	4%
Oestrogens	11 (1, 25)	18%
Vaginal PGE_2 gel	12 (6, 17)	0%
Vaginal PGE_2 tablet	12 (2, 22)	1%
Oral misoprostol tablet (≥ 50mcg)	12 (5, 19)	0%
Nitric oxide donor	12 (3, 21)	0%
Buccal/sublingual misoprostol	12 (3, 23)	0%
Vaginal misoprostol (<50 mcg)	12 (5, 19)	0%
Vaginal PGE_2 pessary (normal release)	17 (3, 25)	1%
Foley catheter	18 (12, 22)	0%
IV oxytocin plus amniotomy	18 (6, 24)	0%
Titrated (low dose) oral misoprostol solution	19 (6, 24)	0%
Relaxin	19 (1, 25)	9%
Placebo	20 (8, 24)	0%
Intracervical PGE_2	21 (9, 25)	0%
Double balloon catheter	23 (17, 25)	0%
Amniotomy	24 (15, 25)	0%

There is considerable uncertainty in the estimates for the ranking of all interventions.

Subgroup analysis for women with a Bishop score ≤6

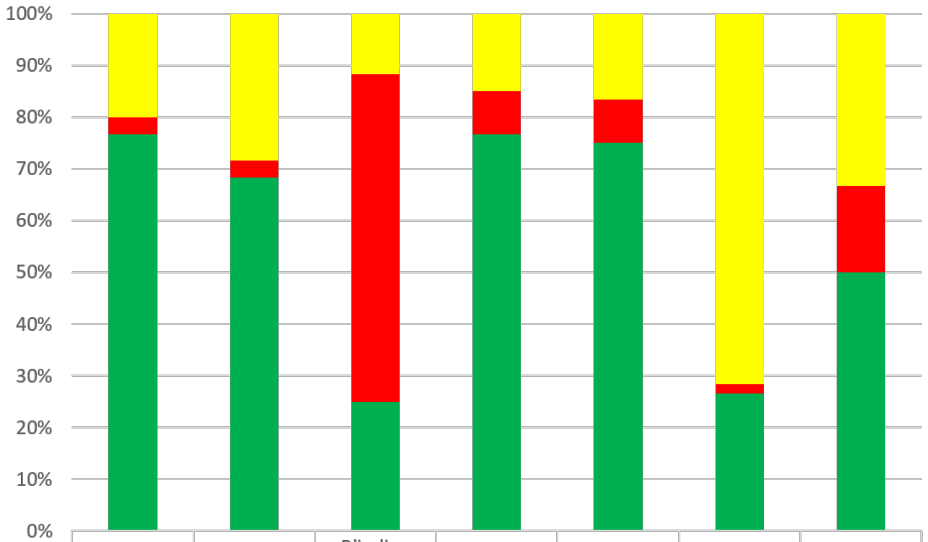
After excluding studies that reported no data, 60 studies, comparing a total of 21 different interventions in 17,623 women were included in this analysis. The network plot for this outcome is shown below.

Figure 34: Network for use of epidural: subgroup analysis for women with Bishop score ≤6



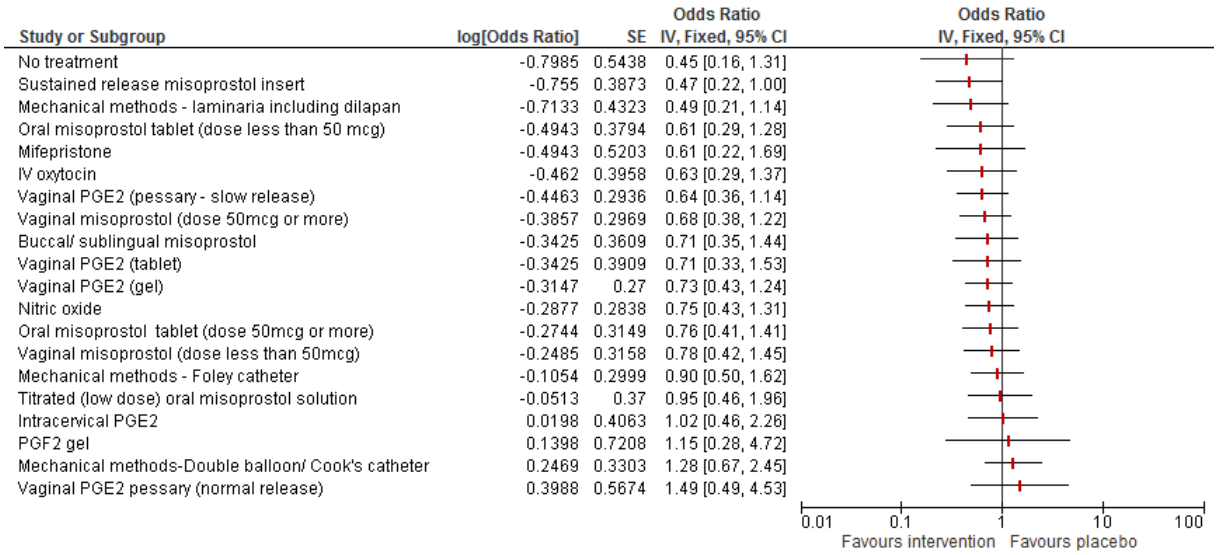
Treatment codes are as follows (in alphabetical order): Amnio: Amniotomy; bMiso: Buccal/sublingual misoprostol; icPGE$_2$: Intracervical PGE$_2$; iMiso: Misoprostol vaginal insert; ivOxy: IV oxytocin; ivOxyAmino: IV oxytocin plus amniotomy; mDblBal: Double balloon or Cook's catheter; mFolCat: Foley catheter; Mife: Mifepristone; mLam: Osmotic cervical dilators; NO: Nitric oxide; NoTrt: No intervention; Oest: Oestrogens; oMiso_a50: Oral misoprostol ≥50mcg; oMiso_b50: Oral misoprostol <50mcg; oMiso_tit: Titrated oral (low dose) misoprostol; PGF$_2$_gel: $_{PGF2}$ gel; Plac: placebo; Rel: Relaxin; vMiso_a50: Vaginal misoprostol ≥50mcg; vMiso_b50: Vaginal misoprostol <50mcg; vPGE$_2$ gel: Vaginal PGE$_2$_gel; vPGE$_2$_norm: Vaginal PGE$_2$ pessary (normal release); vPGE$_2$_slow: Vaginal PGE$_2$ pessary (slow release); vPGE$_2$_tab: vaginal PGE$_2$ tablet. The size of the nodes is proportional to the number of women in the network randomised to a particular intervention. The thickness of the connecting lines is proportional to the number of studies directly comparing 2 interventions.

Figure 35: Use of epidural (subgroup analysis for women with a Bishop score ≤6): risk of bias assessment



	Random sequence generation	Allocation concealment	Blinding participants and personnel	Blinding outcome assessors	Incomplete outcome data	Selective reporting	Other bias
Unclear risk (number of studies)	12	17	7	9	10	43	20
High risk (number of studies)	2	2	38	5	5	1	10
Low risk (number of studies)	46	41	15	46	45	16	30

Figure 36: Forest plot showing NMA derived OR for use of epidural for all interventions compared to placebo: subgroup analysis for women with a Bishop score ≤6



OR <1 favours the stated intervention, OR > 1 favours placebo

Table 24: OR and 95% CrI for use of epidural for all interventions compared to placebo: subgroup analysis for women with a Bishop score ≤6

Intervention	NMA OR (95% CrI)	NMA direct evidence only OR (95% CrI)	Number of studies reporting direct evidence
No treatment	0.45 (0.16, 1.27)	-	
Sustained release misoprostol insert	0.47 (0.22, 1.02)	-	
Osmotic cervical dilators	0.49 (0.22, 1.09)	-	
Oral misoprostol tablet (<50 mcg)	0.62 (0.30, 1.24)	-	
Mifepristone	0.62 (0.22, 1.66)	0.63 (0.21, 1.60)	1
IV oxytocin	0.64 (0.29, 1.38)	-	
Vaginal PGE_2 pessary (slow release)	0.65 (0.36, 1.16)	1.28 (0.42, 3.88)	1
Vaginal misoprostol tablet (≥50mcg)	0.68 (0.38, 1.19)	-	
Vaginal PGE_2 tablet	0.71 (0.34, 1.50)	-	
Buccal/sublingual misoprostol	0.72 (0.36,1.44)	-	
Vaginal PGE2 gel	0.74 (0.43, 1.23)	-	
Nitric oxide donor	0.75 (0.44, 1.24)	0.84 (0.45, 1.57)	1
Oral misoprostol tablet (≥50mcg)	0.77 (0.41, 1.41)	-	
Vaginal misoprostol tablet (<50mcg)	0.78 (0.43, 1.41)	-	
Foley catheter	0.90 (0.51, 1.55)	-	
Titrated (low dose) oral misoprostol solution	0.95 (0.46, 1.93)	-	
Intracervical PGE_2	1.02 (0.47, 2.18)	-	
PGF_2 gel	1.16 (0.29, 4.94)	0.84 (0.19, 3.80)	1
Double balloon or Cook's catheter	1.28 (0.67, 2.42)	-	
Vaginal PGE_2 pessary (normal release)	1.49 (0.49, 4.51)	-	

Results from overall NMA and using only direct evidence from unrelated mean effect model. An OR >1 favours placebo (fewer women required epidural analgesia in the placebo arm), and OR <1 favours the active intervention (fewer women required epidural analgesia in the intervention arm).

No interventions were identified as having a statistically significant impact at reducing or increasing the rate of epidural as compared to placebo.

Table 25: Median treatment ranks and probability of being the best treatment for all interventions, for use of epidural: subgroup analysis for women with a Bishop score ≤6

Intervention	Median (95% CrI) treatment rank	Probability of being best
No treatment	3 (1, 18)	31%
Osmotic cervical dilators	3 (1, 15)	11%

Intervention	Median (95% CrI) treatment rank	Probability of being best
Sustained release misoprostol insert	3 (1, 14)	24%
Oral misoprostol tablet (<50 mcg)	6 (1, 17)	4%
Mifepristone	6 (1, 21)	18%
Vaginal PGE_2 pessary (slow release)	7 (2, 15)	0%
IV oxytocin	7 (1, 18)	4%
Vaginal misoprostol (≥50 mcg)	8 (3, 15)	0%
Vaginal PGE_2 tablet	9 (2, 19)	2%
Buccal/sublingual misoprostol	10 (2, 19)	1%
Vaginal PGE_2 gel	10 (6, 15)	0%
Nitric oxide donor	11 (3, 18)	1%
Oral misoprostol tablet (≥ 50mcg)	12 (4, 18)	0%
Vaginal misoprostol (<50 mcg)	12 (5, 18)	0%
Foley catheter	15 (10, 19)	0%
Titrated (low dose) oral misoprostol solution	16 (5, 21)	0%
Placebo	17 (6, 21)	0%
Intracervical PGE_2	17 (5, 21)	0%
PGF_2 gel	19 (1, 21)	5%
Double balloon or Cook's catheter	19 (15, 21)	0%
Vaginal PGE_2 pessary (normal release)	20 (5, 21)	0%

There is considerable uncertainty in the ranking of the interventions.

The majority of studies contributing to this outcome were at low risk of bias across most domains although a large proportion of studies were at unclear risk of bias for selective reporting and a high risk of bias due to blinding of participants and personnel. For this essentially objective outcome the committee did not consider the lack of blinding to be particularly impactful. There was also some evidence of inconsistency between the direct and indirect effect estimates (see appendix P for more detail). The committee noted these limitations in the quality of the evidence supporting the NMA when making recommendations.

Subgroup analysis for women with a Bishop score >6

Fewer studies reported on this outcome for this subgroup of women, therefore the data are presented as pairwise comparisons, rather than with NMA – see the relevant forest plots and GRADE tables (appendix E and F).

Economic evidence

Included studies

A systematic review of the economic literature was conducted but no economic studies were identified which were applicable to this review question. The review focused on finding studies which assessed a wide range of induction of labour methods.

See the literature search strategy in appendix B and economic study selection flow chart in appendix G.

Excluded studies

Studies not included in this review with reasons for their exclusions are provided in appendix K.

Summary of studies included in the economic evidence review

See the economic evidence profiles in appendix I.

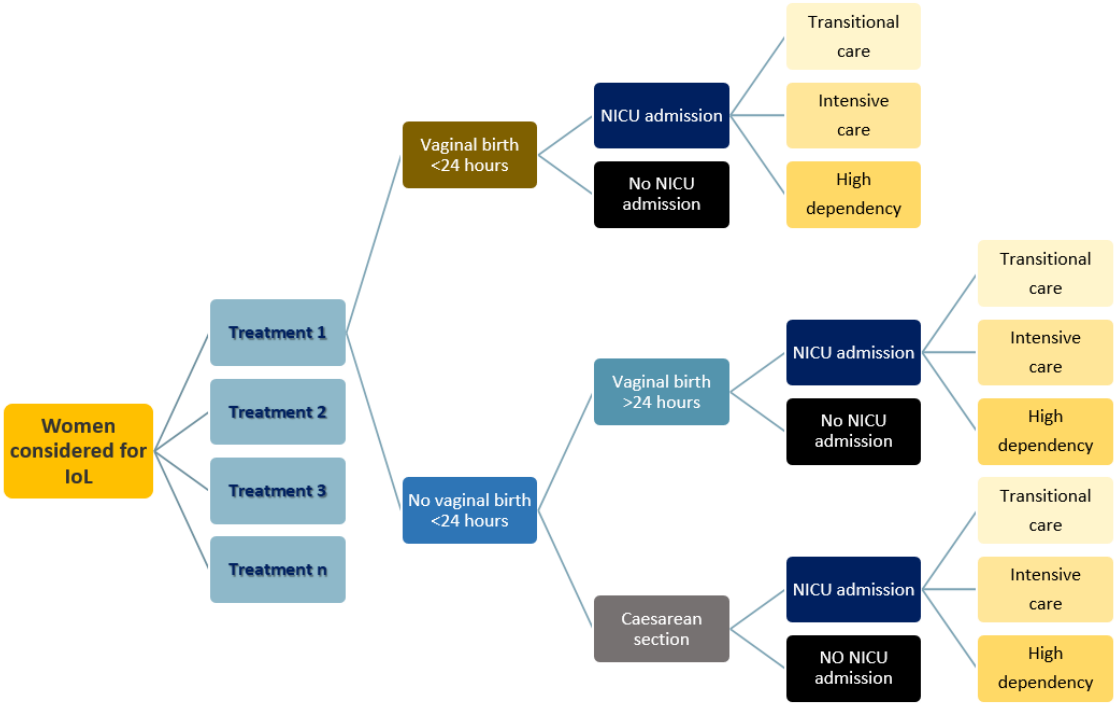
Economic model

A previous health economic analysis produced for a UK HTA Report - UK HTA: Which method is best for the induction? (2016) – was updated to reflect the NMAs undertaken in support of this guideline. The model is summarised below with full details in appendix J.

The model took the form of a cost-utility analysis and evaluated a wide range of induction of labour methods in an NHS setting. The decision analytic framework utilised in the model is shown in Figure 37. The base case analysis focused on a population of all women offered induction of labour for any indication. A subgroup analysis was also undertaken in women with a Bishop score ≤ 6.

Treatment effectiveness data for the 3 model outcomes was based on the NMAs on no vaginal birth within 24 hours, caesarean birth if no vaginal birth within 24 hours and NICU admission. For a NICU admission the probability of different levels of severity were estimated using the same values as used in the UK HTA analysis.

Figure 37: The model decision tree



The model included both treatment costs and those costs associated with mode of birth and NICU admission. This analysis departed from the UK HTA by assigning QALYs to model outcomes, albeit using the same estimates of health state utility as used in the HTA.

All results were generated in the form of probabilistic sensitivity analysis (PSA) which involved repeated Monte Carlo simulation of model inputs from a probability distribution. This was done in order to capture the inherent uncertainty in the model inputs. In each simulation a cost and QALY was calculated for each induction of labour method relative to no treatment. These individual simulation values were then aggregated to determine the incremental net monetary benefit and probability of each method being the most cost-effective. Additional sensitivity analyses were undertaken to reflect that some induction of labour methods are sometimes provided as an outpatient procedure in some settings.

The model results very strongly suggested that induction of labour by some method was cost-effective. However, the evidence did not always strongly favour one particular induction of labour method over the alternatives. The clearest evidence was in support of IV oxytocin plus amniotomy in the whole population analysis. It dominated the alternatives with a 63% probability of being the most cost-effective when all induction of labour was undertaken on an inpatient basis.

For women with a Bishop score ≤ 6 there was considerable uncertainty with respect to the most cost-effective method. For inpatient administration of induction of labour, vaginal PGE_2 pessary (normal release) was top in the cost-effectiveness ranking with a 28% probability of being the most cost-effective. When outpatient administration was considered for some methods, there was some cost-effectiveness evidence to support the use of induction of labour with vaginal PGE_2 as tablet, gel or controlled release pessary.

Evidence statements

Clinical evidence statements

For the outcomes of perinatal death, maternal death and morbidity and maternal satisfaction, and for the subgroup with a Bishop score > 6, there was insufficient data to allow inclusion in the NMA and so pairwise analysis was conducted. See the forest plots in appendix E and GRADE tables in appendix F.

However, due to the large number of comparisons and to aid review of the data the results of pairwise comparisons are summarised below (Table 26 and Table 27).

Blank cells indicate no data were available; NSD means data were available but that no significant differences were found; a green cell indicates a significant difference was found.

Table 26: Pair-wise comparisons for perinatal death, maternal death and morbidity and maternal satisfaction

Comparison	Perinatal death				Maternal death (and morbidity)				Maternal satisfaction
	BS<6	BS>6	Mix/ unclear/ NR	Overall	BS<6	BS>6	Mix/ unclear/ NR	Overall	
Vaginal PGE_2 (tablet) versus placebo		NSD							
Vaginal PGE_2 (tablet) versus vaginal PGE_2 (pessary - slow release)					NSD		NSD	NSD	Satisfaction – favours vaginal PGE_2 pessary (slow release)
Vaginal PGE_2 (tablet) versus intracervical PGE_2	NSD				NSD				
Vaginal PGE_2 (tablet) versus vaginal misoprostol (≥50mcg)	NSD				NSD				
Vaginal PGE_2 (tablet) versus IV oxytocin + amniotomy			NSD						Reaction unfavourable – favours vag PGE_2 Acceptance – favours IVoxy+amnio
Vaginal PGE_2 (tablet) versus Foley catheter	NSD				NSD				
Vaginal PGE_2 (tablet) versus laminaria (dilapan)	NSD								
Vaginal PGE_2 (tablet) versus double balloon									NSD
Vaginal PGE_2 (gel) versus placebo	NSD								
Vaginal PGE_2 (gel) versus vaginal PGE_2 (pessary - slow release)					NSD				Narrative only

Comparison	Perinatal death				Maternal death (and morbidity)				Maternal satisfaction
	BS<6	BS>6	Mix/ unclear/ NR	Overall	BS<6	BS>6	Mix/ unclear/ NR	Overall	
Vaginal PGE_2 (gel) versus intracervical gel	NSD		NSD	NSD	NSD				
Vaginal PGE_2 (gel) versus vaginal misoprostol (<50mcg)	NSD		NSD	NSD	NSD		NSD	NSD	NSD
Vaginal PGE_2 (gel) versus vaginal misoprostol (≥50mcg)					NSD				
Vaginal PGE_2 (gel) versus oral misoprostol (<50mcg)					NSD				
Vaginal PGE_2 (gel) versus oral misoprostol (≥50mcg)			NSD	NSD	NSD		NSD	NSD	NSD
Vaginal PGE_2 (gel) versus titrated oral misoprostol solution	NSD		NSD	NSD	NSD		NSD		Narrative only
Vaginal PGE_2 (gel) versus IV oxytocin			NSD						
Vaginal PGE_2 (gel) versus IV oxytocin + amniotomy			NSD				NSD		
Vaginal PGE_2 (gel) versus oestrogens		NSD							
Vaginal PGE_2 (gel) versus buccal/sublingual misoprostol			NSD						
Vaginal PGE_2 (gel) versus Foley catheter			NSD		NSD		NSD	NSD	Favours Foley catheter
Vaginal PGE_2 (gel) versus nitric oxide									Favours nitric oxide
Vaginal PGE_2 (pessary - slow release) versus placebo	NSD				NSD				
Vaginal PGE_2 (pessary - slow release) versus vaginal misoprostol (<50mcg)	NSD								
Vaginal PGE_2 (pessary - slow release) versus vaginal misoprostol (≥50mcg)	NSD				NSD				

Comparison	Perinatal death				Maternal death (and morbidity)				Maternal satisfaction
	BS<6	BS>6	Mix/ unclear/ NR	Overall	BS<6	BS>6	Mix/ unclear/ NR	Overall	
Vaginal PGE_2 (pessary - slow release) versus titrated oral misoprostol solution	NSD								
Vaginal PGE_2 (pessary - slow release) versus misoprostol insert (sustained release)	NSD				NSD				
Vaginal PGE_2 (pessary - slow release) versus IV oxytocin					NSD				
Vaginal PGE_2 (pessary - slow release) versus Foley catheter	NSD				NSD				NSD
PGF_2 gel versus placebo			NSD						
PGF_2 gel versus IV oxytocin			NSD				NSD		
Intracervical PGE_2 versus no treatment	NSD				NSD				
Intracervical PGE_2 versus placebo	NSD				NSD				
Intracervical PGE_2 versus vaginal PGE_2 (pessary - normal release)	NSD								
Intracervical PGE_2 versus vaginal misoprostol (<50mcg)	NSD				NSD				Narrative only
Intracervical PGE_2 versus vaginal misoprostol (≥50mcg)	NSD				NSD		NSD	NSD	
Intracervical PGE_2 versus oral misoprostol (≥50mcg)	NSD				NSD				
Intracervical PGE_2 versus IV oxytocin	NSD		NSD	NSD					NSD
Intracervical PGE_2 versus IV oxytocin +amniotomy									NSD
Intracervical PGE_2 versus nitric oxide	NSD								
Intracervical PGE_2 versus Foley catheter	NSD								

Comparison	Perinatal death				Maternal death (and morbidity)				Maternal satisfaction
	BS<6	BS>6	Mix/ unclear/ NR	Overall	BS<6	BS>6	Mix/ unclear/ NR	Overall	
Intracervical PGE_2 versus laminaria (dilapan)	NSD				NSD				
Vaginal PGE_2 (pessary - normal release) versus no treatment									NSD
Vaginal PGE_2 (pessary - normal release) versus placebo			NSD						
Vaginal PGE_2 (pessary - normal release) versus titrated oral misoprostol solution	NSD		NSD	NSD	NSD				
Vaginal PGE_2 (pessary - normal release) versus IV oxytocin	NSD								NSD
Vaginal PGE_2 (pessary - normal release) versus IV oxytocin + amniotomy					NSD				
Vaginal PGE_2 (pessary - normal release) versus vaginal misoprostol (≥50mcg)			NSD						
Vaginal PGE_2 (pessary - normal release) versus Foley catheter					NSD				NSD
Vaginal PGE_2 (pessary - normal release) versus extra-amniotic PGE_2/PGF_2			NSD						
Vaginal misoprostol (<50mcg) versus no treatment			NSD						
Vaginal misoprostol (<50mcg) versus placebo					NSD				
Vaginal misoprostol (<50mcg) versus vaginal misoprostol (≥50mcg)	NSD				NSD				Narrative only

Comparison	Perinatal death				Maternal death (and morbidity)				Maternal satisfaction
	BS<6	BS>6	Mix/ unclear/ NR	Overall	BS<6	BS>6	Mix/ unclear/ NR	Overall	
Vaginal misoprostol (<50mcg) versus oral misoprostol (≥50mcg)	NSD		NSD	NSD	NSD		NSD	NSD	NSD
Vaginal misoprostol (<50mcg) versus titrated oral misoprostol solution	NSD				NSD				Narrative only
Vaginal misoprostol (<50mcg) versus Foley catheter	NSD				NSD				NSD
Vaginal misoprostol (<50mcg) versus buccal/sublingual misoprostol	NSD				NSD				Would use again– favours buccal/sublingual Favourable view - NSD Satisfaction – favours vag miso
Vaginal misoprostol (≥50mcg) versus no treatment	NSD		NSD	NSD					
Vaginal misoprostol (≥50mcg) versus oral misoprostol (≥50mcg)	NSD		NSD	NSD	NSD		NSD	NSD	Satisfaction – favours vag miso
Vaginal misoprostol (≥50mcg) versus titrated oral misoprostol solution			NSD				NSD		
Vaginal misoprostol (≥50mcg) versus IV oxytocin	NSD		NSD	NSD	NSD		NSD	NSD	
Vaginal misoprostol (≥50mcg) versus Foley catheter	NSD		NSD	NSD	NSD				Narrative result – favours vag miso
Vaginal misoprostol (≥50mcg) versus extra-amniotic PGE_2/PGF_2			NSD	NSD			NSD		
Vaginal misoprostol (≥50mcg) versus nitric oxide	NSD								Narrative only
Oral misoprostol (<50mcg) versus oral misoprostol (≥50mcg)	NSD				NSD				
Oral misoprostol (<50mcg) versus titrated oral misoprostol solution	NSD				NSD				

Comparison	Perinatal death				Maternal death (and morbidity)				Maternal satisfaction
	BS<6	BS>6	Mix/ unclear/ NR	Overall	BS<6	BS>6	Mix/ unclear/ NR	Overall	
Oral misoprostol (<50mcg) versus Foley catheter	NSD				NSD				Favours oral miso
Oral misoprostol (≥50mcg) versus titrated oral misoprostol					NSD				
Oral misoprostol (≥50mcg) versus buccal/sublingual misoprostol									Narrative only
Oral misoprostol (≥50mcg) versus Foley catheter	NSD				NSD				NSD
Titrated oral misoprostol solution versus extra-amniotic PGE_2/PGF_2			NSD						
Titrated oral misoprostol solution versus IV oxytocin			NSD		NSD				
Titrated oral misoprostol solution versus Foley catheter			NSD				NSD		
Titrated (low dose) oral misoprostol solution versus Sustained release misoprostol insert	NSD								
IV oxytocin versus no treatment	NSD	NSD	NSD	NSD		NSD			
IV oxytocin versus amniotomy			NSD						
IV oxytocin versus mifepristone	NSD				NSD				
IV oxytocin versus IV prostaglandin			NSD				NSD		
IV oxytocin versus oral prostaglandins			NSD						
IV oxytocin versus buccal/sublingual misoprostol						NSD			
IV oxytocin versus Foley catheter			NSD						
IV oxytocin + amniotomy versus no treatment		NSD	NSD	NSD		NSD			

Comparison	Perinatal death				Maternal death (and morbidity)				Maternal satisfaction
	BS<6	BS>6	Mix/ unclear/ NR	Overall	BS<6	BS>6	Mix/ unclear/ NR	Overall	
IV oxytocin + amniotomy versus oral prostaglandins			NSD						
IV oxytocin + amniotomy versus IV oxytocin			NSD						
IV oxytocin + amniotomy versus amniotomy		NSD							Satisfaction with IOL process – favours IV oxy+amniotomy
IV oxytocin + amniotomy versus Foley catheter					NSD				
Oral prostaglandins versus no treatment			NSD						
Foley catheter versus no treatment			NSD						
Foley catheter versus double balloon catheter									NSD
Foley catheter versus extra-amniotic PGE_2/PGF_2	NSD				NSD				
Foley catheter versus hyaluronidase									NSD
Laminaria (dilapan) versus no treatment	NSD								
Nitric oxide versus placebo	NSD				NSD				Would have again – favours placebo
Mifepristone versus placebo	NSD				NSD				
Relaxin versus placebo	NSD	NSD		NSD					

Table 27: Pairwise comparisons for subgroup with a Bishop score >6

Comparison	No VD in 24 hours	Hyperstimulation with FHR changes	Caesarean birth	Instrumental birth	NICU admission	Epidural
Vaginal PGE_2 (tablet) versus placebo		NSD	NSD			
Vaginal PGE_2 (gel) versus amniotomy			NSD		NSD	NSD
Vaginal PGE_2 (gel) versus IV oxytocin +amniotomy			NSD			

Comparison	No VD in 24 hours	Hyperstimulation with FHR changes	Caesarean birth	Instrumental birth	NICU admission	Epidural
Vaginal PGE_2 (gel) versus oestrogens for			NSD			NSD
Intracervical PGE_2 versus vaginal misoprostol (≥50mcg)		NSD	NSD			
Intracervical PGE_2 versus IV oxytocin +amniotomy			NSD	NSD		
Vaginal PGE_2 (pessary - normal release) versus IV oxytocin			NSD	NSD		
Vaginal misoprostol (<50mcg) versus IV oxytocin		NSD	Favours vag miso			
Vaginal misoprostol (≥50mcg) versus IV oxytocin			Favours vag miso	NSD		
Oral misoprostol (≥50mcg) versus IV oxytocin	NSD	Favours IV oxytocin	NSD	NSD	NSD	
Amniotomy versus no treatment			Favours no treatment			
Amniotomy versus IV oxytocin +amniotomy		NSD	NSD	NSD	NSD	NSD
Amniotomy versus Foley catheter			NSD			
Amniotomy versus laminaria (dilapan)			NSD			
IV oxytocin +amniotomy versus no			NSD		NSD	
IV oxytocin +amniotomy versus oral prostaglandins		NSD	NSD	NSD		
IV oxytocin +amniotomy versus buccal/sublingual	NSD		NSD	NSD	NSD	
IV oxytocin versus amniotomy			NSD			
IV oxytocin versus no treatment			NSD	NSD	NSD	
IV oxytocin versus IV oxytocin +amniotomy			NSD	NSD		NSD
IV oxytocin versus	NSD		NSD			

Comparison	No VD in 24 hours	Hyperstimulation with FHR changes	Caesarean birth	Instrumental birth	NICU admission	Epidural
buccal/sublingual misoprostol						
IV oxytocin versus Foley catheter			NSD			
IV oxytocin versus laminaria (dilapan)			NSD			
Foley catheter versus no treatment			NSD			
Foley catheter versus laminaria (dilapan)			NSD			
Relaxin versus placebo		NSD	NSD	NSD		NSD
Laminaria (dilapan) versus no treatment			NSD			
Corticosteroids versus no treatment			NSD			
Corticosteroids versus placebo		NSD	NSD			

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

The committee identified 9 outcomes for this evidence review. The three critical outcomes were: no vaginal birth within 24 hours, caesarean birth and uterine hyperstimulation with fetal heart rate changes. The main aim of induction of labour is to achieve a vaginal birth, without adverse effects for the woman or her baby, therefore the outcomes relating to mode of birth (no vaginal birth within 24 hours and caesarean birth) were deemed critical. While the 24 hour limit may appear artificial, the committee agreed that this is a well-established outcome measure for assessing efficacy when inducing labour, and would provide a good indication of the relative efficacy of different methods. A recognised complication of induction of labour is the risk of uterine hyperstimulation, which may cause adverse effects in the baby (first seen as fetal heart rate changes). Therefore, this was felt to give important information about the safety of induction, and was also deemed to be a critical outcome.

Six further outcomes were included in this review, and these were identified as important. These included serious maternal morbidity or maternal death, and perinatal death. Although the committee recognised the great importance of these outcomes, they were aware that data on these were likely to be sparse, and unlikely to inform decision-making in a meaningful way, therefore they considered them important rather than critical outcomes. Instrumental birth, admission to NICU and use of epidural were also viewed as important outcomes. Finally, maternal satisfaction was considered as an important outcome – the committee were aware that the data identified for this outcome may be sparse and so was less likely to inform decision-making, despite it being of great importance.

The quality of the evidence

The trials included for this evidence review were individually assessed using the Cochrane risk of bias tool, and the summarised quality of the evidence for each of the NMAs is

presented in the evidence review. Overall, the majority of domains were rated as at low risk, or unclear risk of bias. The main area where trials were at risk of bias was due to a lack of blinding – a large number of included studies did not blind participants and personnel to the allocated interventions, therefore this may affect subjective outcomes in the different groups. Many trials were assessed as being at unclear risk of bias for the domain regarding selective reporting. Predominantly this was because the authors had not published the trial protocol in advance, therefore it was impossible to ascertain whether all outcomes had been correctly reported in the publication.

The data presented using pairwise analysis (maternal morbidity/mortality, perinatal mortality, maternal satisfaction and all outcomes for the subgroup of women with a Bishop score >6) were assessed using the GRADE method. The majority of comparisons were assessed as very low to low quality, predominantly due to a high or unclear risk of bias in the conduct of the studies, and imprecision in the estimates. This was largely related to a sparsity of data – either few women were included in the trials, or the outcome was rare (such as maternal death), leading to great uncertainty in the results.

The inconsistency checks (see appendix P for more information) highlighted more inconsistency than would be expected by chance alone for a number of the outcomes including vaginal birth, NICU admission and caesarean birth. For vaginal birth, not only was there inconsistency between the direct and indirect evidence in the comparison between vaginal PGE_2 gel and nitric oxide but the direction of the treatment effect also differed. In the NMA for NICU admissions treatment differences based on direct evidence only were poorly estimated for comparisons involving either nitric oxide or amniotomy. For the caesarean birth outcome, the direct and indirect evidence did not agree for comparisons involving hyaluronidase with placebo and Foley catheter. Also, there was little direct evidence in the network for estimating the effect sizes for IV prostaglandin. The committee noted that this inconsistency reflects some limitations in the data supporting the model, possibly due to the number of arms with zero events for some outcomes or to variability in the ways that studies were conducted or reported. The committee took these limitations into account in their decision making and noted that the true uncertainty in the NMA is likely to be greater than the credible intervals suggest.

The committee discussed the results of the threshold analysis which provided further information on the NMA. The results of the threshold analysis suggested that the committee's decision making was broadly robust to trial level threshold analysis, which suggested that the recommendations made by the committee were not overly dependent on individual trials. The committee noted the uncertainty and heterogeneity around the hyperstimulation evidence, although the general direction of evidence supporting mechanical options as being less likely to cause hyperstimulation was in line with their clinical experience. While IV oxytocin and amniotomy was the intervention most likely to be included in the recommendations based on the hyperstimulation threshold analysis, this was predominantly due to the very wide 95% CrIs for that intervention specifically. The committee noted that threshold analyses are limited in situations such as this where the evidence is relatively heterogeneous and there are multiple outcomes being considered simultaneously. The committee agreed that the threshold analysis did not warrant changing the specific treatments recommended.

Benefits and harms

The committee noted that a number of the interventions reviewed are not licensed for use in induction of labour and that the only preparations currently approved in the UK for this indication are misoprostol 25 microgram tablets and dinoprostone (prostaglandin E_2) vaginal tablets, vaginal gel, controlled release vaginal delivery system, IV infusion and extra-amniotic solution.

The committee discussed the main aim of induction of labour – to promote vaginal birth as safely as possible – and the committee therefore focused primarily on the outcome of no vaginal birth within 24 hours, but also balanced this with the evidence for hyperstimulation as this is one of the main concerns when inducing labour. Much of the data for the other outcomes did not provide much clear evidence of benefit or harm on which the committee could base decisions. For example, there were few clear differences between placebo and any of the interventions for the outcomes of caesarean birth, instrumental birth, NICU admission, use of epidural, maternal mortality or serious morbidity, perinatal mortality, or maternal satisfaction (in either the whole population or the subgroups with higher or lower Bishop score).

The committee discussed the importance of assessing a woman's cervix prior to induction of labour. The cervix undergoes changes throughout the later stages of pregnancy - becoming shorter, softer, and starting to open, prior to the onset of labour. This state of "readiness" for labour is assessed using the Bishop score, with a higher score indicating a cervix that is more ready for the labour to progress. The committee knew from their experience that the Bishop score at the start of induction influences the methods which may be suitable. For example, women with a higher Bishop score (>6) are likely have a shorter labour, and more likely to have a vaginal birth within 24 hours, than those women with a lower Bishop score (≤6); women with a lower Bishop score are more likely to require a preparation to soften and shorten the cervix, and some methods of induction of labour are only feasible when the cervix has reached a given stage of readiness. For example, it is not possible to perform an amniotomy (break the waters) until the cervix has opened sufficiently.

The committee agreed that the cervical readiness is something that is not often discussed with the woman, but that it was of great importance in understanding the process of induction and the choice of methods. They therefore highlighted this in a recommendation.

The committee then focused initially on women with a low Bishop score (≤6). They noted that these women comprised the majority of the population in all the trials, and that this was also the case in obstetric practice – that most women attending for induction of labour were noted to have a low Bishop score.

It was noted that all methods of induction of labour appeared to promote vaginal birth within 24 hours, as compared to placebo. The only methods where this was less clear were mifepristone and extra-amniotic prostaglandins – for these interventions the 95% CrI crossed 1, therefore they were not considered to be effective methods for induction of labour.

A number of preparations of prostaglandins had been included in the review, and for the outcome of no vaginal birth in 24 hours, vaginal dinoprostone (PGE_2) preparations all showed efficacy over placebo, in the population of all women and in the subgroup of women with a Bishop score ≤ 6. The three preparations of vaginal dinoprostone (PGE_2) which are currently available in the UK (controlled release vaginal delivery system, tablet and gel) were all shown to significantly reduce the number of women who did not have a vaginal birth within 24 hours, as compared to placebo. None of these treatments were shown to cause a significant increase in the rate of caesarean births or instrumental births, when compared to placebo. When compared to each other in the NMA, there was no evidence to support the use of one of the preparations of vaginal dinoprostone (PGE_2) over another. The committee therefore recommended that any of the available dinoprostone (PGE_2) preparations should be offered for induction of labour in women with a Bishop score ≤6, and agreed that it was reasonable to offer a choice of these three treatments, depending on the preference of the woman, the availability of the different preparations, and following a discussion with the woman of the possible risks associated with pharmacological methods of induction. The committee also noted that if hyperstimulation did occur, some of these preparations could be easily removed – for example the controlled release vaginal delivery system had a string attached so it could be removed – but other preparations such as the gel could not be

removed. The committee agreed that this may need to be taken into consideration when choosing a dinoprostone (PGE_2) preparation to use.

The effect on hyperstimulation with fetal heart rate changes was very unclear for most interventions, with wide 95% CrIs. The committee noted that hyperstimulation may be increased with vaginal dinosprostone (PGE_2) preparations, as compared to placebo – this increase was significant for the vaginal gel and normal and slow release pessaries. There was more uncertainty with vaginal dinoprostone (PGE_2) tablet, as the 95% CrI crossed 1, but was also very wide (2.72 [95% CrI 0.93, 8.30]). However, when compared to each other in the NMA, there was no evidence that one preparation of vaginal dinoprostone ($PGE_{2)}$ was safer than the others. The committee therefore made a recommendation that the risks of hyperstimulation should be discussed with women when using dinoprostone (PGE_2) preparations, and also made a recommendation that the manufacturer's recommendations must be followed as they specify maximum doses that can be used, monitoring required, and when administration should be discontinued.

For the overall population there was little difference in any of the interventions when compared to placebo in the rate of caesarean birth or instrumental birth, although for the subgroup with a Bishop score ≤6 some of the dinoprostone (PGE_2) preparations did show a lower rate of caesarean birth than placebo, although with many the 95% CrI crossed 1.

There appeared to be a trend towards increasing neonatal unit admission with all vaginal dinoprostone (PGE_2) preparations. However, there was great uncertainty in the effect, and this increase did not reach statistical significance.

There was no evidence that any vaginal dinoprostone (PGE_2) preparations affected the rate of epidural use when compared to placebo, or compared to each other. Similarly, the evidence for maternal morbidity/mortality and perinatal mortality did not show a significant increase in serious adverse effects/mortality with any of these preparations. Moderate quality evidence from a single trial showed that maternal satisfaction was higher for those receiving vaginal dinoprostone (PGE_2) slow release pessary, rather than vaginal dinoprostone (PGE_2) tablet. However, no other trials directly comparing the different vaginal dinoprostone (PGE_2) preparations reported on maternal satisfaction.

Misoprostol preparations were also effective for the outcome of no vaginal birth within 24 hours, in the whole population and in women with a Bishop score ≤6. The committee were aware that the misoprostol vaginal insert preparation of misoprostol had recently been discontinued by the manufacturer, but in its place a misoprostol 25 microgram oral tablet had recently been approved for use in induction of labour in the UK. However, the evidence showed that some preparations of misoprostol significantly increased hyperstimulation with fetal heart rate changes, as compared to placebo, although for the oral lower dose preparations the 95% CrI crossed 1 showing uncertainty around this effect, and the rate of hyperstimulation was lower than that seen with some of the dinoprostone preparations. The committee discussed some manufacturer and MHRA warnings that had been issued relating to the risk of hyperstimulation with misoprostol, and the fact that this hyperstimulation may be resistant to tocolysis. However, the committee noted that these warnings had been based on the now discontinued misoprostol vaginal insert and so may not be applicable to the use of lower dose oral preparations. However, the committee agreed that women should be advised of this potential risk and included this in a recommendation, as well as a recommendation to follow the manufacturer's guidance as this provides important information on contraindications, monitoring requirements, maximum doses and discontinuation. The committee agreed that misoprostol 25 microgram oral tablets should be recommended as an alternative to the dinoprostone preparations. The committee also agreed that misoprostol may be chosen by women who preferred an oral preparation, as all the recommended forms of dinoprostone were administered vaginally.

The committee were aware that some women have a higher risk of developing hyperstimulation – this may include women with grand multiparity, or women who previously had a very rapid labour and birth. In women who had had a previous caesarean birth, hyperstimulation may also increase the risk of uterine rupture. They therefore considered the evidence for the mechanical methods of induction that had the lowest chance of causing hyperstimulation – including single and double balloon catheters and osmotic cervical dilators. The osmotic cervical dilators include two different types of dilators: laminaria tents which are natural products made from dehydrated seaweed that absorb water and expand when inserted into the cervix, and synthetic osmotic dilators, which are polymers that also absorb fluid and also expand to dilate the cervix. In the analysis these two types of osmotic dilators had been grouped together, as the committee agreed that they worked in a similar fashion and the mechanical effects from both would lead to similar outcomes.

The balloon catheters were also shown to have considerable efficacy at promoting vaginal birth within 24 hours, no significant effect on the need for caesarean or instrumental birth, no significant effect on NICU admission or epidural use. The committee therefore agreed that these interventions could be considered as safe and effective to use for induction of labour in those women who are at increased risk of developing hyperstimulation, or who chose a mechanical method rather than a pharmacological method.

The committee noted that most of the studies of balloon catheters used the catheter on its own (68 studies), while some (9 studies) used balloons in combination with extra-amniotic saline infusion (EASI). In the analysis these studies had been grouped together. To check that the beneficial effects seen with this intervention were due primarily to the balloon alone, and were not biased by the small number of studies that used EASI, the committee asked for a post-hoc analysis to be done, to separate the data for these two sets of studies. This was carried out (see appendix M) and showed, for the two outcomes for which enough data was available (caesarean birth and instrumental birth) that there was no difference in the results when all the studies were analysed together, or when the studies that used EASI were removed from the analysis.

For the osmotic cervical dilators however, there was no evidence on how effective these interventions were at promoting vaginal birth, as ‘no vaginal birth within 24 hours’ had not been reported as an outome in the included studies. They had no significant effect on the need for caesarean birth, instrumental birth or need for epidural but they ranked poorly in terms of NICU admission (although the 95% CrIs were wide for this outcome). The committee were aware that there are a number of ongoing studies for synthetic osmotic cervical dilators, and stakeholder feedback at consultation indicated that based on positive results in studies, they were already being used increasingly in the NHS. The committee therefore agreed to recommend them as an alternative to balloons as a mechanical method of induction.

When considering women with a higher Bishop score (>6), the evidence was much more sparse. Few trials had been conducted specifically in this subpopulation of women, and many trials specifically excluded women with a higher Bishop score. The committee noted that the analysis of the whole population showed IV oxytocin and amniotomy to be the most effective intervention at promoting vaginal birth within 24 hours, but they knew from their clinical experience that this intervention was really only feasible when the cervix was sufficiently dilated to allow an amniotomy to be performed. In clinical practice, the experience of the committee members was that this method was widely used for induction, for women who present with a Bishop score >6, or when pharmacological or mechanical methods have already been used to prepare and open the cervix. In the overall analysis, IV oxytocin and amniotomy did not show a significant increase in the risk of caesarean birth or instrumental birth. In keeping with other pharmacological methods, there was a trend towards an increase in NICU admission and hyperstimulation with fetal heart rate changes, but this effect was not significantly increased when compared to other pharmacological methods. There was no

evidence that the rate of epidural use was affected by this intervention. Therefore, the committee agreed that IV oxytocin plus amniotomy was a suitable method for induction of labour in women with a Bishop score >6. The committee were aware that although the evidence showed it was the combination of amniotomy and IV oxytocin that was effective, women often asked if they could have the amniotomy first, and wait to see if labour started spontaneously, before the oxytocin infusion was started. This was therefore added into a supplementary recommendation, with the caveat that women should be warned that labour may take longer, and that prolonged rupture of the membranes could lead to an increased risk of neonatle infection

Cost effectiveness and resource use

A health economic model was developed for this guideline which compared the cost-effectiveness of a large number of pharmacological and mechanical methods for the induction of labour. Whilst the model provides very strong evidence that induction of labour is cost-effective in general compared with no treatment, the conclusions from the economic analysis with respect to individual methods were frequently not clear cut and did not provide evidence to support recommendations that would lead to substantial changes in current practice.

The strongest economic evidence was found for the use of IV oxytocin and amniotomy alone where it had a 63% probability of being the most cost-effective treatment if compared to all methods being administered in an inpatient setting. Whilst, this was in a whole population analysis this intervention did not figure in the subgroup analysis as it is not considered an appropriate treatment in women with a Bishop score ≤6. Therefore, the committee considered that there was good supporting economic evidence to justify a strong recommendation to offer induction of labour with amniotomy and an intravenous oxytocin infusion in women with a Bishop score >6. The use of IV oxytocin and amniotomy alone in women with a Bishop score >6 should standardise care, and may result in a small cost saving, by avoiding the use of vaginal prostaglandins in these women.

There was some cost-effectiveness evidence to support the use of vaginal dinoprostone (PGE_2) preparations especially in the context of outpatient administration, where the probability that either gel, controlled release vaginal delivery system or tablet was most cost-effective reached 70%. Therefore, the committee thought it reasonable to make a recommendation to offer induction of labour with vaginal dinoprostone (PGE_2) as tablet, gel or controlled release vaginal delivery system. The recommendations broadly support current practice in women with a Bishop score ≤6. The majority of hospitals currently use vaginal dinoprostone (PGE_2) preparations for the induction of labour in line with the recommendations of the previous NICE guideline, therefore this recommendation should not impact adversely on resource use.

There was some but more limited cost-effectiveness evidence to support the use of mechanical methods, with a 21% probability that either Foley or double balloon/Cook's catheter would be cost-effective in women with a Bishop score ≤6 if administered in an outpatient setting, and therefore the committee felt it appropriate to only make a weak recommendation with respect to their use.

The model also provided some evidence for the cost-effectiveness of misoprostol use, especially in the context of induction only offered in an inpatient setting, and the committee recommended the newly licensed low dose (25 microgram) oral misoprostol tablets as an option to induce labour in women with a Bishop score ≤6. The committee had concerns with respect to uterine hyperstimulation in high dose misoprostol, an outcome which was not included explicity in the economic analysis as it was thought that the costs and harms would largely be captured in other outcomes.

Other factors the committee took into account

The committee reviewed the list from the previous guideline of methods that are not recommended for the induction of labour, and agreed that the list should reflect preparations that are not available in the UK, are not licensed for the induction of labour, or those which are available but for which there was not good evidence of effectiveness. The committee were aware that oral and intracervical prostaglandins, hyaluronidase, vaginal PGF_2 gel, corticosteroids, oestrogen, relaxin, mifepristone and nitric oxide donors were not available or not licesnsed. They also agreed that intravenous oxytocin alone, and extra-amniotic or intravenous dinospprostone did not show a favourable results and so would not be used routinely in clinical practice.

The committee reviewed the recommendations from the previous guideline on membrane-sweeping which is a procedure often used at term to encourage labour to begin, prior to a more formal method of induction of labour. The committee made some minor amendments to the wording of these recommendations so they reflected current practice and also added a new recommendation on consent. They were aware that as membrane sweeping may be regarded as part of a vaginal examination in late pregnancy, it was not always discussed with the woman and her consent obtained. However, based on their knowledge and experience of consent procedures and the fact that some women may not want a membrane sweep, the committee agreed that consent should be obtained before performing membrane sweeping and that this should be made clear in the recommendations.

Recommendations supported by this evidence review

This evidence review supports recommendations 1.3.4 to 1.3.10 in the NICE guideline.

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Main references are in bold, followed by additional references to the same trial.

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Appendices

Appendix A – Review protocol

Review protocol for review question: What are the benefits and harms of pharmacological and mechanical methods in induction of labour?

Table 28: Review protocol for pharmacological and mechanical methods to induce labour

Field (based on PRISMA-P)	Content
Review question	What are the benefits and harms of pharmacological and mechanical methods in induction of labour?
Type of review question	Intervention review
Objective of the review	The aim of the review is to compare the effectiveness and safety of different methods of induction of labour for pregnant women (and their infants). Induction of labour is a relatively common intervention, offered to women with prolonged pregnancy, or a variety of other maternal/fetal indications to expedite birth. Many different methods may be employed to induce labour, and it is unclear which of these provides the safest, yet most effective way to induce labour.
Eligibility criteria – population/disease/condition/issue/domain	Pregnant women offered induction of labour for any indication ○ include women in the third trimester (≥28 weeks + 0 days) ○ include women with viable fetus only
Eligibility criteria – intervention(s)/exposure(s)/prognostic factor(s)	Any method used for induction of labour **Pharmacological methods** *1. Prostaglandins:* a) Vaginal and intracervical administration - Dinoprostone (PGE2) vaginal tablets (lactose based) - Dinoprostone (PGE2) vaginal pessaries normal release (sometimes referred to as suppositories, manufactured using various base materials including wax and glycerine)

Field (based on PRISMA-P)	Content
	- Dinoprostone (PGE2) vaginal pessaries sustained release (10-12mg pessaries, single application) - Dinoprostone (PGE2) gel, introduced via vaginal applicator - Dinoprostone (PGE2) for intracervical administration - PGF2 gel b) Extra-amniotic administration c) Intravenous administration d) Oral administration 2. *Misoprostol* - vaginal misoprostol (dose < 50 microgram) - vaginal misoprostol (dose ≥ 50 microgram) - oral misoprostol tablet (dose < 50 microgram) - oral misoprostol tablet (dose ≥ 50 microgram) - titrated (low-dose) oral misoprostol solution - sustained-release misoprostol insert - buccal/sublingual misoprostol 3. *Oxytocin* - IV oxytocin alone - IV oxytocin with amniotomy 4. *Nitric oxide donors* 5. *Mifepristone* 6. *Oestrogens*

Field (based on PRISMA-P)	Content
	7. Corticosteroids *8. Relaxin* *9. Hyaluronidase* **Mechanical methods** *10. Foley catheters* *11. Osmotic cervical dilators (also known as laminaria and dilapan)* *12. Double balloon or Cook's catheter* *13. Amniotomy* **The interventions below will only be included if they act as the sole connectors of the interventions of interest in the network:** ***Mechanical methods:*** - *Membrane sweep* - *Breast stimulation* - *Sexual intercourse* ***Complementary and alternative methods*** - *Castor oil* - *Acupuncture* - *Homeopathy* - *Hot baths* - *Enemas* - *Herbal supplements*

Field (based on PRISMA-P)	Content
	- Active interventions that are not part of the decision problem will not be considered in the analysis, unless they act as the sole connectors of the interventions of interest in the network.
Eligibility criteria – comparator(s)/control or reference (gold) standard	No treatment Placebo Any intervention (in the above list) compared to any other intervention
Outcomes and prioritisation	**Critical outcomes:** ○ Vaginal birth not achieved within 24 hours ○ Uterine hyperstimulation with fetal heart rate changes ○ Caesarean birth **Important outcomes:** ○ Serious neonatal morbidity or perinatal death ○ Serious maternal morbidity or death ○ Maternal satisfaction ○ Instrumental birth ○ NICU admission ○ Use of epidural
Eligibility criteria – study design	Randomised controlled trials Systematic reviews of randomised controlled trials *(If network meta-analysis is not feasible for a specific outcome then systematic reviews of RCTs will also be considered for inclusion in any pairwise analyses)*
Other inclusion exclusion criteria	Include English language papers only Exclude trials where all women had a previous caesarean birth

Field (based on PRISMA-P)	Content
	Exclude trials where all women had ruptured membranes - trials that included a mixed population of women will be included providing at least 2/3 of the population had intact membranes and no previous caesarean birth.
Proposed sensitivity/sub-group analysis, or meta-regression	If sufficient evidence is available the following subgroup analysis will be conducted: - Favourable cervix (Bishop score >6) - Unfavourable cervix (Bishop score ≤6) Sensitivity analysis will also be conducted to exclude trials where <100% of women had intact membranes and no previous caesarean birth.
Selection process – duplicate screening/selection/analysis	Dual sifting will be performed on at least 10% of records. Agreement for inclusion will be achieved through resolving disagreements via discussion and consultation with senior staff.
Data management (software)	For NMA: data will be entered into excel spreadsheets. WinBUGS will be used to fit NMA and unrelated mean effects models. The gemtc package in R will be used to run node splitting analyses. Threshold analysis will be conducted in R. For outcomes with insufficient data for NMA: Pairwise meta-analyses will be undertaken where possible; these will be performed using Cochrane Review Manager (RevMan). GRADE will be used to assess the quality of evidence for each outcome. STAR will be used for bibliographies/citations, study sifting, data extraction and critical appraisal.

Field (based on PRISMA-P)	Content
Information sources – databases and dates	Sources to be searched: Medline, Medline In-Process, CCTR, CDSR, DARE, HTA and Embase. Limits (e.g. date, study design): Study design will be limited to RCTs. Standard animal/non-English language filters will be applied. Date will be limited to 2014 onwards. Additional trials published prior to this date limit will be identified from the existing NMA and included if they meet the inclusion criteria for this protocol (Alfirevic 2016). Supplementary search techniques: No supplementary search techniques will be used. See appendix B for full strategies. Key papers: Which method is best for the induction of labour? A systematic review, network meta-analysis and cost-effectiveness analysis Zarko Alfirevic, Edna Keeney, Therese Dowswell, Nicky J Welton, Nancy Medley, Sofia Dias, Leanne V Jones, Gillian Gyte and Deborah M Caldwell. Health Technology Assessment 2016 Volume 20 No. 65
Identify if an update	Yes, this is an update. Previously this review was addressed as two separate review questions pertaining to pharmacological and mechanical methods of induction of labour.
Author contacts	Developer: National Guideline Alliance

Field (based on PRISMA-P)	Content
Highlight if amendment to previous protocol	The protocol has been amended to align outcomes with standard outcome reporting suggested by the Cochrane Pregnancy and Childbirth Group. Additional outcomes (NICU admission) were identified from a recently published NMA on the induction of labour, which will be updated as part of this review. Epidural anaesthesia was added by the GC as an important outcome.
Search strategy – for one database	For details please see appendix B.
Data collection process – forms/duplicate	A standardised evidence table format will be used, and published as appendix D (clinical evidence tables) or H (economic evidence tables).
Data items – define all variables to be collected	For details please see evidence tables in appendix D (clinical evidence tables) or H (economic evidence tables).
Methods for assessing bias at outcome/study level	Study quality will be assessed using the Cochrane Risk of Bias tool. Threshold analysis will be performed for outcomes included in the NMA which are identified as directly influencing the recommendations/HE model. This will estimate thresholds for how large the potential bias adjustments would need to be within studies and contrasts before they would change the recommendations. For any outcomes where there is insufficient data for NMA, the risk of bias across all available evidence will be evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/
Criteria for quantitative synthesis	For details please see section 6.4 of Developing NICE guidelines: the manual For NMA, studies which report 0 or 100% events in both arms will not be included. In addition, a NMA can only be conducted when there is evidence on at least 3 treatments connected in a network. To conduct inconsistency checks in a network, there must be at least one closed loops of direct evidence on 3 treatments that is informed by at least 3 independent sources of evidence.
Methods for quantitative analysis – combining studies and exploring (in)consistency	○ Network meta-analysis will be conducted within a Bayesian framework using WinBUGS (TSU Bristol Unit).

Field (based on PRISMA-P)	Content
	○ The exact model structure will be agreed with the NICE Technical Support Unit (TSU) following the review of available clinical evidence. Fixed and random effects NMA models will be fitted to the data and compared based on the posterior mean residual deviance and DIC. The model with the best fit and meaningfully lower DIC will be selected. Differences of at least 3 will be considered meaningful. ○ Posterior median ORs and 95% credible intervals (CrIs) will be used to report the results ○ Ranking of treatments will be provided (posterior median ranks and 95% CrIs, rankograms, probability being best). ○ Inconsistency checks will be conducted by comparing the posterior mean residual deviance, DIC, and where appropriate (random effects models), posterior median between study standard deviation, of the base case NMA model and unrelated mean effects (UME) model. Further checks will be conducted using node splitting analysis. Pairwise estimates will be obtained from the UME model the aid comparison of the direct estimates with the NMA estimates. For outcomes where NMA cannot be conducted, standard pairwise meta-analysis will be conducted using Cochrane Review Manager.
Meta-bias assessment – publication bias, selective reporting bias	For details please see section 6.2 of Developing NICE guidelines: the manual.
Confidence in cumulative evidence	For details please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual
Rationale/context – what is known	For details please see the introduction to the evidence review in the full guideline.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the guideline. The committee was convened by the NGA and chaired by Sarah Fishburn in line with section 3 of Developing NICE guidelines: the manual. Staff from the NGA undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the guideline in collaboration with the committee. For details please see the methods chapter.
Sources of funding/support	The NGA is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists
Name of sponsor	The NGA is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists

Field (based on PRISMA-P)	Content
Roles of sponsor	NICE funds the NGA to develop guidelines for those working in the NHS, public health, and social care in England
PROSPERO registration number	Not registered with PROSPERO

CDSR: Cochrane Database of Systematic Reviews; CENTRAL: Cochrane Central Register of Controlled Trials; CrI credible interval; CS caesarean section; DARE: Database of Abstracts of Reviews of Effects; DIC deviance information criterion; GRADE: Grading of Recommendations Assessment, Development and Evaluation; HTA: Health Technology Assessment; MID: minimally important difference; NGA: National Guideline Alliance; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; NICU neonatal intensive care unit; NMA network meta-analysis; RCT: randomised controlled trial; RoB: risk of bias; SD: standard deviation; TSU Technical Support Unit

Appendix B – Literature search strategies

Search strategies for review question: What are the benefits and harms of pharmacological and mechanical methods in induction of labour?

Review question search strategies

Databases: Medline; Medline EPub Ahead of Print; and Medline In-Process & Other Non-Indexed Citations

Date of last search: 13/05/2020

#	Searches
1	META-ANALYSIS/
2	META-ANALYSIS AS TOPIC/
3	(meta analy* or metanaly* or metaanaly*).ti,ab.
4	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
5	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
6	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
7	(search* adj4 literature).ab.
8	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
9	cochrane.jw.
10	or/1-9
11	randomized controlled trial.pt.
12	controlled clinical trial.pt.
13	pragmatic clinical trial.pt.
14	randomi#ed.ab.
15	placebo.ab.
16	randomly.ab.
17	CLINICAL TRIALS AS TOPIC/
18	trial.ti.
19	or/11-18
20	LABOR, INDUCED/
21	(labo?r adj5 induc$).ti,ab.
22	CERVICAL RIPENING/
23	(cervi$ adj3 ripen$).ti,ab.
24	((unfavo?rabl$ or un-favo?abl$ or unripe$ or un-ripe$) adj3 cervi$).ti,ab.
25	((bishop$ or cerv$) adj3 scor$).ti,ab.
26	or/20-25
27	limit 26 to english language
28	LETTER/
29	EDITORIAL/
30	NEWS/
31	exp HISTORICAL ARTICLE/
32	ANECDOTES AS TOPIC/
33	COMMENT/
34	CASE REPORT/
35	(letter or comment*).ti.
36	or/28-35
37	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
38	36 not 37
39	ANIMALS/ not HUMANS/
40	exp ANIMALS, LABORATORY/
41	exp ANIMAL EXPERIMENTATION/
42	exp MODELS, ANIMAL/
43	exp RODENTIA/
44	(rat or rats or mouse or mice).ti.
45	or/38-44
46	27 not 45

#	Searches
47	10 and 46
48	19 and 46
49	or/47-48
50	(2014$ or 2015$ or 2016$ or 2017$ or 2018$ or 2019$ or 2020$).ed,yr.
51	49 and 50

Databases: Embase; and Embase Classic

Date of last search: 13/05/2020

#	Searches
1	SYSTEMATIC REVIEW/
2	META-ANALYSIS/
3	(meta analy* or metanaly* or metaanaly*).ti,ab.
4	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
5	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
6	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
7	(search* adj4 literature).ab.
8	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
9	((pool* or combined) adj2 (data or trials or studies or results)).ab.
10	cochrane.jw.
11	or/1-10
12	random*.ti,ab.
13	factorial*.ti,ab.
14	(crossover* or cross over*).ti,ab.
15	((doubl* or singl*) adj blind*).ti,ab.
16	(assign* or allocat* or volunteer* or placebo*).ti,ab.
17	CROSSOVER PROCEDURE/
18	SINGLE BLIND PROCEDURE/
19	RANDOMIZED CONTROLLED TRIAL/
20	DOUBLE BLIND PROCEDURE/
21	or/12-20
22	LABOR INDUCTION/
23	(labo?r adj5 induc$).ti,ab.
24	UTERINE CERVIX RIPENING/
25	(cervi$ adj3 ripen$).ti,ab.
26	((unfavo?rabl$ or un-favo?abl$ or unripe$ or un-ripe$) adj3 cervi$).ti,ab.
27	((bishop$ or cerv$) adj3 scor$).ti,ab.
28	or/22-27
29	limit 28 to english language
30	letter.pt. or LETTER/
31	note.pt.
32	editorial.pt.
33	CASE REPORT/ or CASE STUDY/
34	(letter or comment*).ti.
35	or/30-34
36	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
37	35 not 36
38	ANIMAL/ not HUMAN/
39	NONHUMAN/
40	exp ANIMAL EXPERIMENT/
41	exp EXPERIMENTAL ANIMAL/
42	ANIMAL MODEL/
43	exp RODENT/
44	(rat or rats or mouse or mice).ti.
45	or/37-44
46	29 not 45
47	11 and 46
48	21 and 46
49	or/47-48
50	(2014$ or 2015$ or 2016$ or 2017$ or 2018$ or 2019$ or 2020$).dd,yr.
51	49 and 50

Databases: Cochrane Central Register of Controlled Trials; Cochrane Database of Systematic Reviews; Database of Abstracts of Reviews of Effects; and Health Technology Assessment

Date of last search: 13/05/2020

#	Searches
#1	MeSH descriptor: [Labor, Induced] this term only
#2	((labor or labour) near/5 induc*):ti,ab
#3	MeSH descriptor: [Cervical Ripening] this term only
#4	(cervi* near/3 ripen*):ti,ab
#5	((unfavo* or un-favo* or unripe* or un-ripe*) near/3 cervi*):ti,ab
#6	((bishop* or cerv*) near/3 scor*):ti,ab
#7	#1 or #2 or #3 or #4 or #5 or #6 with Publication Year from 2014 to 2020, with Cochrane Library publication date Between Jan 2014 and May 2020, in Trials

Health economic search strategies

Databases: Medline; Medline EPub Ahead of Print; and Medline In-Process & Other Non-Indexed Citations

Date of last search: 13/05/2020

#	Searches
1	ECONOMICS/
2	VALUE OF LIFE/
3	exp "COSTS AND COST ANALYSIS"/
4	exp ECONOMICS, HOSPITAL/
5	exp ECONOMICS, MEDICAL/
6	exp RESOURCE ALLOCATION/
7	ECONOMICS, NURSING/
8	ECONOMICS, PHARMACEUTICAL/
9	exp "FEES AND CHARGES"/
10	exp BUDGETS/
11	budget*.ti,ab.
12	cost*.ti,ab.
13	(economic* or pharmaco?economic*).ti,ab.
14	(price* or pricing*).ti,ab.
15	(financ* or fee or fees or expenditure* or saving*).ti,ab.
16	(value adj2 (money or monetary)).ti,ab.
17	resourc* allocat*.ti,ab.
18	(fund or funds or funding* or funded).ti,ab.
19	(ration or rations or rationing* or rationed).ti,ab.
20	ec.fs.
21	or/1-20
22	LABOR, INDUCED/
23	(labo?r adj5 induc$).ti,ab.
24	CERVICAL RIPENING/
25	(cervi$ adj3 ripen$).ti,ab.
26	((unfavo?rabl$ or un-favo?abl$ or unripe$ or un-ripe$) adj3 cervi$).ti,ab.
27	((bishop$ or cerv$) adj3 scor$).ti,ab.
28	or/22-27
29	limit 28 to english language
30	LETTER/
31	EDITORIAL/
32	NEWS/
33	exp HISTORICAL ARTICLE/
34	ANECDOTES AS TOPIC/

#	Searches
35	COMMENT/
36	CASE REPORT/
37	(letter or comment*).ti.
38	or/30-37
39	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
40	38 not 39
41	ANIMALS/ not HUMANS/
42	exp ANIMALS, LABORATORY/
43	exp ANIMAL EXPERIMENTATION/
44	exp MODELS, ANIMAL/
45	exp RODENTIA/
46	(rat or rats or mouse or mice).ti.
47	or/40-46
48	29 not 47
49	21 and 48
50	(2014$ or 2015$ or 2016$ or 2017$ or 2018$ or 2019$ or 2020$).ed,yr.
51	49 and 50

Databases: Embase; and Embase Classic

Date of last search: 13/05/2020

#	Searches
1	HEALTH ECONOMICS/
2	exp ECONOMIC EVALUATION/
3	exp HEALTH CARE COST/
4	exp FEE/
5	BUDGET/
6	FUNDING/
7	RESOURCE ALLOCATION/
8	budget*.ti,ab.
9	cost*.ti,ab.
10	(economic* or pharmaco?economic*).ti,ab.
11	(price* or pricing*).ti,ab.
12	(financ* or fee or fees or expenditure* or saving*).ti,ab.
13	(value adj2 (money or monetary)).ti,ab.
14	resourc* allocat*.ti,ab.
15	(fund or funds or funding* or funded).ti,ab.
16	(ration or rations or rationing* or rationed).ti,ab.
17	or/1-16
18	LABOR INDUCTION/
19	(labo?r adj5 induc$).ti,ab.
20	UTERINE CERVIX RIPENING/
21	(cervi$ adj3 ripen$).ti,ab.
22	((unfavo?rabl$ or un-favo?abl$ or unripe$ or un-ripe$) adj3 cervi$).ti,ab.
23	((bishop$ or cerv$) adj3 scor$).ti,ab.
24	or/18-23
25	limit 24 to english language
26	letter.pt. or LETTER/
27	note.pt.
28	editorial.pt.
29	CASE REPORT/ or CASE STUDY/
30	(letter or comment*).ti.
31	or/26-30
32	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
33	31 not 32
34	ANIMAL/ not HUMAN/
35	NONHUMAN/
36	exp ANIMAL EXPERIMENT/
37	exp EXPERIMENTAL ANIMAL/
38	ANIMAL MODEL/
39	exp RODENT/
40	(rat or rats or mouse or mice).ti.
41	or/33-40

#	Searches
42	25 not 41
43	17 and 42
44	(2014$ or 2015$ or 2016$ or 2017$ or 2018$ or 2019$ or 2020$).dd,yr.
45	43 and 44

Databases: Cochrane Central Register of Controlled Trials

Date of last search: 13/05/2020

#	Searches
#1	MeSH descriptor: [Economics] this term only
#2	MeSH descriptor: [Value of Life] this term only
#3	MeSH descriptor: [Costs and Cost Analysis] explode all trees
#4	MeSH descriptor: [Economics, Hospital] explode all trees
#5	MeSH descriptor: [Economics, Medical] explode all trees
#6	MeSH descriptor: [Resource Allocation] explode all trees
#7	MeSH descriptor: [Economics, Nursing] this term only
#8	MeSH descriptor: [Economics, Pharmaceutical] this term only
#9	MeSH descriptor: [Fees and Charges] explode all trees
#10	MeSH descriptor: [Budgets] explode all trees
#11	budget*:ti,ab
#12	cost*:ti,ab
#13	(economic* or pharmaco?economic*):ti,ab
#14	(price* or pricing*):ti,ab
#15	(financ* or fee or fees or expenditure* or saving*):ti,ab
#16	(value near/2 (money or monetary)):ti,ab
#17	resourc* allocat*:ti,ab
#18	(fund or funds or funding* or funded):ti,ab
#19	(ration or rations or rationing* or rationed) .ti,ab.
#20	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19
#21	MeSH descriptor: [Labor, Induced] this term only
#22	((labor or labour) near/5 induc*):ti,ab
#23	MeSH descriptor: [Cervical Ripening] this term only
#24	(cervi* near/3 ripen*):ti,ab
#25	((unfavo* or un-favo* or unripe* or un-ripe*) near/3 cervi*):ti,ab
#26	((bishop* or cerv*) near/3 scor*):ti,ab
#27	#21 or #22 or #23 or #24 or #25 or #26 with Publication Year from 2014 to 2020, in Trials
#28	#20 and #27

Databases: Health Technology Assessment; and NHS Economic Evaluation Database

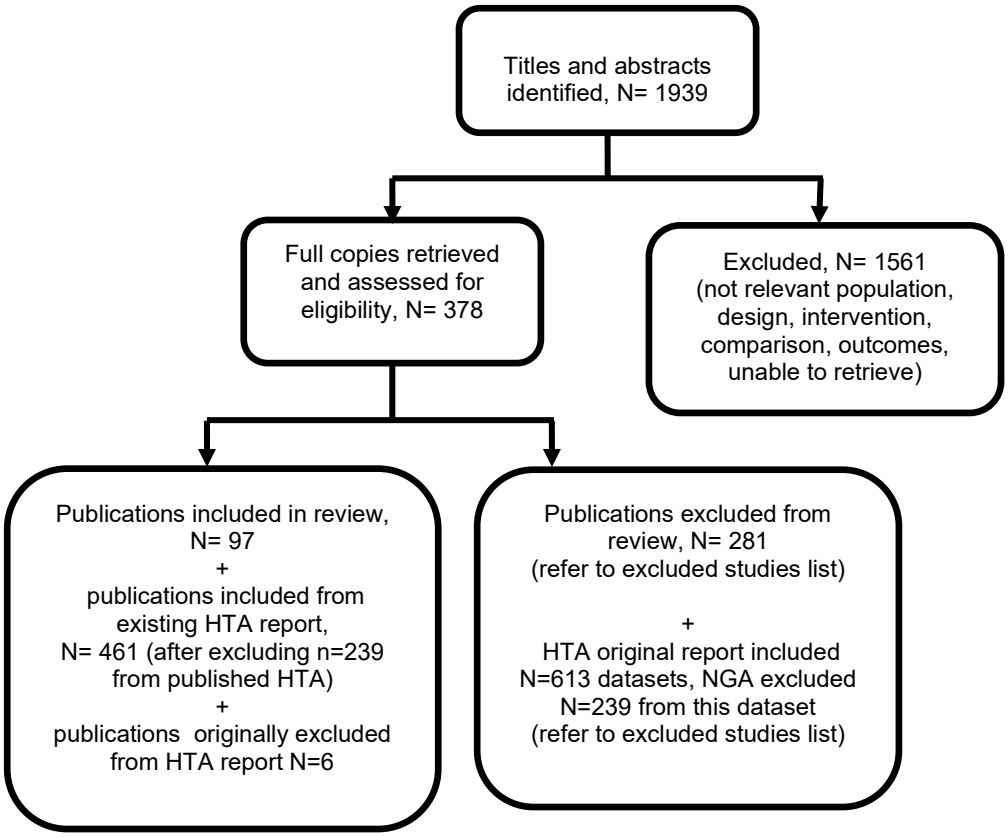
Date of last search: 13/05/2020

#	Searches
1	MeSH descriptor: [Labor, Induced] this term only
2	((labor or labour) near/5 induc*):ti,ab
3	MeSH descriptor: [Cervical Ripening] this term only
4	(cervi* near/3 ripen*):ti,ab
5	((unfavo* or un-favo* or unripe* or un-ripe*) near/3 cervi*):ti,ab
6	((bishop* or cerv*) near/3 scor*):ti,ab
7	#1 or #2 or #3 or #4 or #5 or #6 Publication Year from 2014 to 2020

Appendix C – Clinical evidence study selection

Clinical study selection for review question: What are the benefits and harms of pharmacological and mechanical methods in induction of labour?

Figure 38: Study selection flow chart



Appendix D – Clinical evidence tables

Clinical evidence tables for review question: What are the benefits and harms of pharmacological and mechanical methods in induction of labour?

Due to the size and complexity of these tables they are provided in a separate document. See Supplement 3.

Appendix E – Forest plots

Forest plots for review question: What are the benefits and harms of pharmacological and mechanical methods in induction of labour?

This section includes forest plots only for outcomes that are meta-analysed, but were not included in the NMA. Outcomes from single studies are not presented here; the quality assessment for such outcomes is provided in the GRADE profiles in appendix F.

Important outcomes: Perinatal death and maternal death/morbidity

Comparison 1. Nitric oxide versus placebo

Figure 39: Perinatal death – risk difference

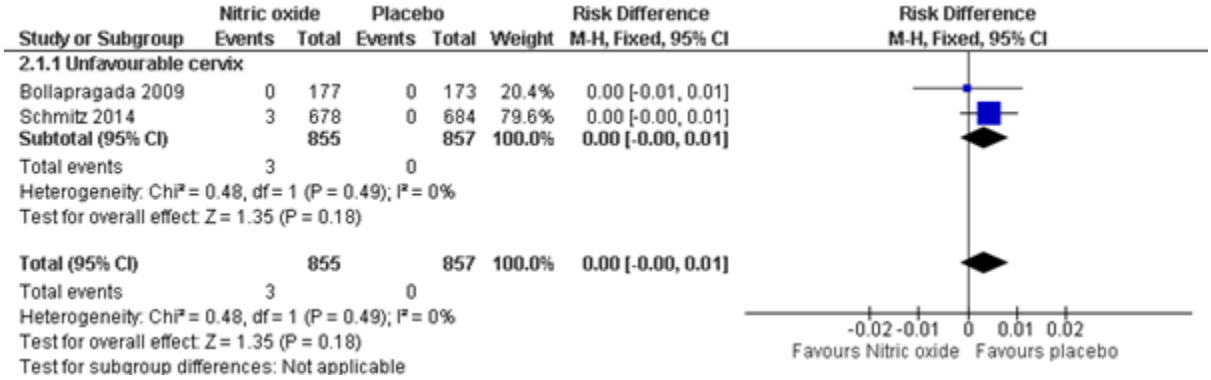


Figure 40: Perinatal death – Peto odds ratio

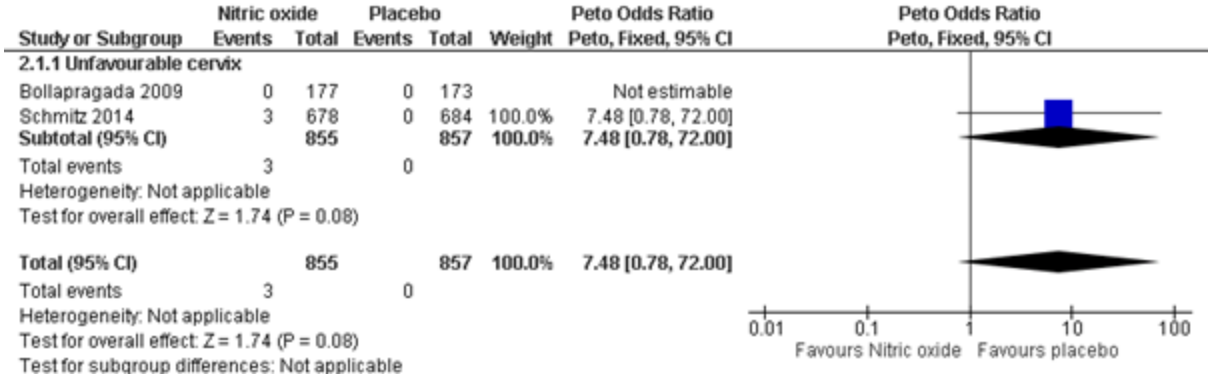
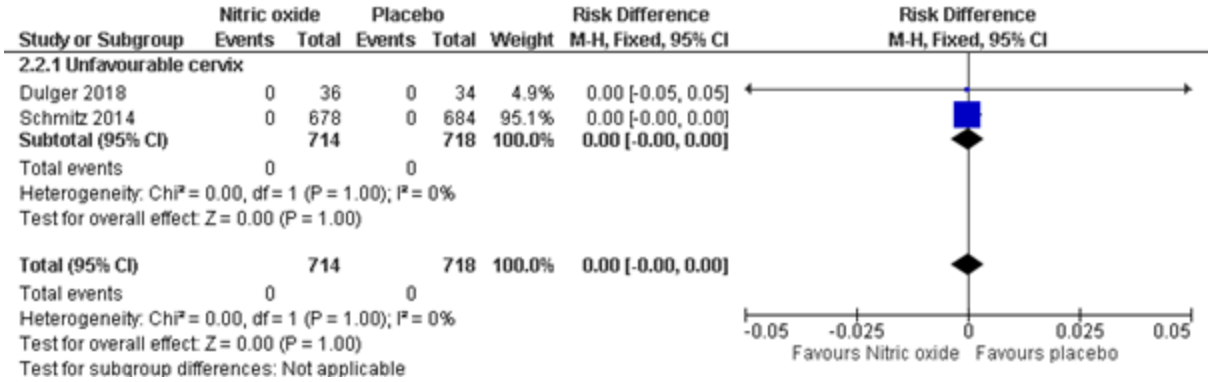
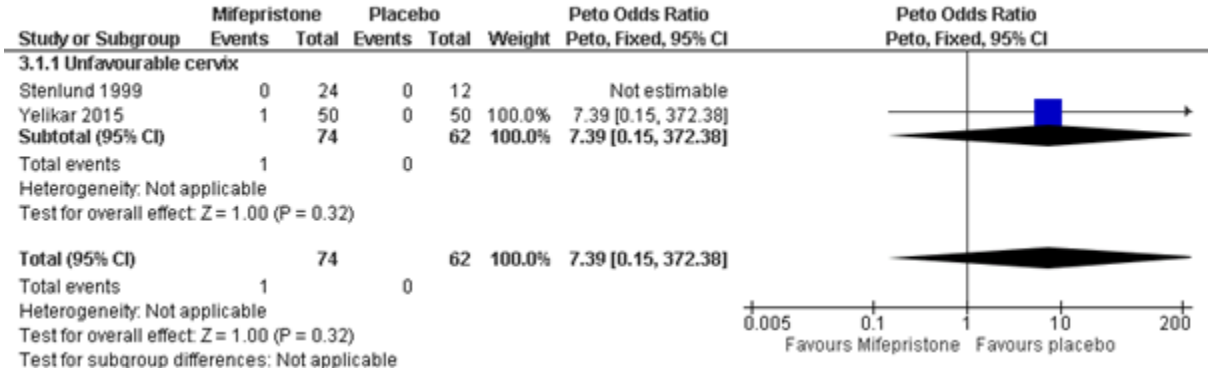


Figure 41: Maternal death/morbidity – risk difference



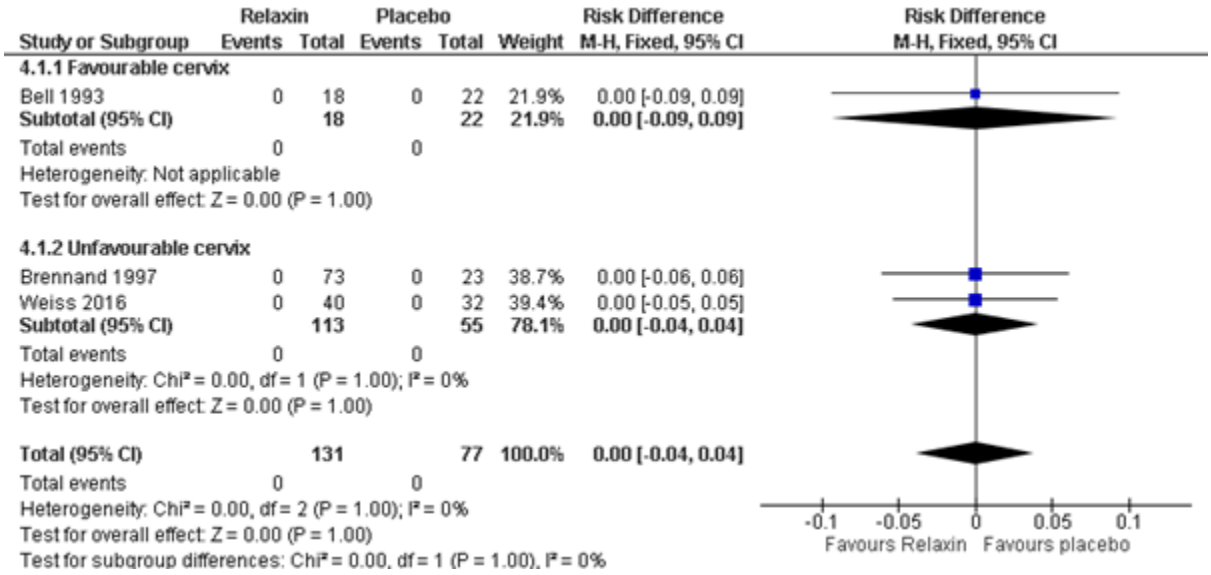
Comparison 2. Mifepristone versus placebo

Figure 42: Perinatal death – Peto odds ratio



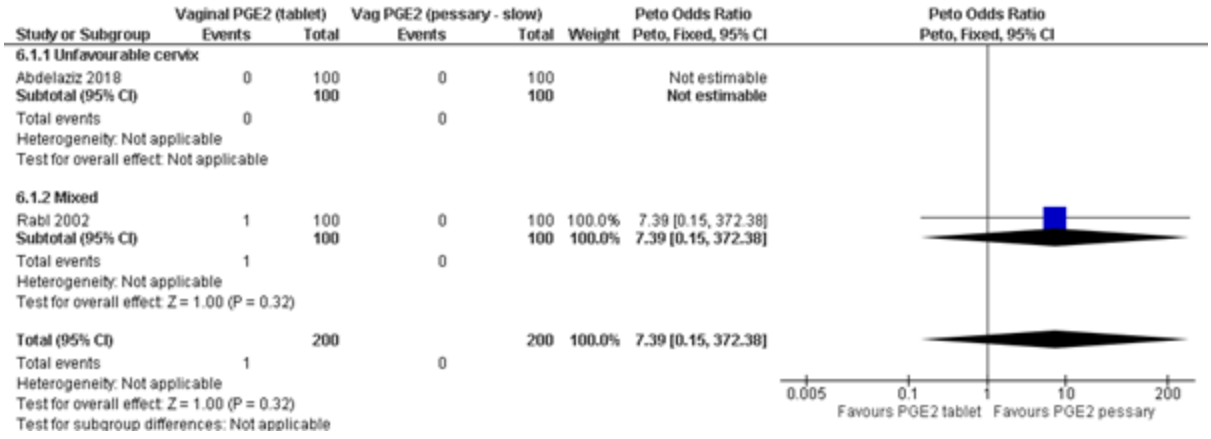
Comparison 3. Relaxin versus placebo

Figure 43: Perinatal death – risk difference



Comparison 4. PGE_2 tablet versus PGE_2 pessary (slow)

Figure 44: Maternal death/morbidity – Peto odds ratio



Comparison 5. Vaginal PGE_2 (tablet) versus vaginal misoprostol (≥50mcg)

Figure 45: Perinatal death – Peto odds ratio

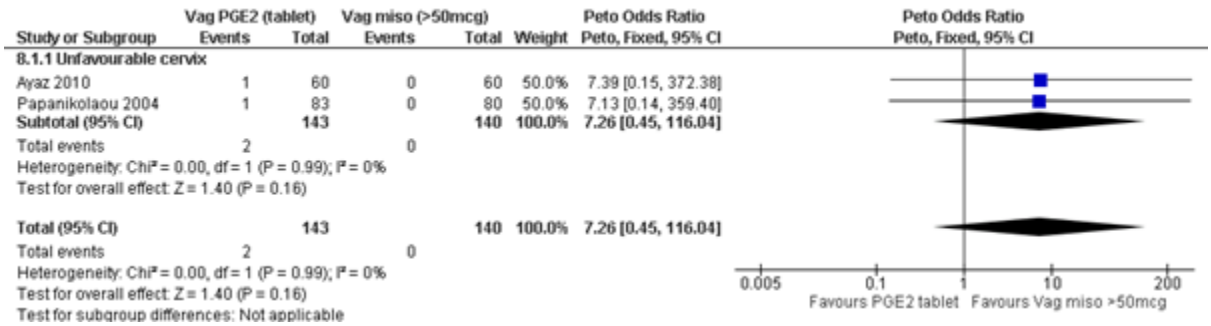
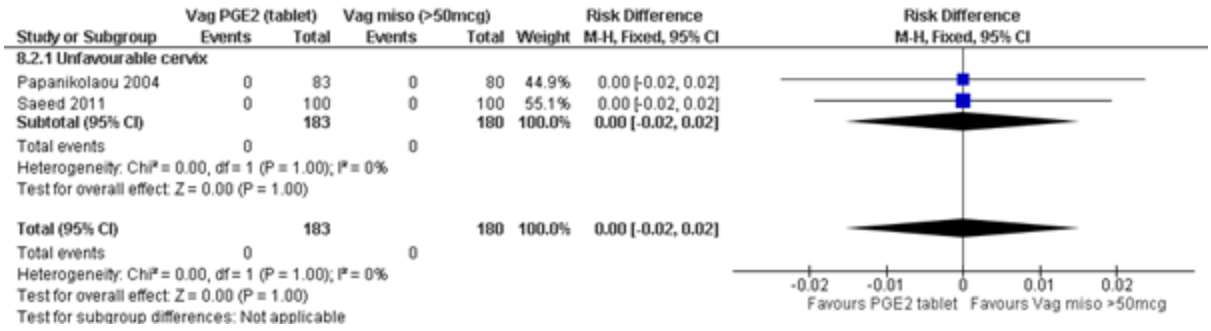
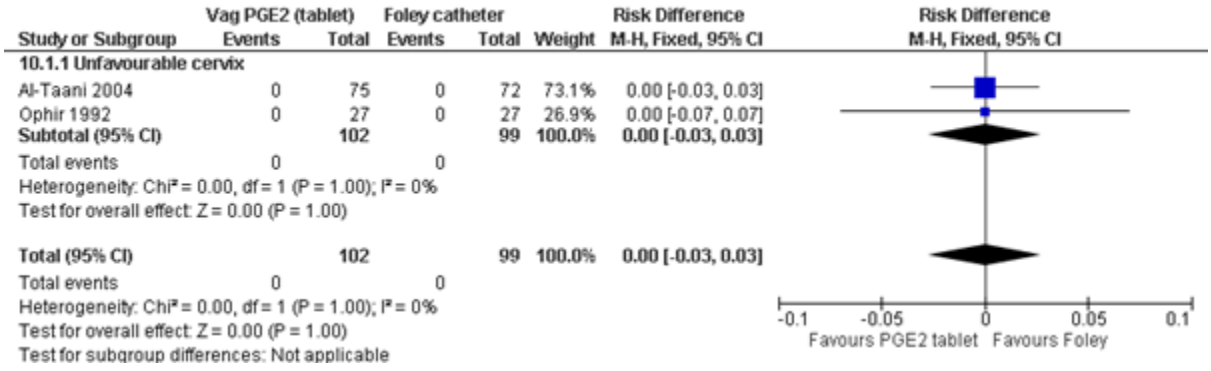


Figure 46: Maternal death/morbidity – risk difference



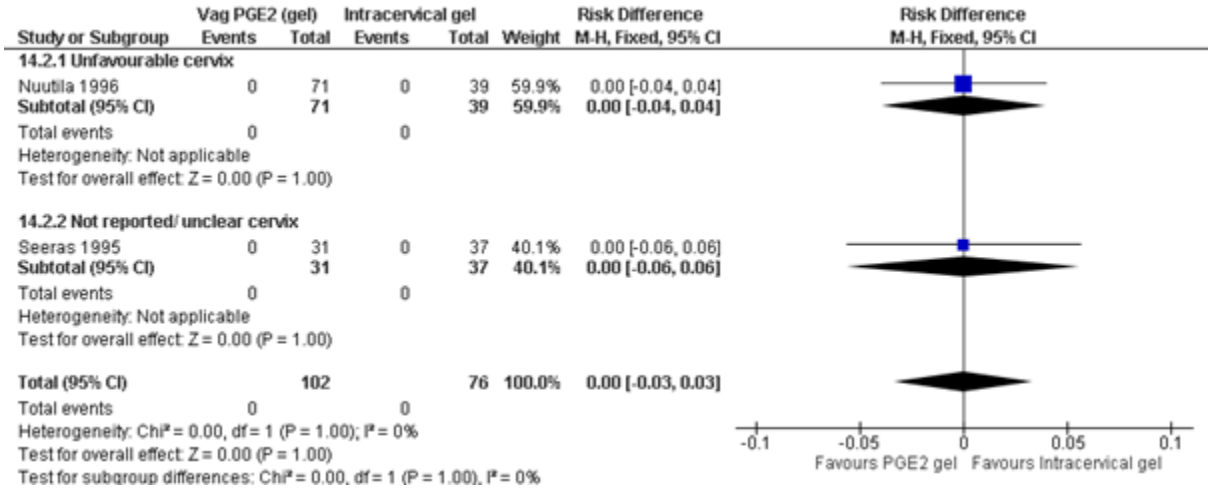
Comparison 6. Vaginal PGE_2 (tablet) versus Foley catheter

Figure 47: Perinatal death – risk difference



Comparison 7. Vaginal PGE_2 (gel) versus intracervical gel

Figure 48: Perinatal death – risk difference



Comparison 8. Vaginal PGE_2 (gel) versus vaginal misoprostol (<50mcg)

Figure 49: Perinatal death – risk difference

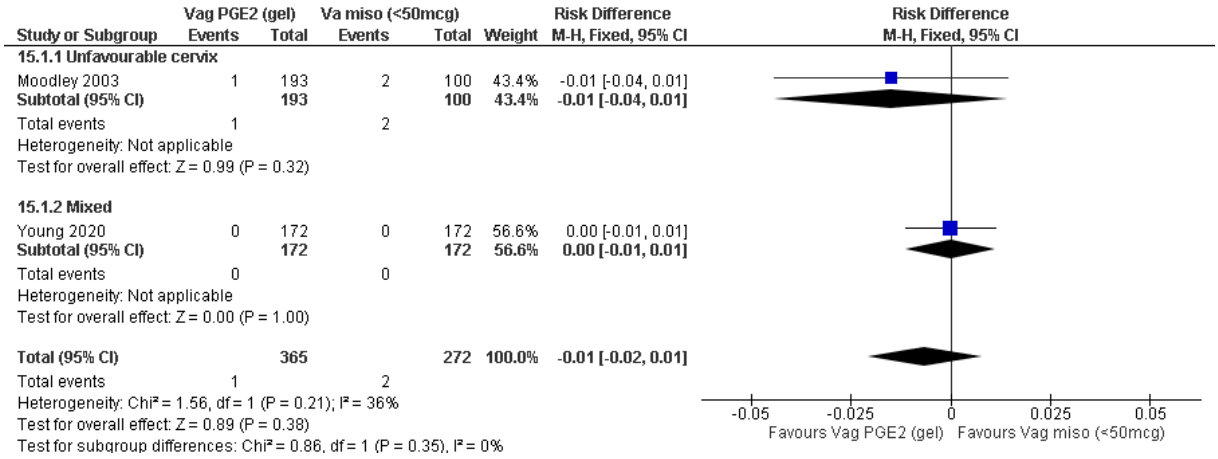
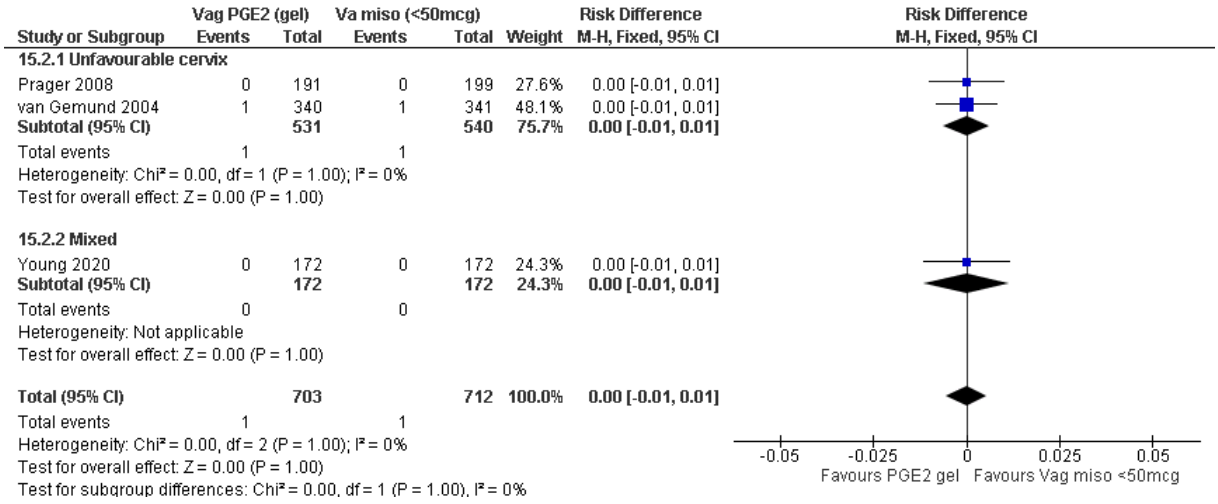


Figure 50: Maternal death/morbidity – risk difference



Comparison 9. Vaginal PGE_2 (gel) versus oral misoprostol (≥50mcg)

Figure 51: Perinatal death – risk diference

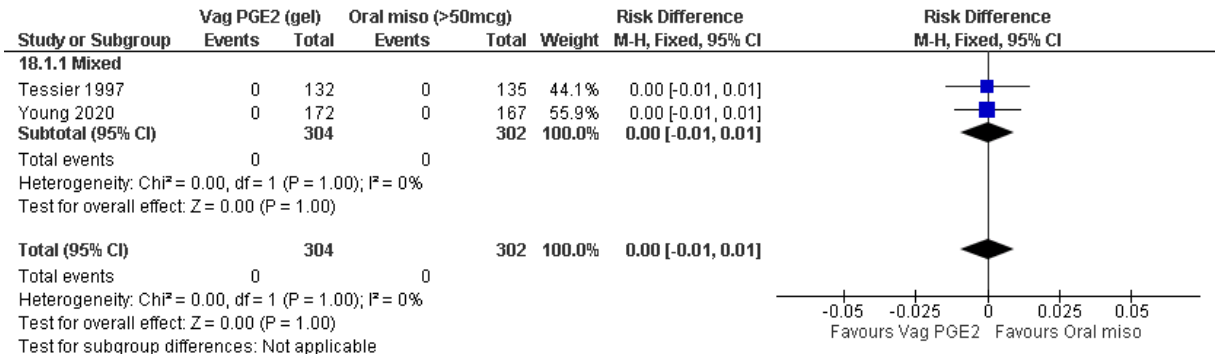
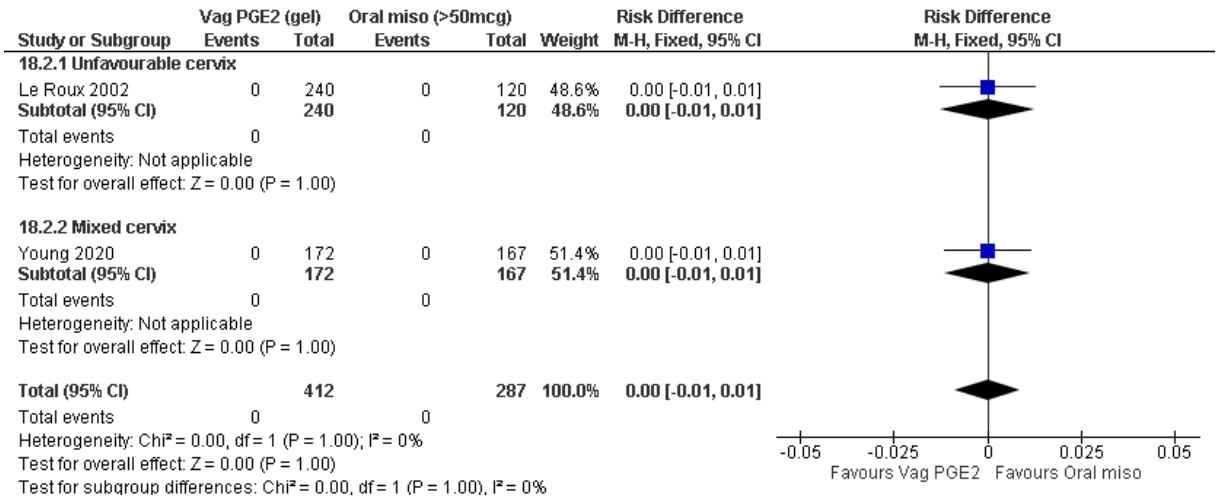


Figure 52: Maternal death/morbidity – risk difference



Comparison 10. Vaginal PGE_2 (gel) versus titrated oral misoprostol solution

Figure 53: Perinatal death – Peto odds ratio

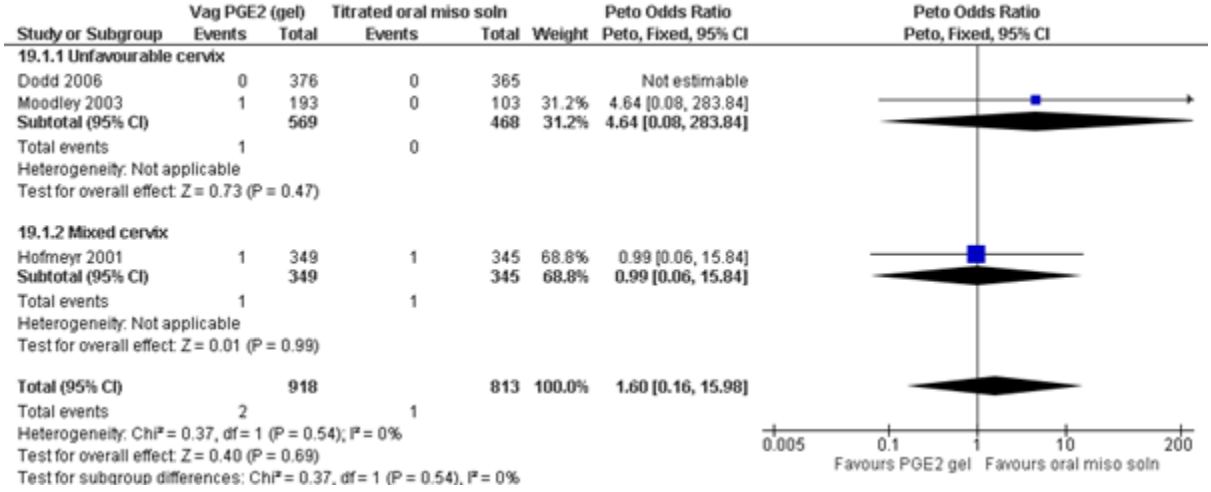
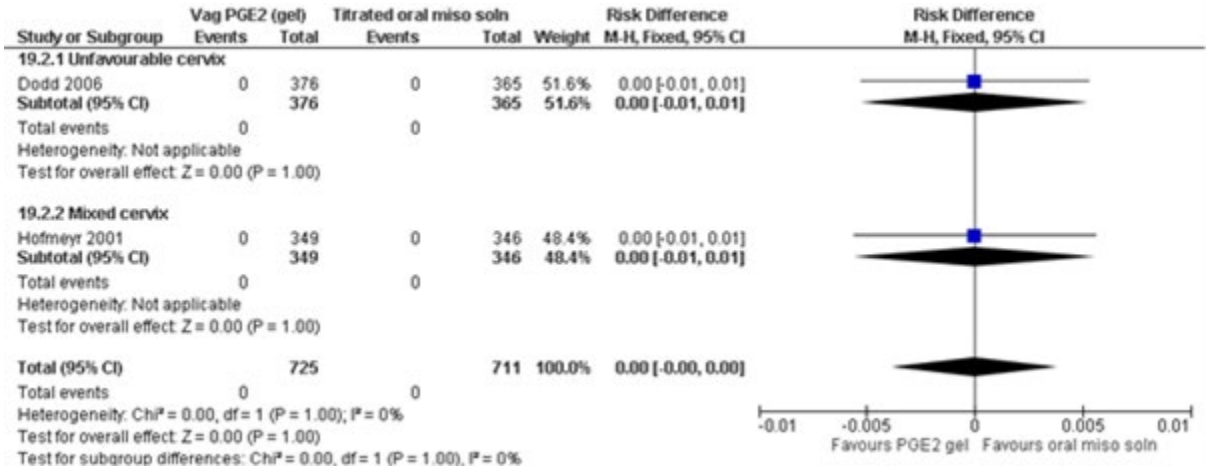
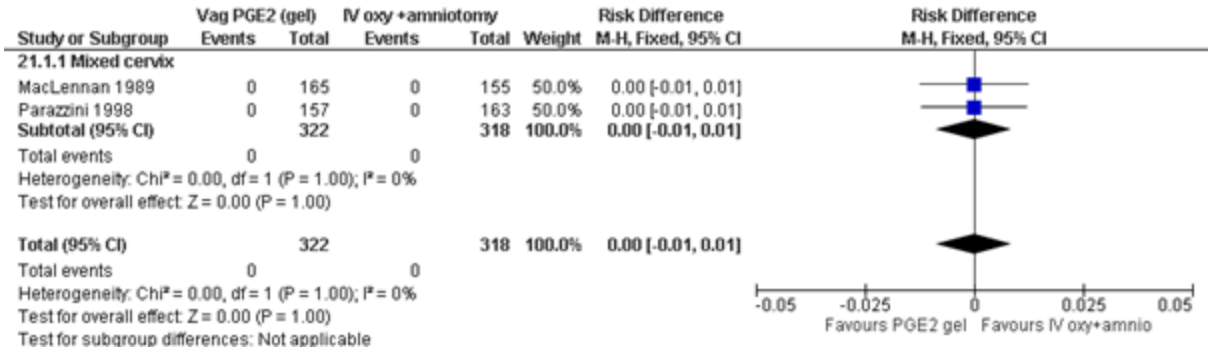


Figure 54: Maternal death/morbidity – risk difference



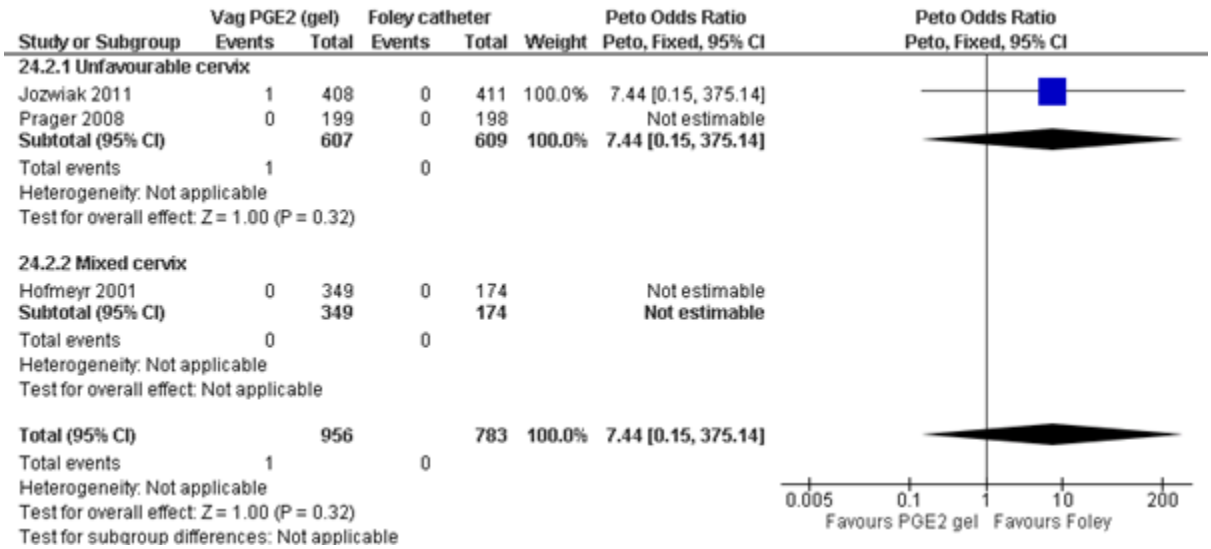
Comparison 11. Vaginal PGE_2 (gel) versus IV oxytocin + amniotomy

Figure 55: Perinatal death – risk difference



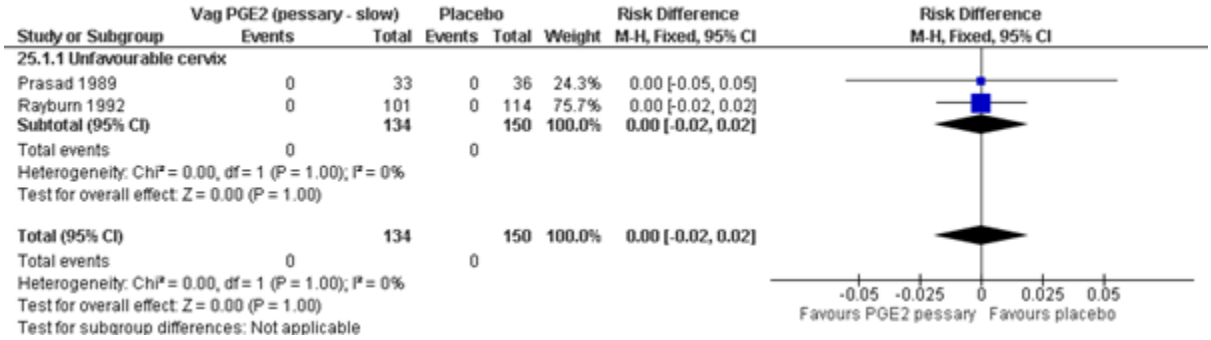
Comparison 12. Vaginal PGE_2 (gel) versus Foley catheter

Figure 56: Maternal death/morbidity – Peto odds ratio



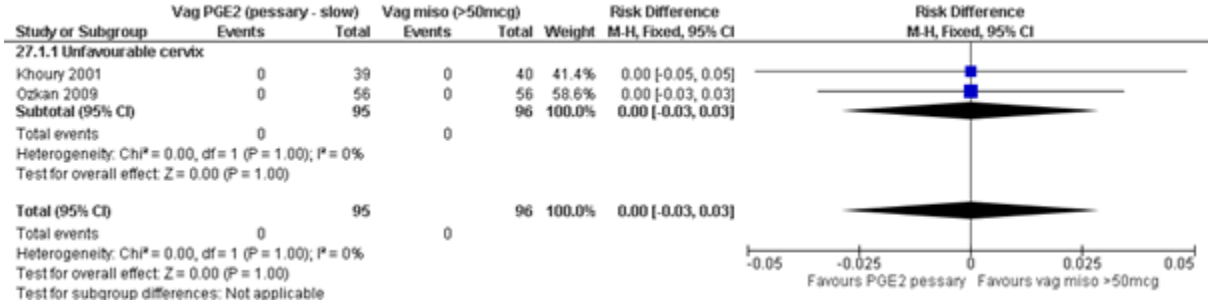
Comparison 13. Vaginal PGE_2 (pessary - slow release) versus placebo

Figure 57: Perinatal death – risk difference



Comparison 14. Vaginal PGE_2 (pessary - slow release) versus vaginal misoprostol (≥50mcg)

Figure 58: Perinatal death – risk difference



Comparison 15. Vaginal PGE_2 (pessary - slow release) versus misoprostol insert (sustained release)

Figure 59: Perinatal death – risk difference

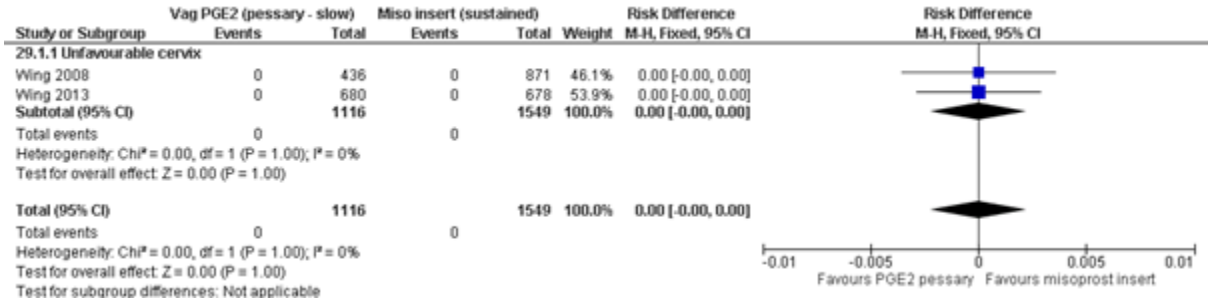
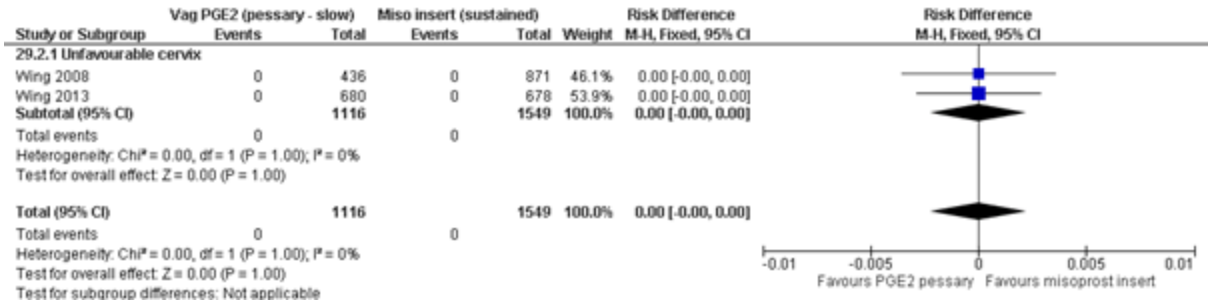


Figure 60: Maternal death/morbidity – risk difference



Comparison 16. Intracervical PGE_2 versus no treatment

Figure 61: Perinatal death – Peto odds ratio

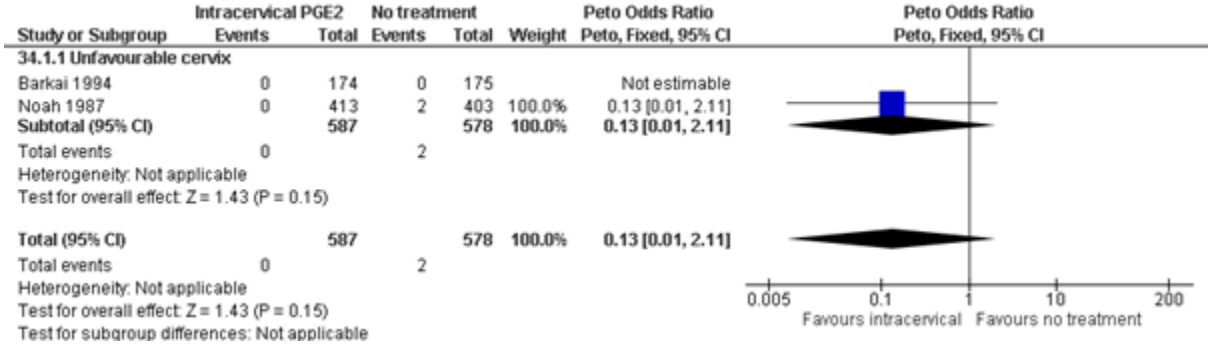
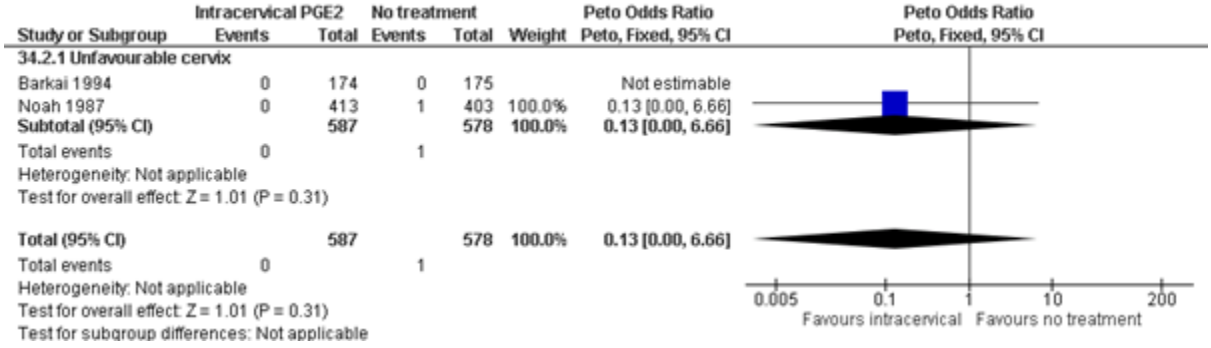
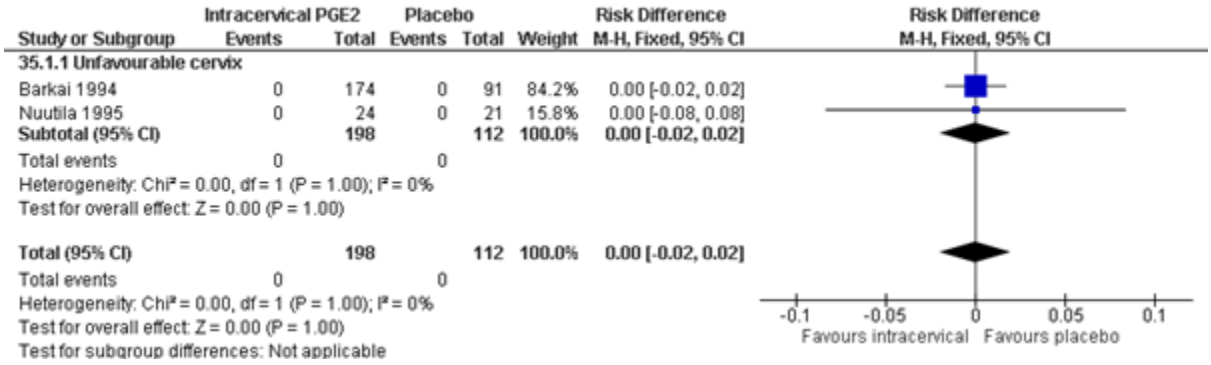


Figure 62: Maternal death/morbidity – Peto odds ratio



Comparison 17. Intracervical PGE_2 versus placebo

Figure 63: Perinatal death – risk difference



Comparison 18. Intracervical PGE_2 versus vaginal misoprostol (<50mcg)

Figure 64: Perinatal death – risk difference

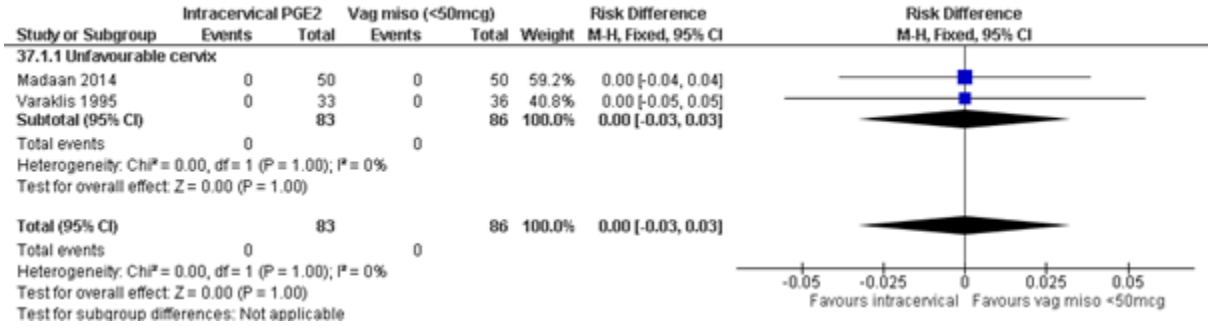
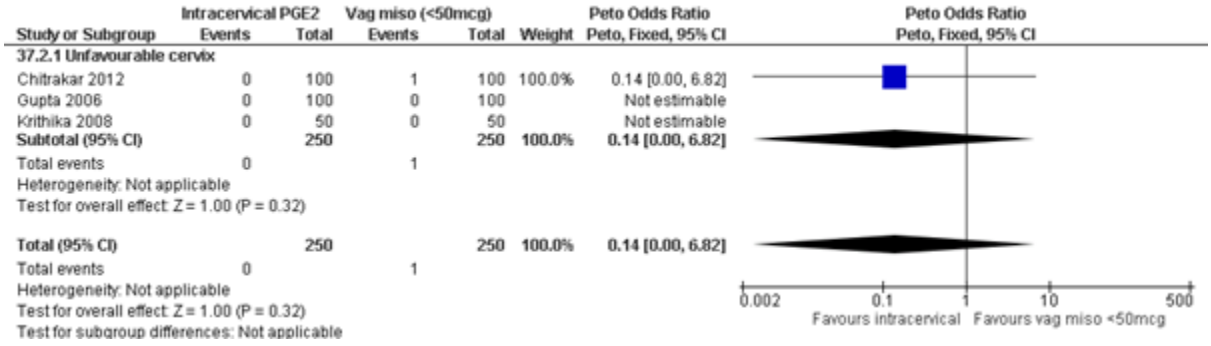


Figure 65: Maternal death/morbidity – Peto odds ratio



Comparison 19. Intracervical PGE_2 versus vaginal misoprostol (≥50mcg)

Figure 66: Perinatal death – Peto odds ratio

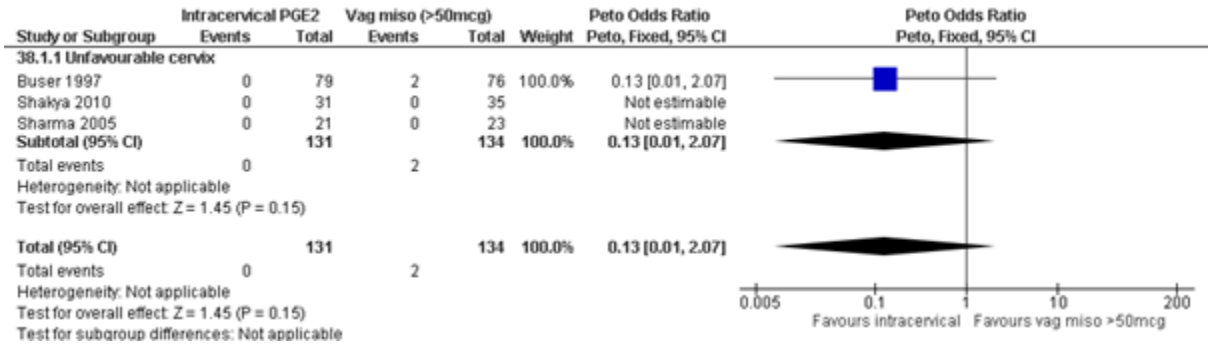
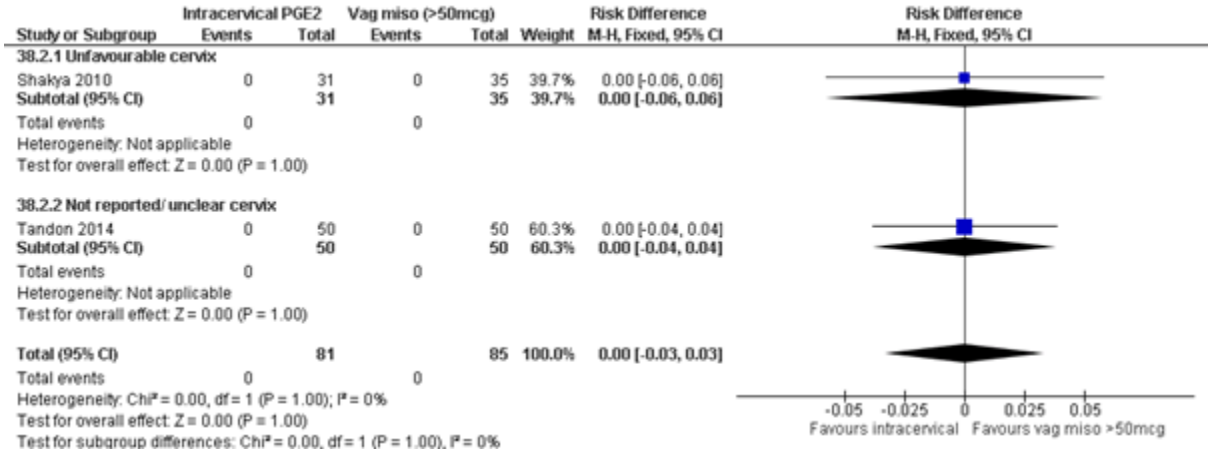
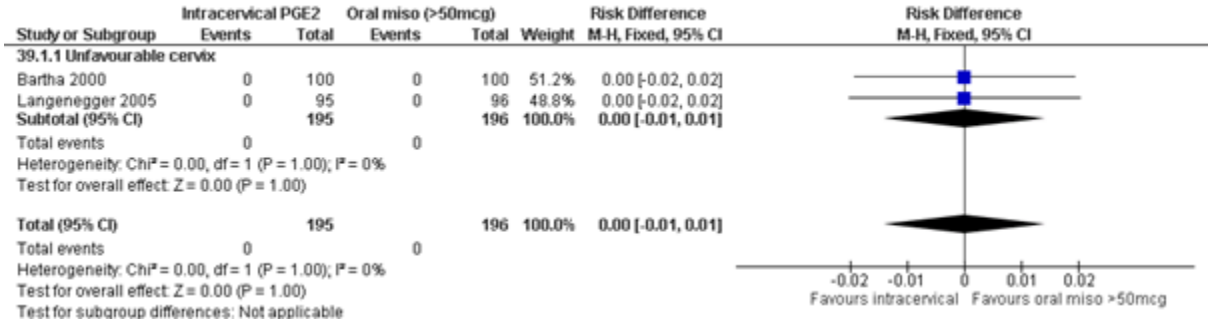


Figure 67: Maternal death/morbidity – risk difference



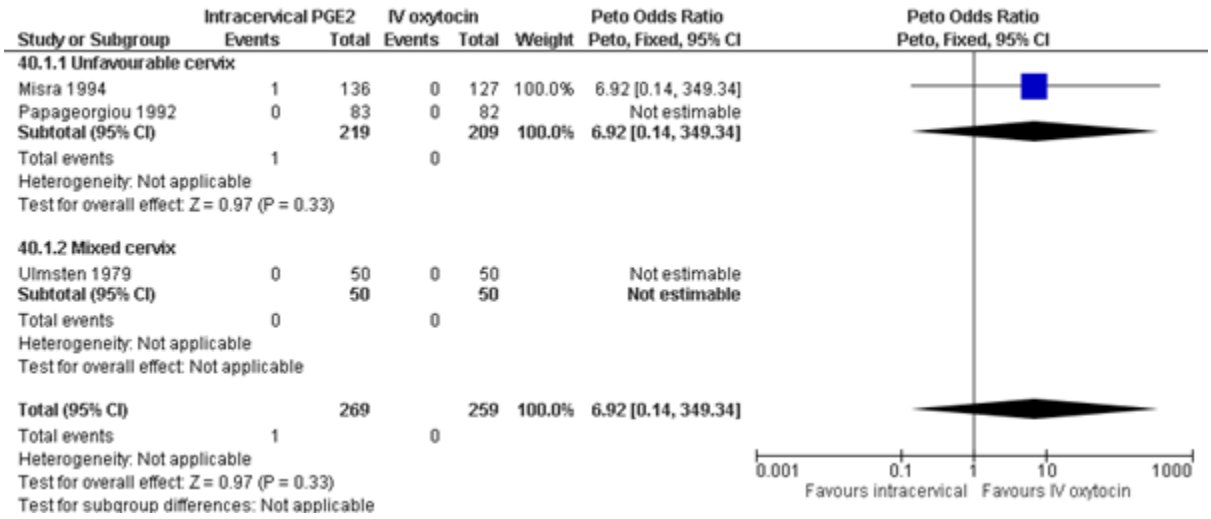
Comparison 20. Intracervical PGE_2 versus oral misoprostol (≥50mcg)

Figure 68: Perinatal death – risk difference



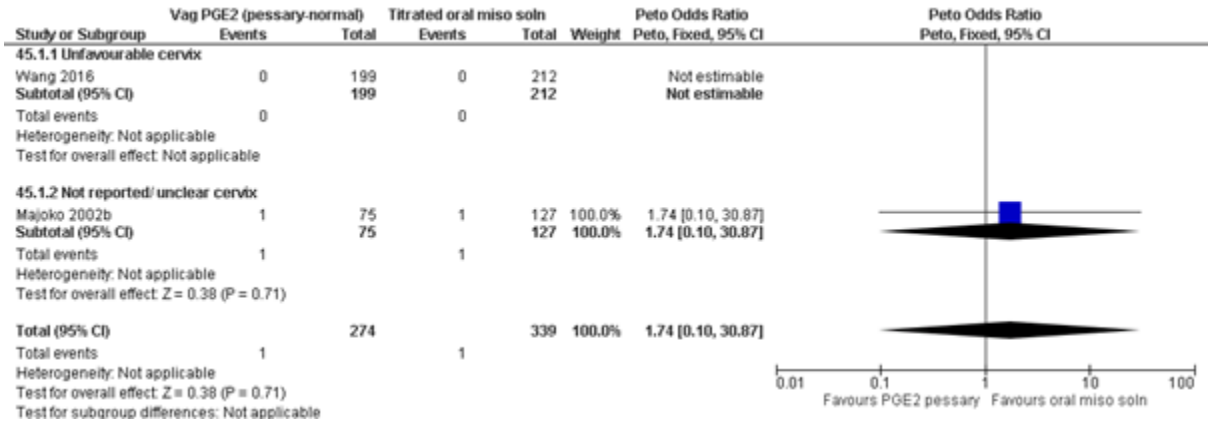
Comparison 21. Intracervical PGE_2 versus IV oxytocin

Figure 69: Perinatal death – Peto odds ratio



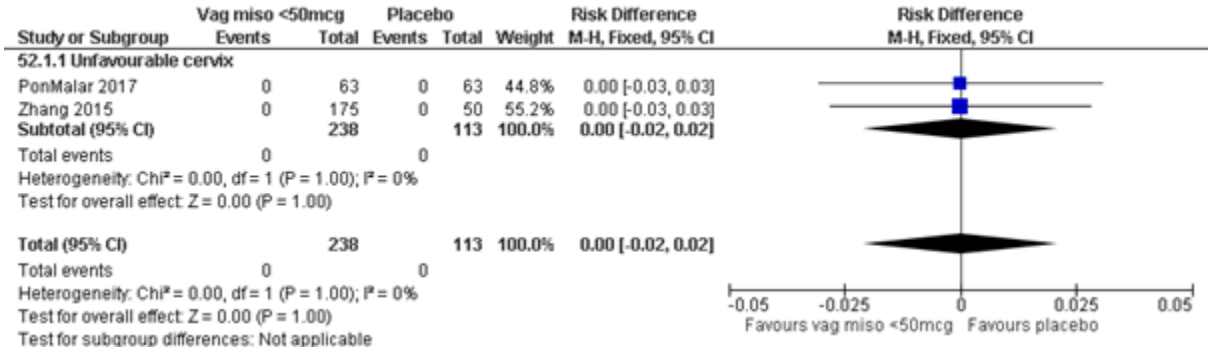
Comparison 22. Vaginal PGE_2 (pessary - normal release) versus titrated oral misoprostol solution

Figure 70: Perinatal death – Peto odds ratio



Comparison 23. Vaginal misoprostol (<50mcg) versus placebo

Figure 71: Maternal death/morbidity – risk difference



Comparison 24. Vaginal misoprostol (<50mcg) versus vaginal misoprostol (≥50mcg)

Figure 72: Perinatal death – Peto odds ratio

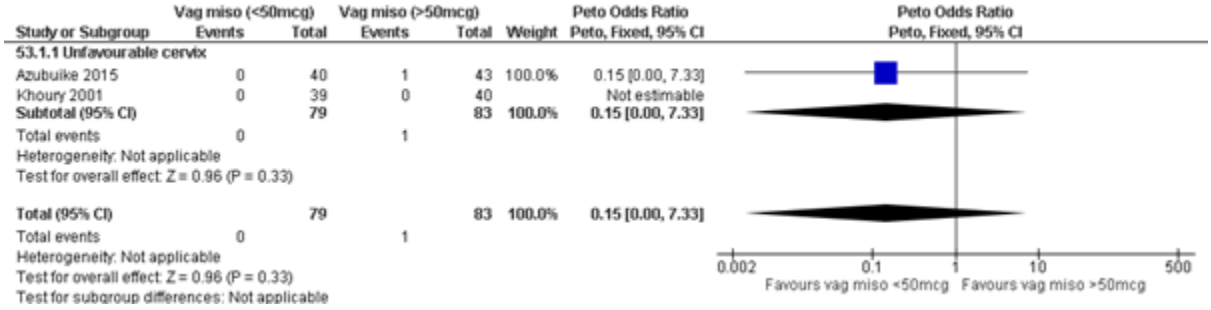
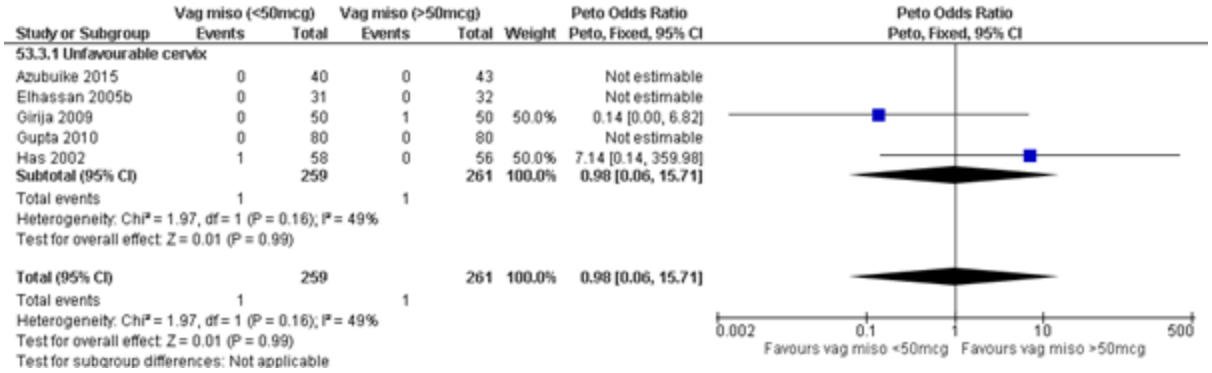


Figure 73: Maternal death/morbidity – Peto odds ratio



Comparison 25. Vaginal misoprostol (<50mcg) versus oral misoprostol (≥50mcg)

Figure 74: Perinatal death – risk difference

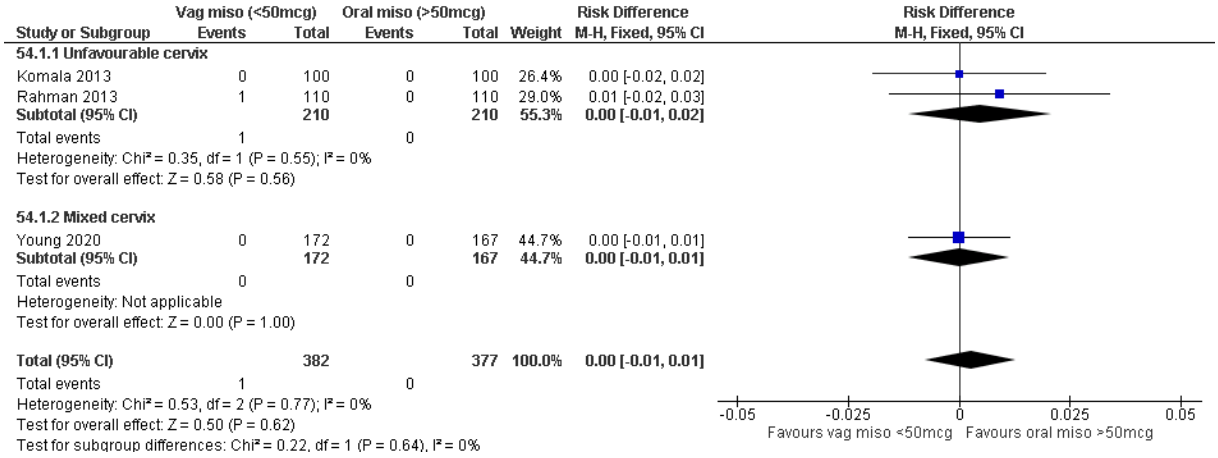
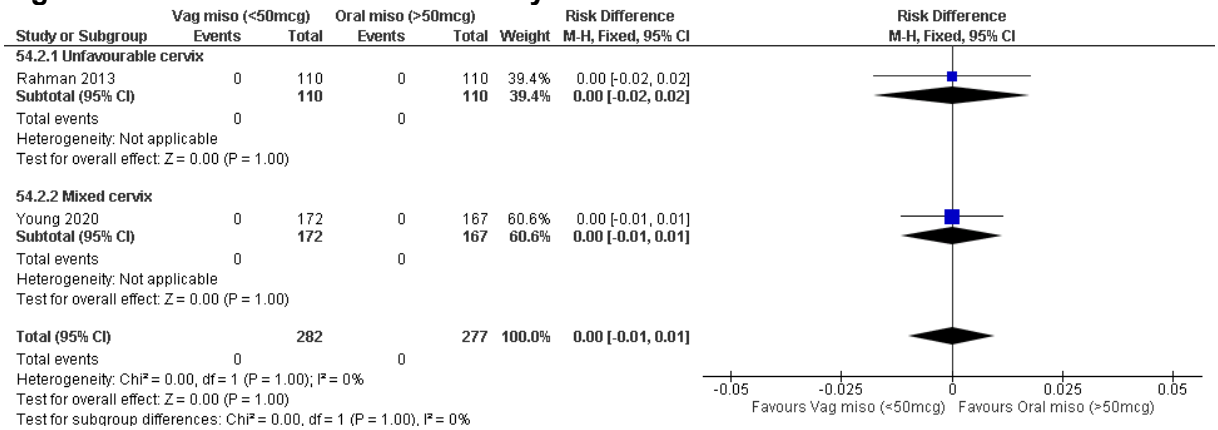


Figure 75: Maternal death/morbidity – risk difference



Comparison 26. Vaginal misoprostol (<50mcg) versus titrated oral misoprostol solution

Figure 76: Perinatal death – Peto odds ratio

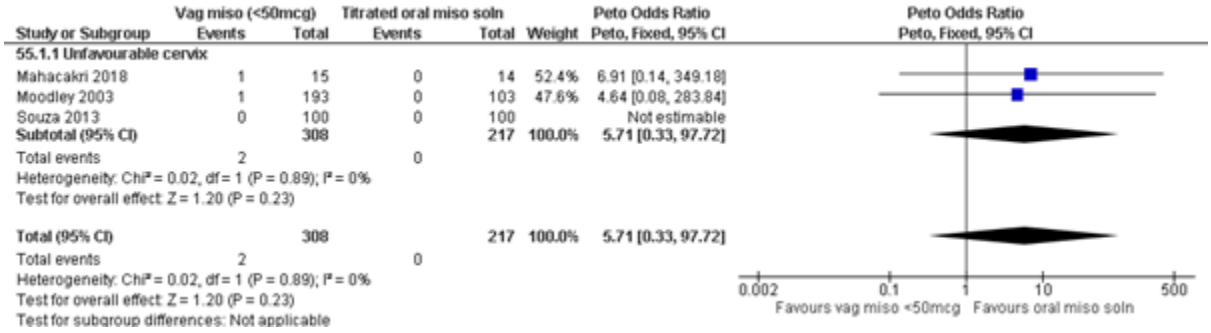
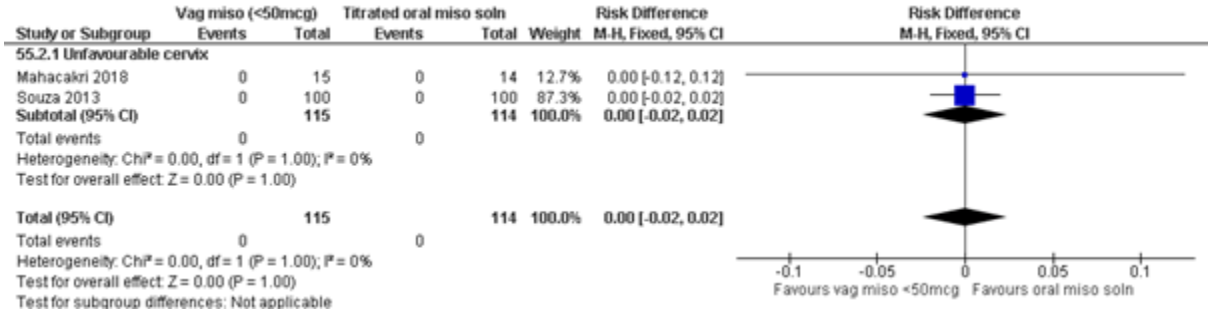
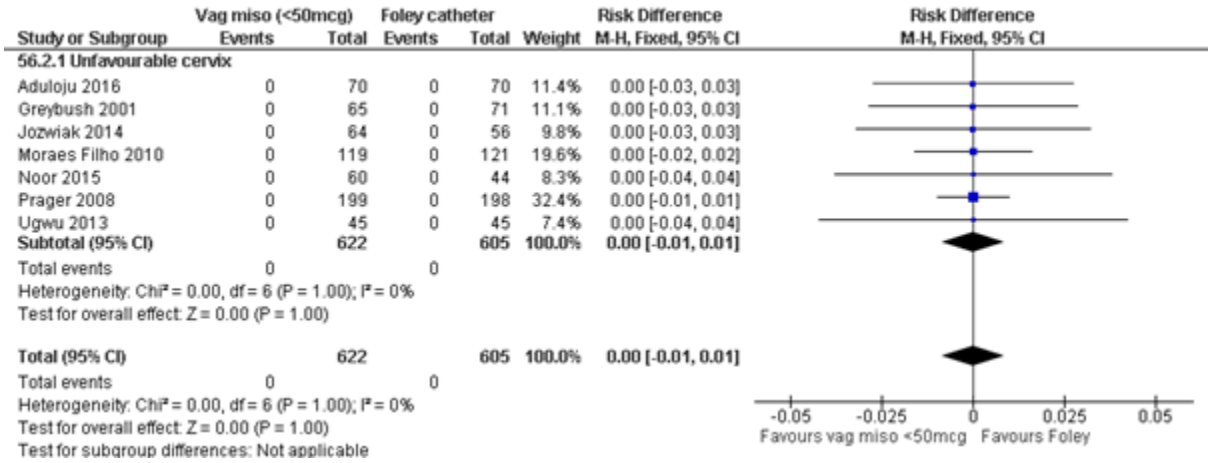


Figure 77: Maternal death/morbidity – risk difference



Comparison 27. Vaginal misoprostol (<50mcg) versus Foley catheter

Figure 78: Maternal death/morbidity – risk difference



Comparison 28. Vaginal misoprostol (<50mcg) versus buccal/sublingual

Figure 79: Perinatal death – risk difference

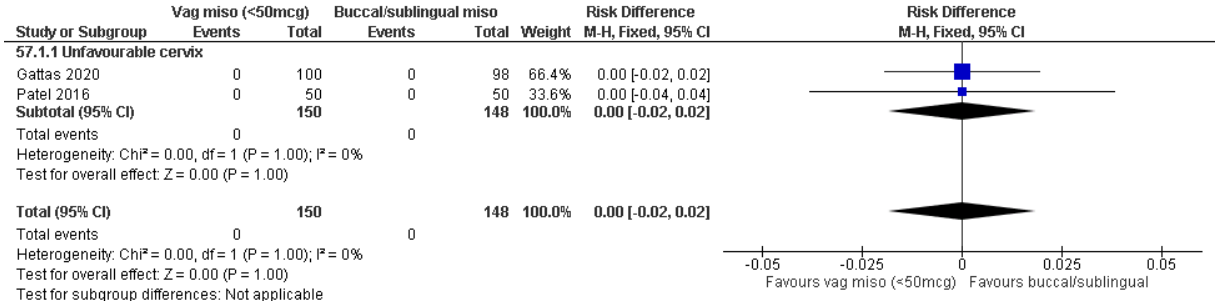
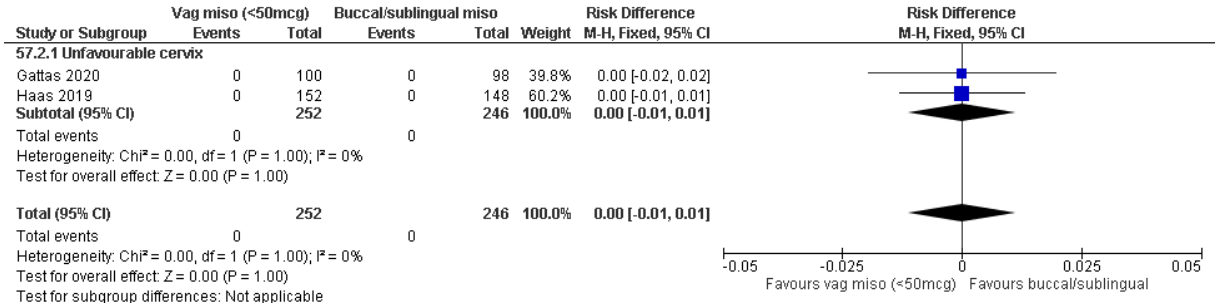
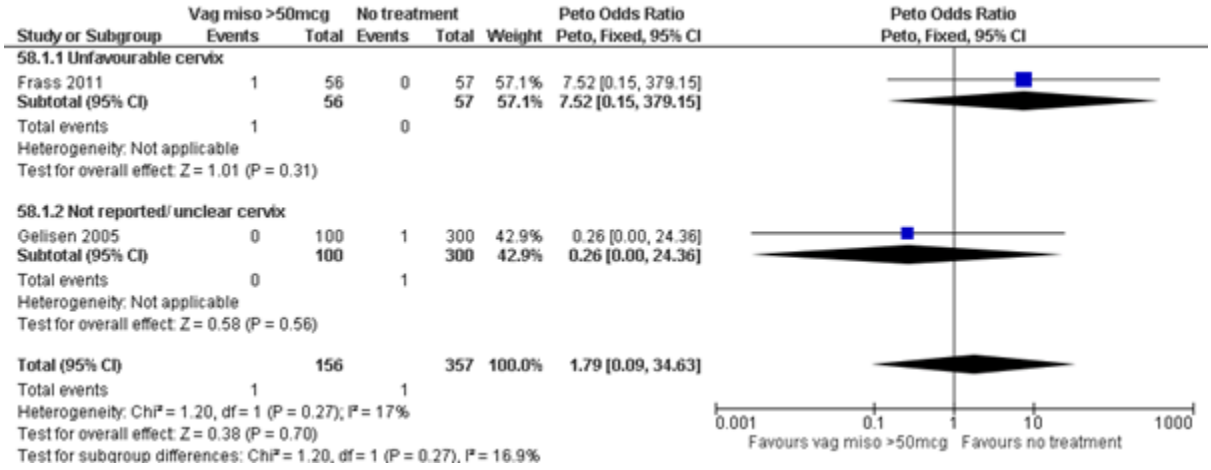


Figure 80: **Maternal death/morbidity – risk difference**



Comparison 29. Vaginal misoprostol (≥50mcg) versus no treatment

Figure 81: **Perinatal death – Peto odds ratio**



Comparison 30. Vaginal misoprostol (≥50mcg) versus oral misoprostol (≥50mcg)

Figure 82: Perinatal death – Peto odds ratio

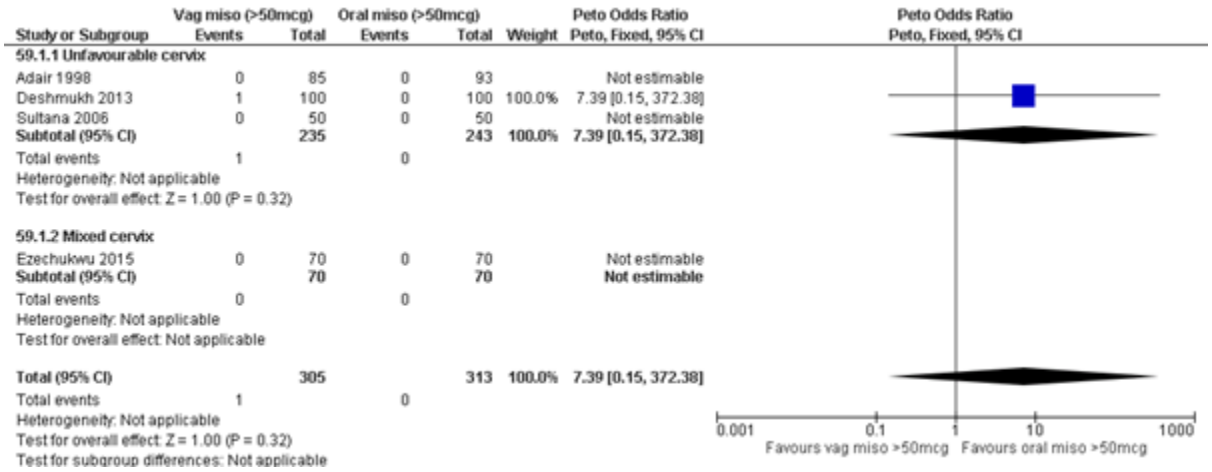


Figure 83: Maternal death/morbidity – Peto odds ratio

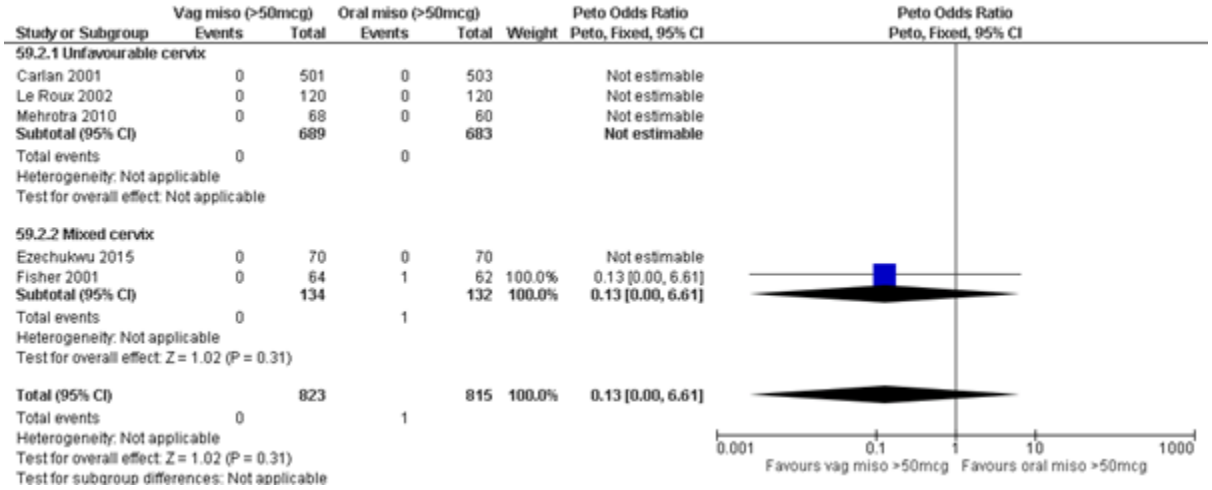
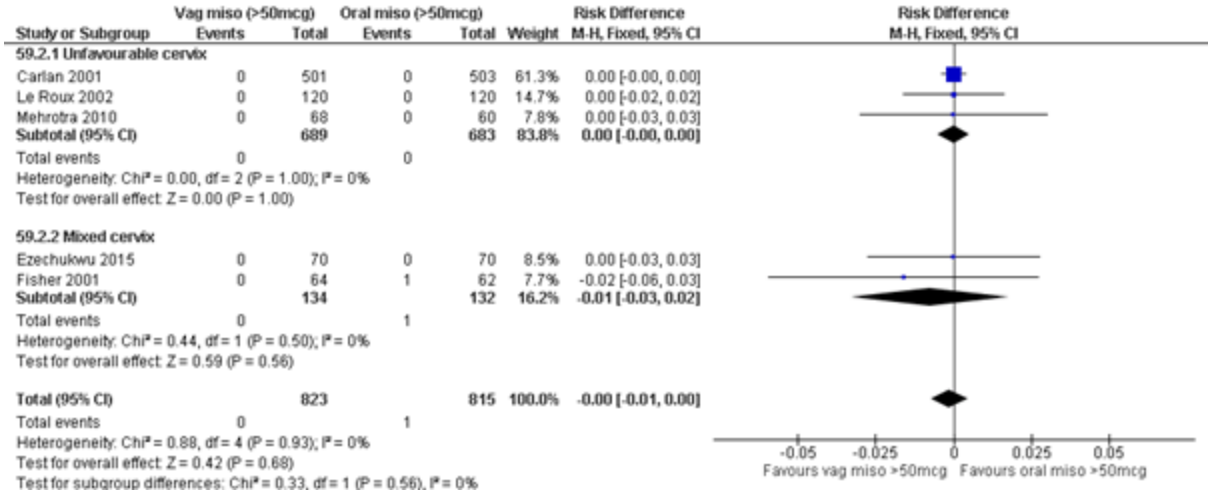
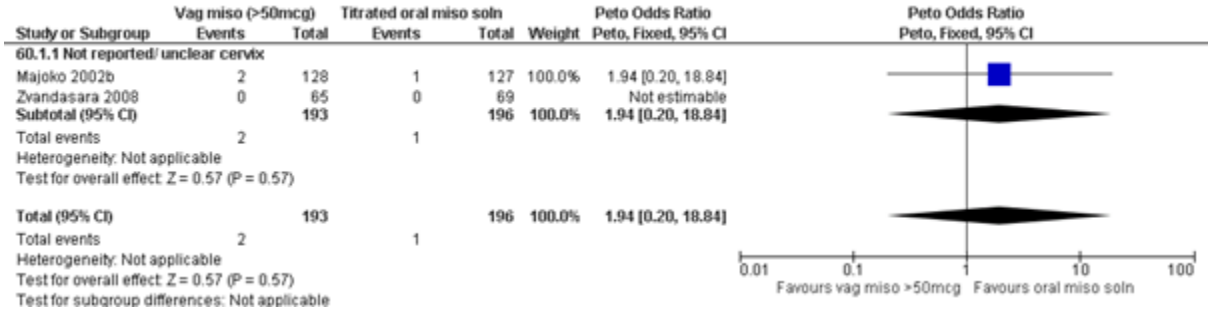


Figure 84: Maternal death/morbidity – risk difference



Comparison 31. Vaginal misoprostol (≥50mcg) versus titrated oral misoprostol solution

Figure 85: Perinatal death – Peto odds ratio



Comparison 32. Vaginal misoprostol (≥50mcg) versus IV oxytocin

Figure 86: Perinatal death – Peto odds ratio

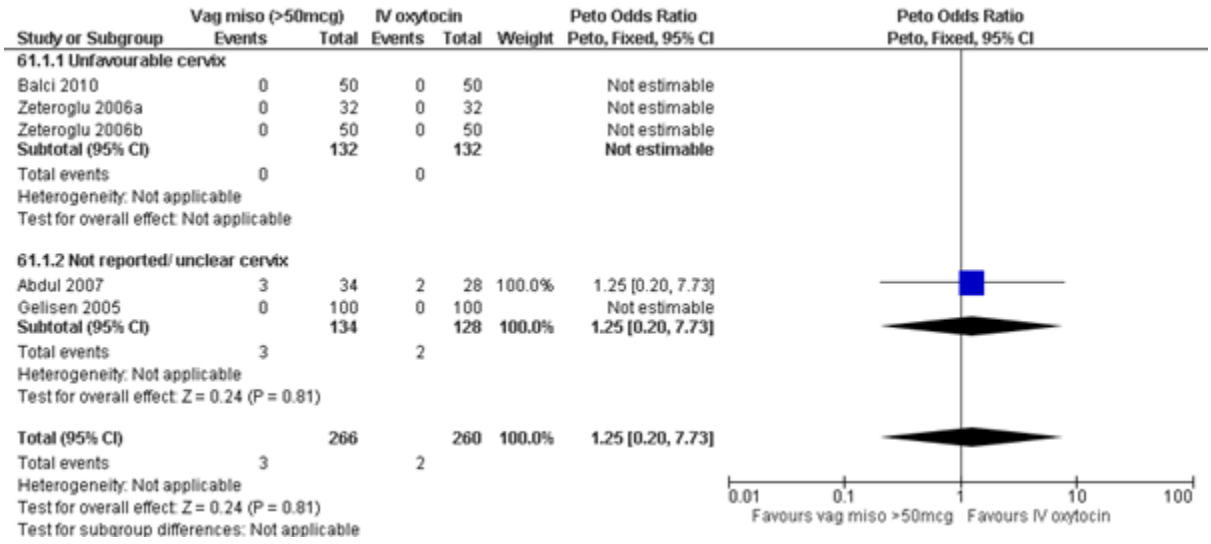


Figure 87: Perinatal death – risk difference

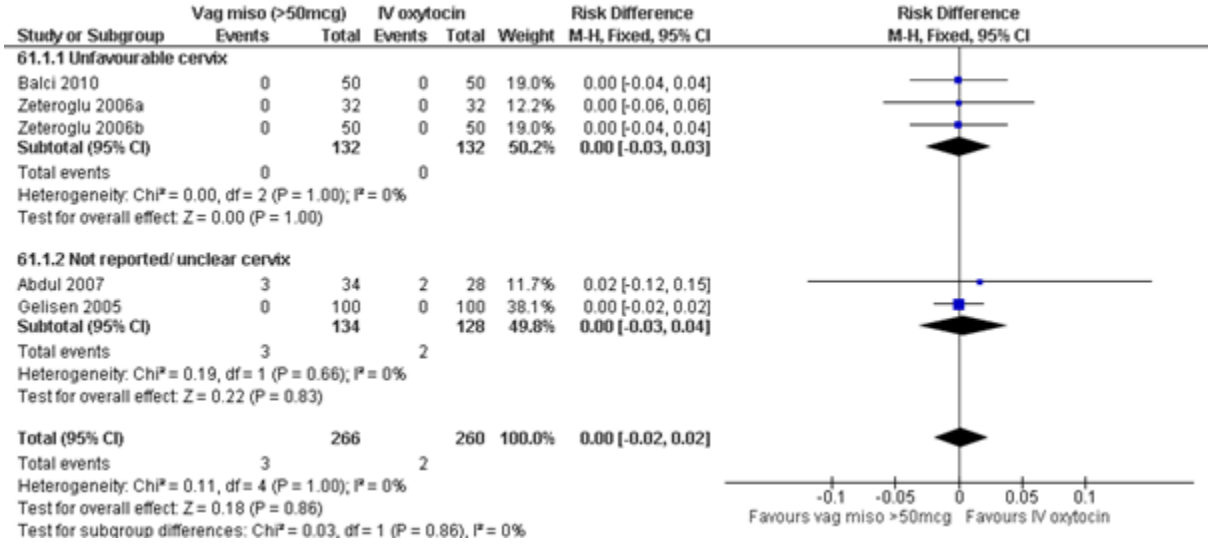


Figure 88: Maternal death/morbidity – Peto odds ratio

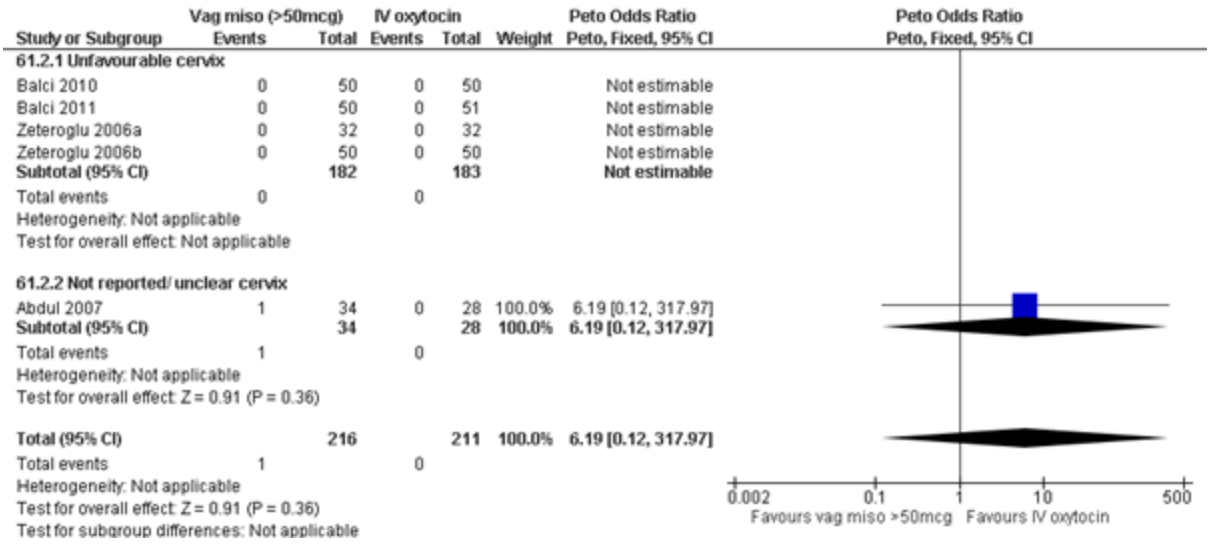
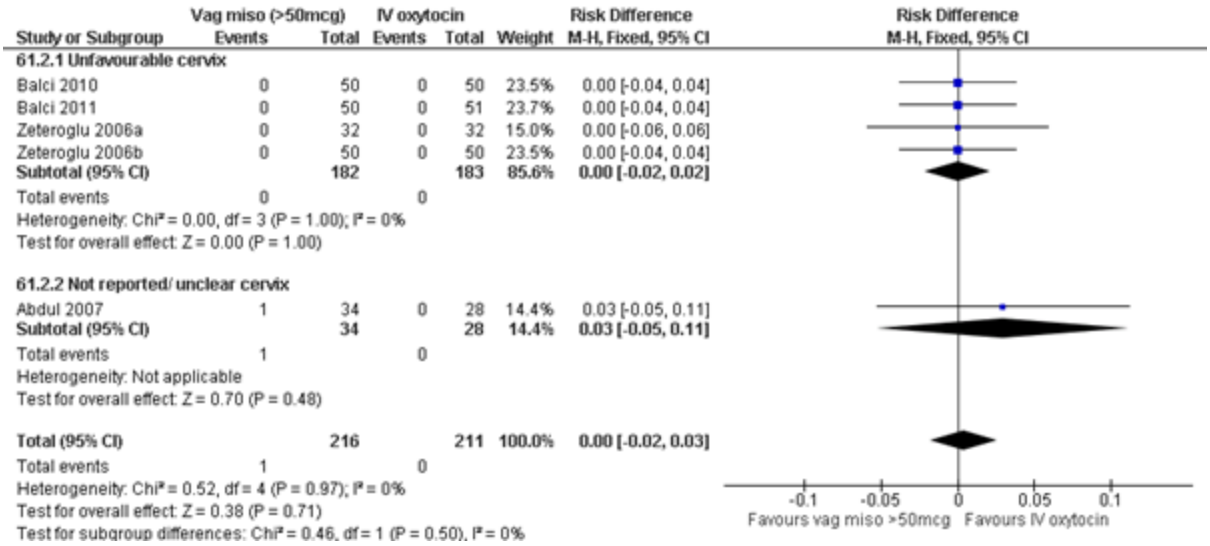
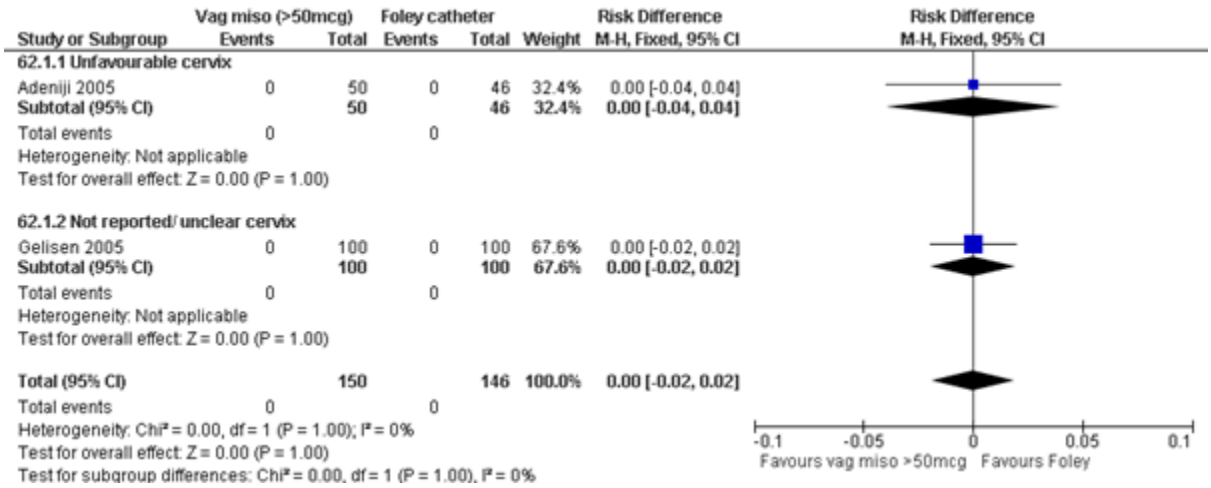


Figure 89: Maternal death/morbidity – risk difference



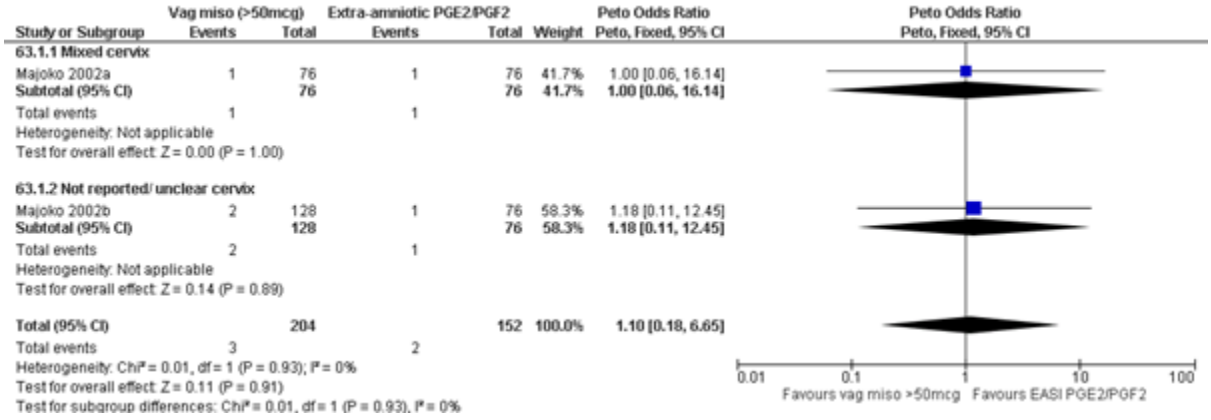
Comparison 33. Vaginal misoprostol (≥50mcg) versus Foley catheter

Figure 90: Perinatal death – risk difference



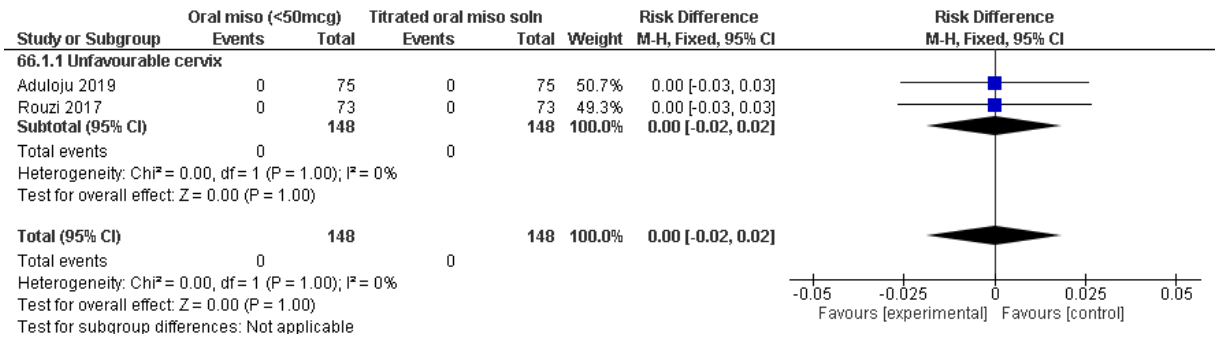
Comparison 34. Vaginal misoprostol (≥50mcg) versus extra-amniotic PGE_2/PGF_2

Figure 91: Perinatal death – Peto odds ratio



Compaison 35. Oral misoprostol (<50mcg) versus titrated oral misoprostol solution

Figure 92: Perinatal death – risk difference



Compaison 36. Oral misoprostol (≥50mcg) versus Foley catheter

Figure 93: Perinatal death – Peto odds ratio

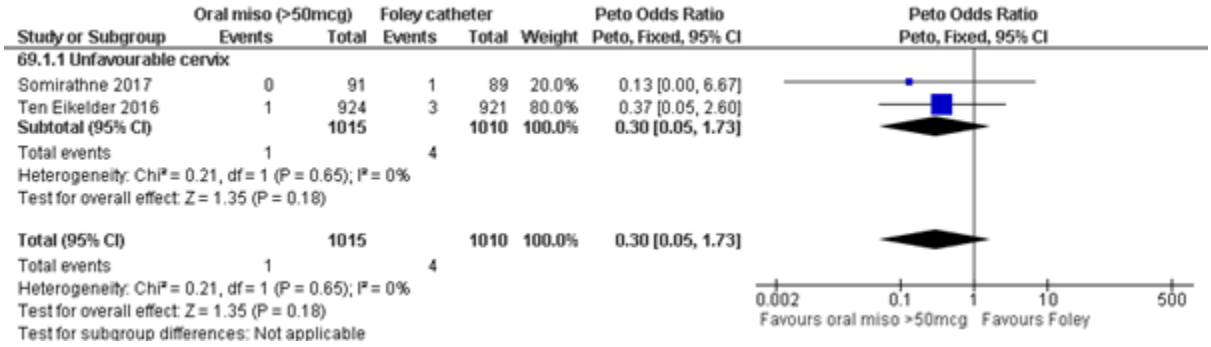
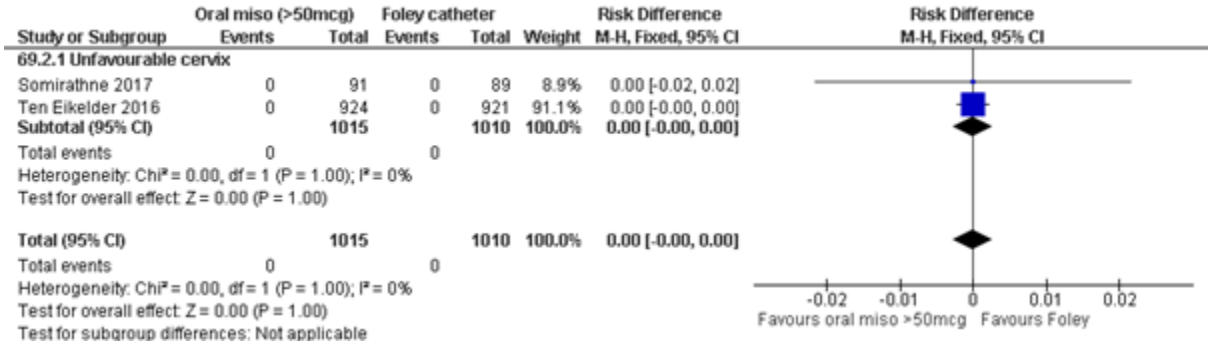
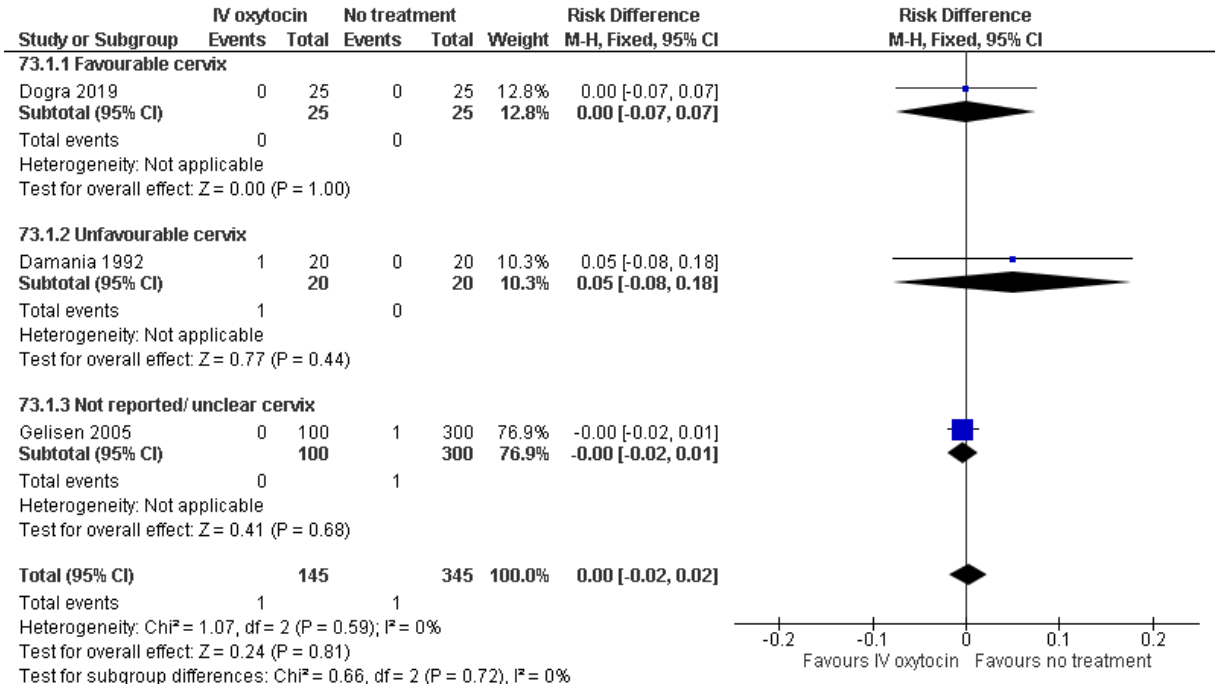


Figure 94: Maternal death/morbidity – risk difference



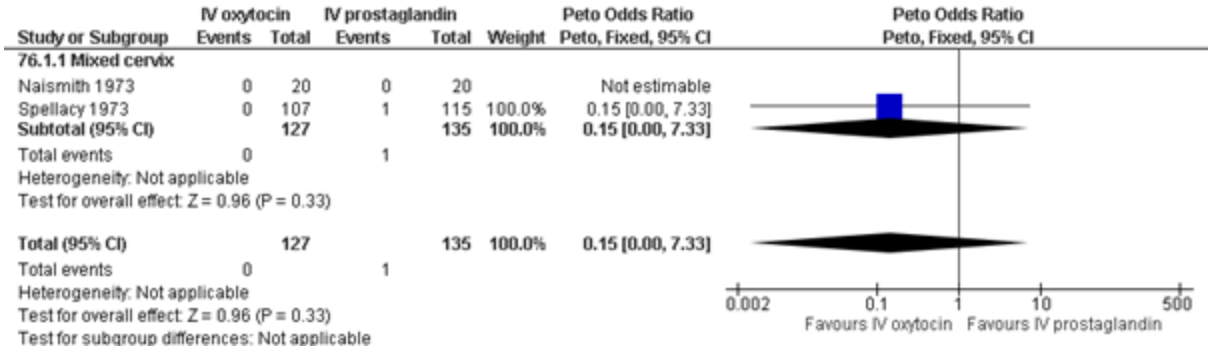
Comparison 37. IV oxytocin versus no treatment

Figure 95: Perinatal death – risk difference



Comparison 38. IV oxytocin versus IV prostaglandin

Figure 96: Perinatal death – Peto odds ratio



Comparison 39. IV oxytocin+amniotomy versus no treatment

Figure 97: Perinatal death – Peto odds ratio

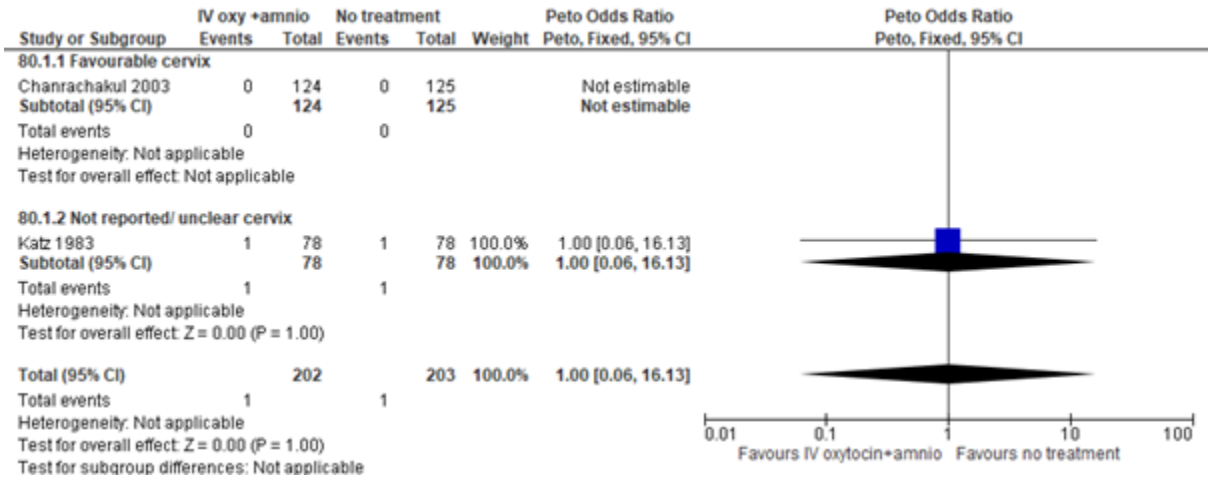
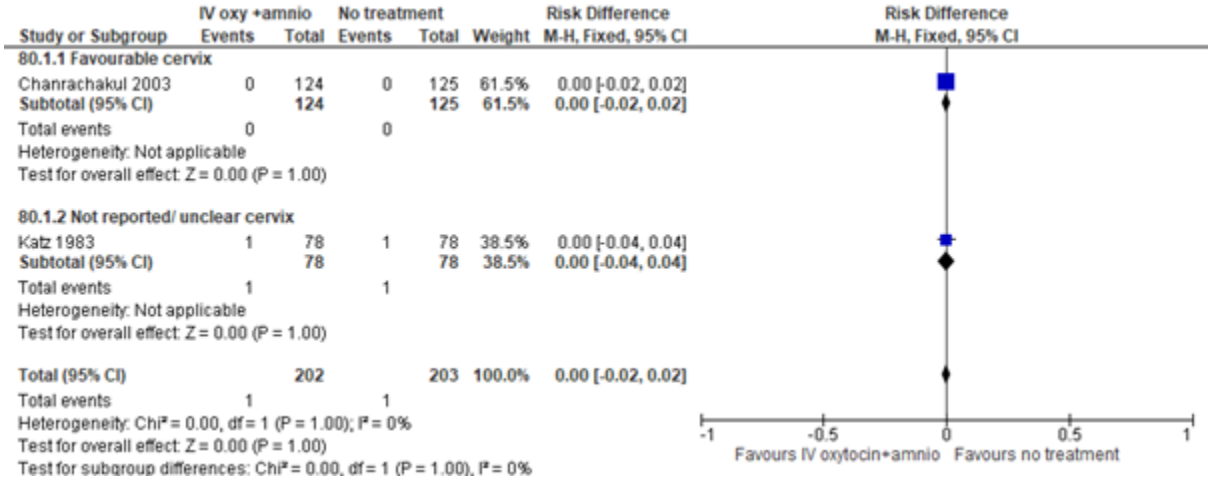
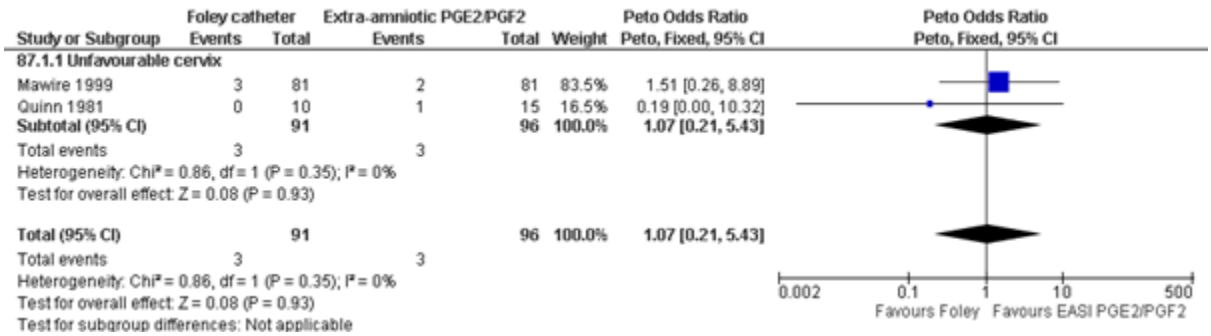


Figure 98: Perinatal death – risk difference



Comparison 40. Foley catheter versus extra-amniotic PGE_2/PGF_2

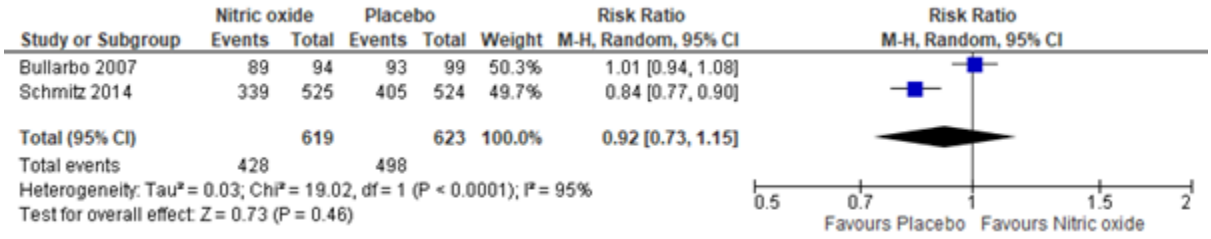
Figure 99: Perinatal death – Peto odds ratio



Important outcome: Maternal satisfaction

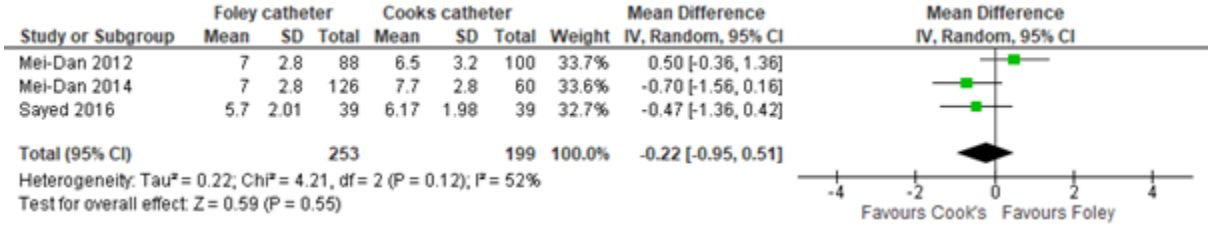
Comparison 41. Nitric oxide versus placebo

Figure 100: Would recommend – risk ratio



Comparison 42. Foley catheter versus double balloon catheter (Cook's)

Figure 101: Satisfaction (0 to 10)



Comparison 43. Vaginal misoprostol (<50mcg) versus buccal/sublingual misoprostol

Figure 102: Would use again – risk ratio

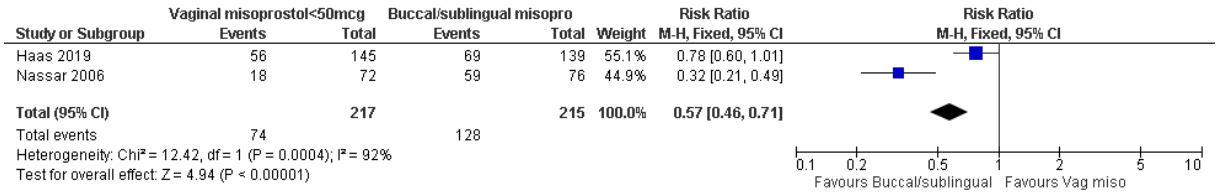
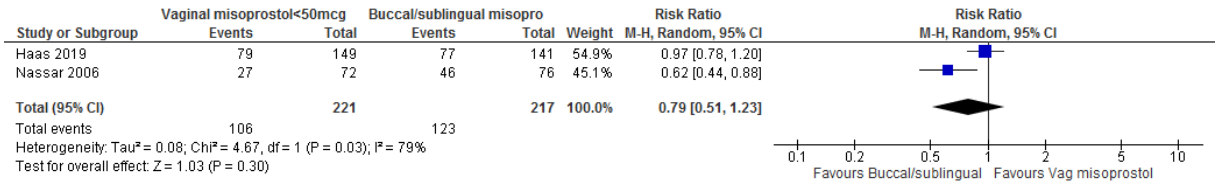
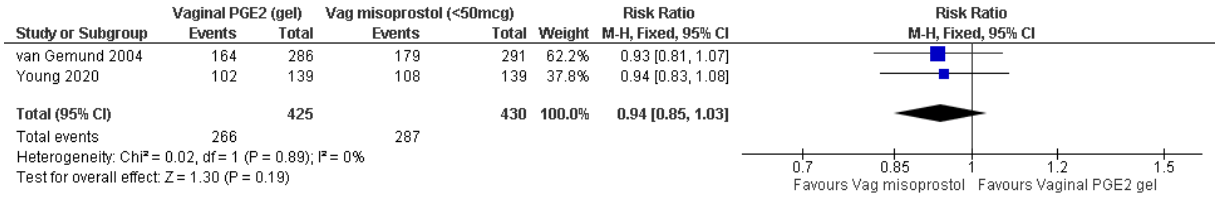


Figure 103: Favourable view of induction – risk ratio



Comparison 44. Vaginal PGE2 (gel) versus vaginal misoprostol (<50mcg)

Figure 104: Would use same method again – risk ratio

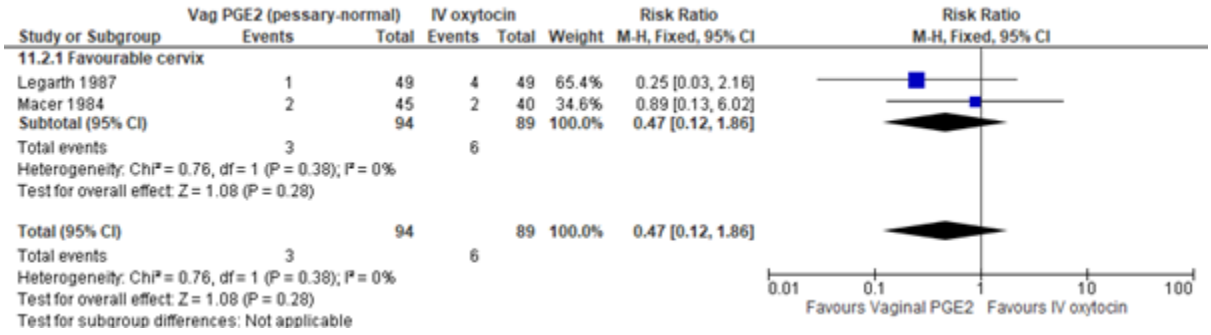


Sub-group analysis for women with Bishop score >6

Comparison 45. Vaginal PGE_2 (pessary –normal release) versus IV oxytocin

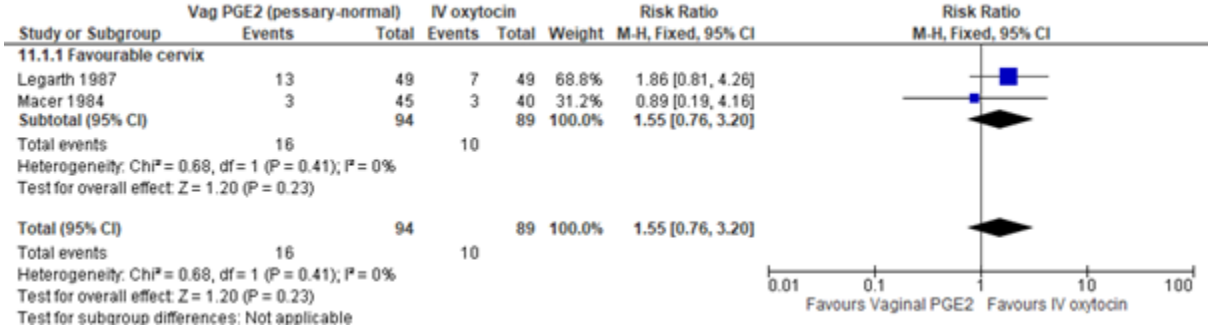
Critical outcome

Figure 105: Caesarean birth – risk ratio



Important outcome

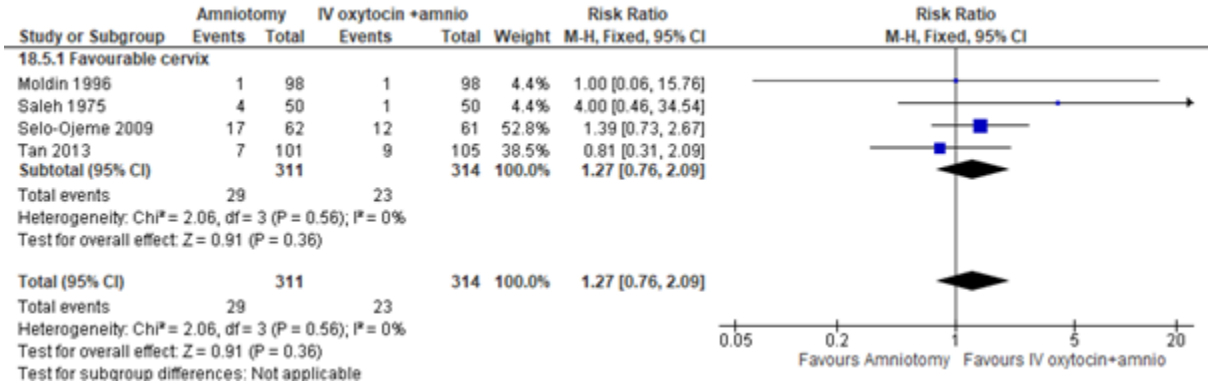
Figure 106: Instrumental birth – risk ratio



Comparison 46. Amniotomy versus IV oxytocin+amniotomy

Critical outcome

Figure 107: Caesarean birth – risk ratio



Important outcomes

Figure 108: Instrumental birth – risk ratio

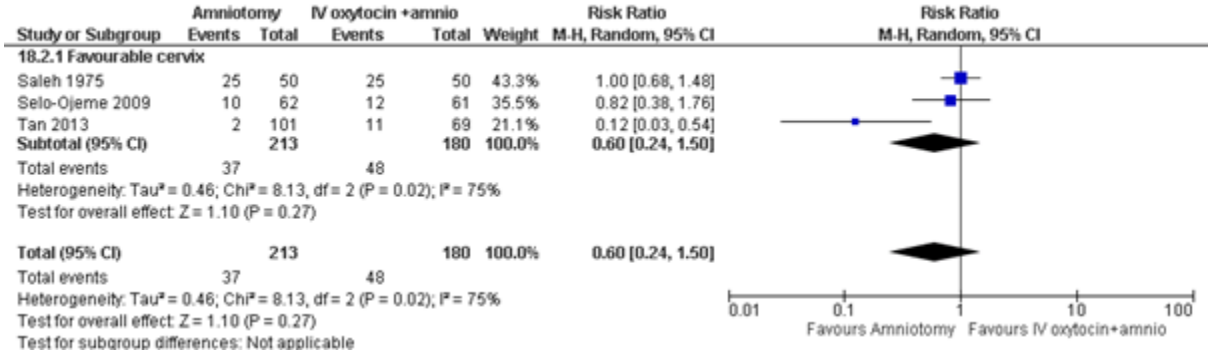


Figure 109: NICU admission – Peto odds ratio

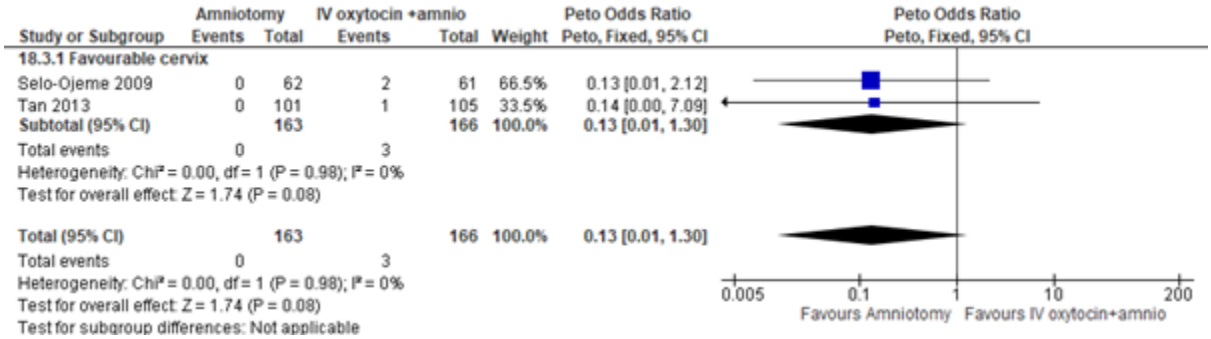
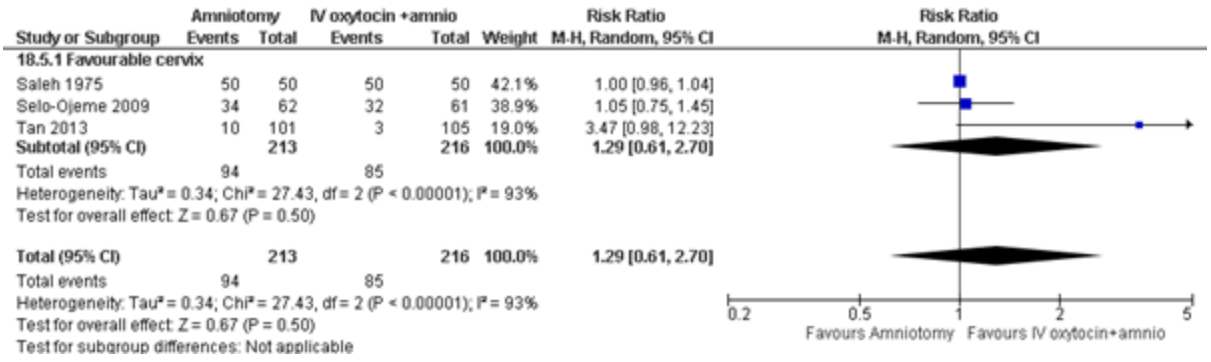


Figure 110: Epidural – risk ratio



Appendix F – GRADE tables

GRADE tables for review question: What are the benefits and harms of pharmacological and mechanical methods in induction of labour?

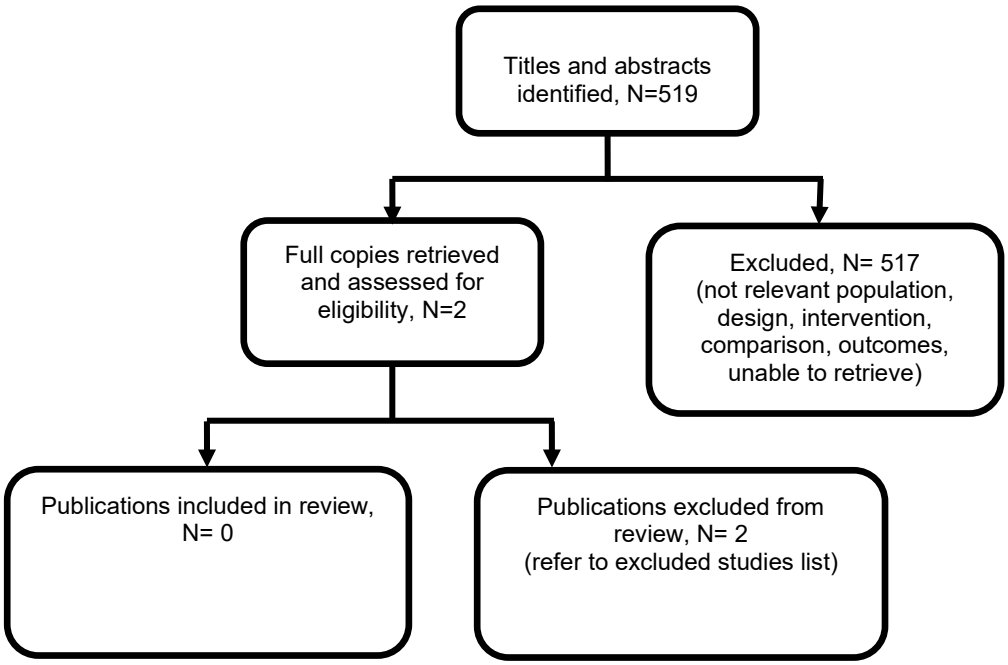
Due to the size and complexity of these tables they are provided in a separate document. See Supplement 4.

Appendix G – Economic evidence study selection

Economic evidence study selection for review question: What are the benefits and harms of pharmacological and mechanical methods in induction of labour?

No evidence was identified which was applicable to this review question.

Figure 111: Study selection flow chart



Appendix H – Economic evidence tables

Economic evidence tables for review question: What are the benfits and harms of pharmacological and mechanical methods in induction of labour?

No evidence was identified which was applicable to this review question.

Appendix I – Economic evidence profiles

Economic evidence profiles for review question: What are the benefits and harms of pharmacological and mechanical methods in induction of labour?

Table 29: Economic evidence profiles for different induction of labour methods

Study and country	Limitations	Applicability	Other comments	Incremental costs[2]	Incremental effects[2]	iNMB[2]	Uncertainty
National Guideline Alliance model Cost-utility analysis of different induction of labour methods	Potentially serious limitations[1]	Directly applicable[2]	**Type of economic analysis:** Cost-utility analysis **Time horizon:** 4 days **Primary measure of outcome:** Incremental net monetary benefit	**Base case analysis (all women)** **Vaginal PGE_2 (pessary normal release)** -£827 **Sub-group analysis (Bishop score≤6)** **Vaginal PGE_2 (pessary normal release)** -£804	**Base case analysis (all women)** **Vaginal PGE_2 (pessary normal release)** 0.0006 QALYs **Sub-group analysis (Bishop score≤6)** **Vaginal PGE_2 (pessary normal release)** 0.0006 QALYs	**Base case analysis (all women)** **Vaginal PGE_2 (pessary normal release)** £839[3] **Sub-group analysis (Bishop score≤6)** **Vaginal PGE_2 (pessary normal release)** £815[3]	**Base case analysis (all women) PSA** **Vaginal PGE_2 (pessary normal release)** 37% probability most cost-effective **Sub-group analysis (Bishop score≤6)** **Buccal/sublingual misoprostol** 32% probability most cost-effective Additional sensitivity analyses found that IV oxytocin

Study and country	Limitations	Applicability	Other comments	Incremental costs[2]	Incremental effects[2]	iNMB[2]	Uncertainty
							plus amniotomy had a 63% probability of being cost-effective in all women when it was included in the analysis Vaginal PGE_2 gel had a 48% probability most cost-effective in women with a Bishop score<6 when undertaken on an outpatient basis

1. *Health state utilities not based on EQ-5D and crude estimate of time horizon to inform QALY calculations*
2. *Limited to the most cost-effective intervention in each analysis relative to no treatment*
3. *Incremental net monetary benefit calculated as a cost-effectiveness threshold of £20,000 per QALY*

Appendix J – Economic analysis

Economic evidence analysis for review question: What are the benefits and harms of pharmacological and mechanical methods in induction of labour?

Cost-utility analysis of different induction of labour methods

Introduction

A large number of births in the NHS are preceded by induction of labour. There are many different methods, pharmacological and mechanical, and they differ in terms of their treatment costs. Furthermore, differing efficacy of alternative methods would lead to differences in outcome related costs and health related quality of life. Therefore, it is important to consider the cost-effectiveness of these alternative methods in the context of a resource constrained publicly funded health service and the potentially large resource impact given the number of women treated.

Since the previous NICE guideline was published in 2008 there has been new clinical evidence published as well as a UK health technology assessment (UK HTA): Which method is best for the induction of labour? (Alfirevic 2016). This HTA synthesised the clinical effectiveness evidence for different methods of induction of labour using an NMA. An economic evaluation was included as part of this HTA. However, it was decided that the NMA needed to be updated for this NICE guideline update and as the NMA informed the previous economic evaluation it was decided that the health economic model needed to be updated too. The developers of the health economic model used in the HTA allowed the NICE guideline developers to use their model when updating the analysis for the purposes of this guideline (see acknowledgements at the end of Appendix J).

Methods

As this analysis updated a previous model, further details on the methods are provided in that UK HTA report.

Setting and population

The model was for NHS settings where induction of labour is undertaken and the population was pregnant women offered third trimester induction of labour for any indication. The time horizon for the analysis was starting induction of labour to hospital discharge. A sub-group analysis was undertaken in which the population was pregnant women with a Bishop score of 6 or less offered induction of labour.

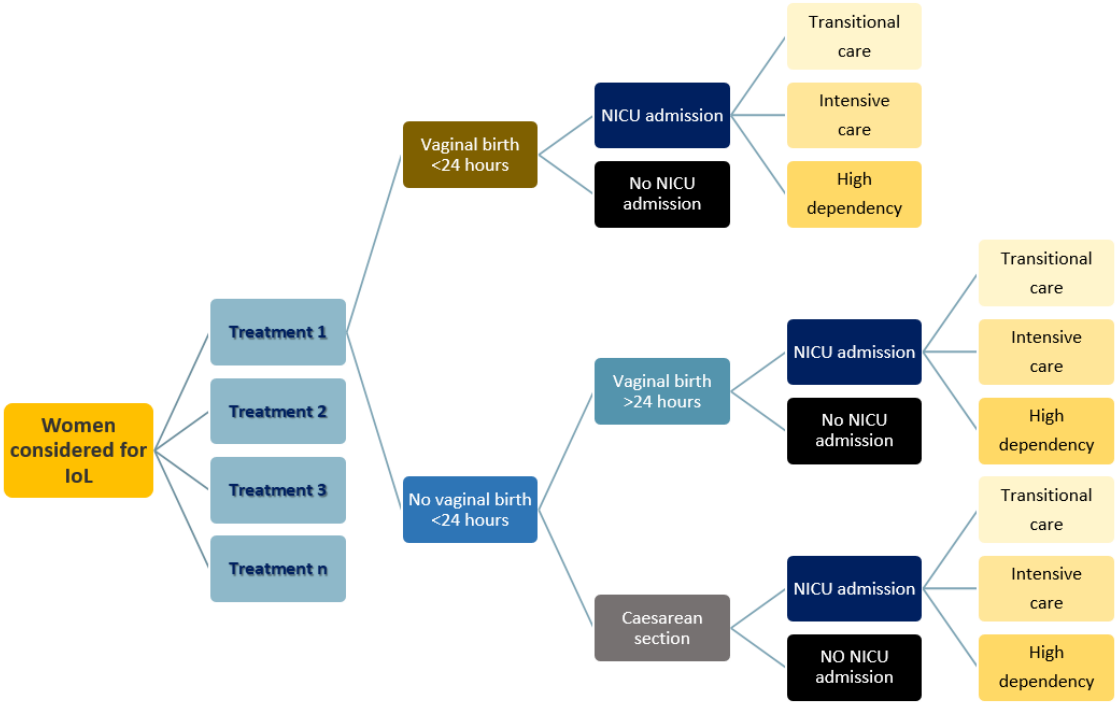
Model structure

A decision analytic model was developed in Microsoft Excel® to assess the cost-utility of different induction of labour methods. It essentially utilises the same model structure as used in the UK HTA report with the only substantive difference being the way that, in this analysis, a duration was attached to the health states in order to generate QALY estimates.

A schematic of the model is shown in Figure 112. As a result of induction of labour, the model first categorises women into those that have a vaginal birth within 24 hours for a given induction of labour method, and those that do not. Women who do not give birth vaginally

within 24 hours, are further categorised into those who have a caesarean birth (at any time following induction of labour) and those who have a vaginal birth occurring more than 24 hours after induction of labour. A proportion of births resulted in a neonatal intensive care unit (NICU) admission, with different level of severity. The probability of a NICU admission depended on whether there was a vaginal birth or caesarean birth, however given a NICU admission the level of severity was assumed to be independent of the mode of birth. Costs were attached to treatment and model outcomes and quality adjusted life years (QALYs) were assigned on the basis of outcome.

Figure 112: A schematic of the model decision tree



Clinical outcomes

The clinical outcomes incorporated into the model were the same as those utilised in the HTA economic evaluation:

i. No vaginal birth within 24 hours of starting induction of labour

ii. Caesarean birth

iii. NICU admission

As with the HTA economic evaluation, the relative treatment effectiveness for different induction of labour methods was estimated from 3 NMAs. These NMAs were updated for this guideline.

There are 3 possible birth outcomes which are derived from 2 of the NMAs:

a. Vaginal birth within 24 hours of starting induction of labour

b. Vaginal birth after 24 hours of starting induction of labour

c. Caesarean birth

For the clinical review reported earlier in the evidence review, the caesarean birth NMA was based on the relative treatment effect for all births. Similarly, the NMA for no vaginal birth within 24 hours of induction of labour was also based on all births. However, it is not possible to calculate the proportion of vaginal births after 24 hours from this data, as those not having a vaginal birth within 24 hours could have either a later vaginal or caesarean birth, whilst those women not having a caesarean birth would include all vaginal births regardless of timing. Therefore, the caesarean birth NMA utilised in this model was based on a population of women who had not had a vaginal birth within 24 hours and therefore it differs from the caesarean birth NMA reported earlier in the clinical evidence profile of this report. The dataset for this adapted NMA was derived from the caesarean birth NMA and no vaginal birth within 24 hours NMA reported in that clinical evidence profile. The numerators in the no vaginal birth within 24 hours NMA give the denominators for the adapted NMA of caesarean birth given no vaginal birth within 24 hours, the population who didn't achieve vaginal birth within 24 hours. The numerators (or events) in the caesarean birth NMA are the same numerators for the adapted NMA for caesarean birth given no vaginal birth within 24 hours by definition. This meant it was possible to use the caesarean birth NMA to estimate the conditional probability of caesarean birth or vaginal birth after 24 hours in those women who did not have a vaginal birth within 24 hours of induction of labour.

NICU admission was considered as an adverse outcome in the model and serves as an intermediate proxy for a range of adverse birth outcomes with a potentially detrimental impact on health related of quality of life. Data on relative treatment effects were taken from the NMA undertaken for this guideline update. Other assumptions and model inputs relating to NICU admission were as per the HTA economic evaluation. It was assumed that the risk of NICU admission was related to mode of birth but not to duration from labour. Using data from 2,837 live births with induction of labour at Liverpool Women's NHS Foundation Trust in 2014, as no more recent evidence was found, it was estimated that NICU admission was 50% higher for caesarean birth than for vaginal birth[a]. Based on this estimate, the following formula was derived to obtain the probability of NICU admission according to mode of birth from the NMA data, which did not distinguish mode of birth:

Vaginal birth

$p(NICU_{VB}) = p(NICU_{NMA}) \times 2/(2 + p(CS_{NMA}))$

Caesarean birth

$p(NICUcs) = p(NICU_{NMA}) \times 3/(2 + p(CS_{NMA}))$

Where:

- $p(NICU_{VB})$ is the probability of a NICU admission for a vaginal birth
- $p(NICUcs)$ is the probability of a NICU admission for a caesarean birth
- $p(NICU_{NMA})$ is the probability of a NICU admission sampled from the NMA for the treatment of interest
- $p(CS_{NMA})$ is the probability of caesarean birth sampled from the NMA for the treatment of interest

a Whilst the committee considered that the Liverppol data was likely to be applicable to the general population they acknowledged that this could depend on whether their timings for induction of labour for low risk women were different from what was typical elsewhere in England. However, a sensitivity analysis (not presented) which varied the multiplier for NICU admission for caesarean birth relative to vaginal birth between 1.0 and 2.0, found that conclusions were robust across this range of values for this model input.

As shown in Figure 112, NICU admission is divided into 3 levels of care which reflects the severity of adverse birth outcomes:

i. Transitional care

ii. High dependency care

iii. Intensive care

Induction of labour methods

The induction methods included in the analysis reflected the interventions for which there was effectiveness data in the 3 NMAs that were incorporated in the health economic model. The 'vaginal PGE_2 tablet' was the reference intervention against which all relative treatment effects in the NMA were calculated The base case analysis included all the induction methods for which there was NMA data for all model outcomes. In addition, 'no treatment' was also included in the base case analysis. There was only NICU NMA data for 'no treatment' and therefore effectiveness data for the other 2 NMAs was imputed by assuming the same relative treatment effects as for 'placebo'.

In addition, a sensitivity analysis was undertaken which included 'amniotomy' and 'IV oxytocin plus amniotomy' which both lacked complete NMA data. 'Amniotomy' lacked NMA data for both the no vaginal birth in 24 hours and caesarean birth outcomes and so relative treatment effectiveness was imputed using NMA relative treatment effects for 'double balloon' at the suggestion from the guideline topic advisor and agreed by the committee. 'IV oxytocin and amniotomy' was only missing NMA data for the caesarean birth outcome and the committee agreed that relative treatment effectiveness for that outcome could reasonably be imputed from 'oxytocin' alone. Indeed, they thought that treatment reported as 'oxytocin' alone would often have been preceded by amniotomy in practice. Table 30 summarises the full list of induction methods assessed in the health economic model.

Table 30: Methods of induction of labour included in the analysis

Method of induction of labour	NMA data	Base case analysis	Treatment used for imputation
Vaginal PGE_2 tablet	Reference intervention	Yes	-
Placebo	All outcomes	Yes	-
No treatment	NICU	Yes	Placebo
Vaginal PGE_2 gel	All outcomes	Yes	-
Vaginal PGE_2 pessary (slow release)	All outcomes	Yes	-
Intracervical PGE_2	All outcomes	Yes	-
Vaginal PGE_2 pessary (normal release)	All outcomes	Yes	-
Vaginal misoprostol (dose less than 50mcg)	All outcomes	Yes	-
Vaginal misoprostol tablet (dose 50mcg or more)	All outcomes	Yes	-

Method of induction of labour	NMA data	Base case analysis	Treatment used for imputation
Oral misoprostol tablet (dose less than 50mcg)	All outcomes	Yes	-
Oral misoprostol tablet (dose 50mcg or more)	All outcomes	Yes	-
Titrated (low dose) oral misoprostol solution	All outcomes	Yes	-
IV oxytocin	All outcomes	Yes	-
Amniotomy	NICU	Sensitivity analysis	Double balloon
IV oxytocin plus amniotomy	NICU, No vaginal birth <24 hours	Sensitivity analysis	IV oxytocin
Nitric oxide	All outcomes	Yes	-
Mifepristone	All outcomes	Yes	-
Mechanical methods - Foley catheter	All outcomes	Yes	-
Mechanical methods - Double balloon or Cook's catheter	All outcomes	Yes	-
Extra-amniotic PGE_2	All outcomes	Yes	-
Buccal/sublingual misoprostol	All outcomes	Yes	-

In the NMAs for the subgroup analysis for women with a Bishop score ≤6 there was no NMA data for 'amniotomy' or 'IV oxytocin plus amniotomy' and so those methods of induction of labour were not included in the subgroup analysis. These methods are not generally considered appropriate in this clinical context and therefore it is not surprising that there was not data in the NMA. Extra-amniotic PGE_2 was also not included as an intervention in the sub-group analysis as NMA data was only available for NICU in those with a Bishop score ≤6.

Baseline

The NMA provided evidence on relative treatment effectiveness relative to a reference intervention. The choice of reference intervention is not crucial but this analysis, like the UK economic evaluation, used vaginal PGE_2 tablet as the reference intervention, as it was included in a number of UK RCTs which contributed to the NMAs which inform the health economic model.

Absolute probabilities and standard deviations for the vaginal PGE_2 tablet for the 3 model outcomes were available from the economic evaluation undertaken for the HTA economic evaluation. These data are summarised in Table 31.

Table 31: Probabilities of events on the reference intervention, vaginal PGE_2 tablet

Outcomes	Probability	Standard deviation	Distribution
No vaginal birth within 24 hours	0.5999	0.0820	Normal
Caesarean birth	0.2389	0.0487	Gamma
NICU admission	0.1335	0.1864	Lognormal

The economic spreadsheet model for the HTA economic evaluation provided simulated absolute probabilities for vaginal PGE_2 tablet for each NMA outcome. To find the best fit probability distribution for these outcomes, the cumulative density function (CDF) at 0.01, 0.25, 0.50, 0.75 and 0.99 for normal, lognormal and gamma distributions using the parameters in Table 31 was compared with the equivalent CDF values estimated from the simulated absolute probabilities. The distribution which gave the closest fit to the simulated probabilities was chosen for the base case analysis. Sensitivity analysis (not presented) found that the cost-effectiveness conclusions were robust to the choice of distribution for these parameters.

Given an admission to NICU, the probability of admission to one of the different levels of care was taken from data on 100 term NICU admissions at Liverpool Women's NHS Foundation Trust between July and October 2014, which remains the best available published evidence for these model inputs. This data is summarised in Table 32 below.

Table 32: Probability of level of care for a NICU admission

NICU level	Probability	Distribution
Transitional care	0.74	Dirichlet
High dependency care	0.07	Dirichlet
Intensive care	0.19	Dirichlet

A Dirichlet distribution was used in the PSA to sample the probability of admission to the various levels of NICU. The count for each level of care was obtained from the Liverpool Women's NHS Foundation Trust NICU admission data and sampled using the cumulative gamma function. The sampled probability of each level of NICU was then calculated as its sample count ÷ sum of the sample counts for all levels of care.

Treatment effectiveness

The previous section outlined the method for estimating the absolute probability for the reference intervention for the outcomes of no vaginal birth within 24 hours, caesarean birth given no vaginal birth within 24 hours or NICU admission. The relevant NMA provided data on the relative treatment effectiveness for each of these 3 outcomes. The output from the NMAs for the economic analysis provided sampled sets of log odds ratios (LORs), measured relative to the reference intervention for each outcome for all induction of labour methods included in the NMA. The absolute probability for each method of induction of labour for each outcome was calculated from the LORs as follows[b]:

probOUTCOME is the sampled absolute probability for the reference intervention.

Logit = LN (probOUTCOME/(1-probOUTCOME))

Log-odds = Logit + sample LOR

Absolute probability = EXP(log-odds)/(1+EXP(log-odds))

Costs

In accordance with NICE methodology a NHS and Personal Social Services (PSS) perspective was adopted for this analysis

[b] probOUTCOME is used to represent the probability of any of the 3 model outcomes, no vaginal birth within 24 hours, caesarean birth given no vaginal birth within 24 hours and NICU admission. The sample of the LOR is taken from a row of NMA output or CODA

(https://www.nice.org.uk/Media/Default/About/what-we-do/our-programmes/developing-NICE-guidelines-the-manual.pdf). Costs were mostly based on a 2020/21 price year. However, NHS Reference Costs were based on the most recent available at the time of writing. The short time horizon of the model meant that all costs occurred within a few days of the start of induction of labour, meaning that there were no future costs to discount.

a) Treatment costs

Treatment costs for each method of induction of labour are summarised in Table 33 below. As a simplifying assumption, pharmacological treatment costs are based on the initial dose and whilst further doses maybe administered if labour is not established we did not have the data on typical dose during induction. Treatment costs were treated deterministically in the model as the values are largely based on a published price which is not subject to sampling uncertainty. Where the value was based on the HTA analysis, prices were uprated to a 2020 value using a combination of the hospital and community health services (HCHS) index and the new NHS Cost Inflation Index (NHSCII). A combination of indices had to be used as the HCHS was discontinued in 2018 with a final index calculated for 2016/17 and the costs used for the HTA analysis were based on a price year of 2012/13 which preceded the earliest index calculated for the new NHSCII for 2015/16. Using both indices gave a multiplier of 1.099 in order to convert 2012/13 prices to an equivalent 2019/20 value.

Table 33: Costs of induction of labour methods assessed in the analysis

Induction of labour method	Cost per dose/induction	Dose	Source
Vaginal PGE_2 tablet	£13.28	1 tablet containing 3mg of dinoprostone	BNF (accessed 05/02/2021)[a]
Placebo	£0.00	N/A	
No treatment	£0.00	N/A	
Vaginal PGE_2 gel	£13.28	2.5 mL (1mg of dinoprostone)	BNF (accessed 05/02/2021)[b]
Vaginal PGE_2 pessary (slow release)	£33.00	1 pessary containing 10mg of dinoprostone released over 24 hours	BNF (accessed 05/02/2021)[c]
Intracervical PGE_2	£13.28	2.5 mL (0.5mg dinoprostone)	BNF (accessed 05/02/2021)[d]
Vaginal PGE_2 pessary (normal release)	£33.00	1 pessary	BNF (accessed 05/02/2021)[e]
Vaginal misoprostol (dose less than 50mcg)	£0.17	<50mcg	BNF (accessed 05/02/2021)[f]
Vaginal misoprostol tablet (dose 50mcg or more)	£0.17	>50mcg	BNF (accessed 05/02/2021)[f]
Oral misoprostol tablet (dose less than 50mcg)	£10.39	<50mcg	BNF (accessed 23/08/2021)[g]
Oral misoprostol tablet (dose 50mcg or more)	£0.17	>50mcg	BNF (accessed 05/02/2021)[h]
Titrated (low dose) oral misoprostol solution	£93.00	Vaginal delivery system containing	BNF (accessed 05/02/2021)[i]

Induction of labour method	Cost per dose/induction	Dose	Source
		200mcg of misoprostol released over 24 hours	
IV oxytocin	£4.01	5 units/1ml solution	BNF (accessed 05/02/2021)[j]
Amniotomy	£1.11	N/A	UK HTA 2016[k]
IV oxytocin plus amniotomy	£5.12	5 units/1ml solution	UK HTA 2016, BNF (accessed 05/02/2021)[l]
Nitric oxide	£0.04	40mg isosorbide mononitrate	BNF (accessed 24/08/2021)[m]
Mifepristone	£10.14	200mg	BNF (accessed 05/02/2021)[n]
Mechanical methods - Foley catheter	£4.62	N/A	UK HTA 2016[h]
Mechanical methods - Double balloon or Cook's catheter	£55.33	N/A	UK HTA 2016[h]
Extra-amniotic PGE_2	£55.33	250 – 500mcg dinoprostone	UK HTA 2016[h]
Buccal/sublingual misoprostol	£0.17	25mcg	BNF (accessed 05/02/2021)[f]

(a) 8 x 300mg dinoprostone for £106.23, so £13.28 per tablet
(b) Price is £13.28 for 2.5 ml with 400 mcg per ml (1mg dose)
(c) Pack of 5 is £165, so £33 each
(d) Not listed in BNF so assumed same price as vaginal PGE_2 gel
(e) Not listed in BNF so assumed same price as vaginal PGE_2 pessary (slow release)
(f) No price listed in BNF so assumed same price as for 200mcg oral tablets
(g) 8 x 25mcg tablets for £83.14, so £10.39 per tablet
(h) 60 x 200mcg tablets for £10.03, so £0.17 per tablet
(i) £465 for a pack of 5, so £93.00 each
(j) 5units/1ml solution for injection ampoules at £4.01
(k) Uprated for inflation by a multiplier of 1.099
(l) Combined cost of amniotomy and IV oxytocin
(m) 56 x 40mg isosorbide mononitrate for £2.15, so £0.04 each
(n) 1 x 200mg for £10.14

Whilst the committee noted that practice varied, they suggested that the following induction of labour methods could be given on an outpatient basis:

- Vaginal PGE_2 tablet
- Vaginal PGE_2 pessary (slow release)
- Vaginal PGE_2 gel
- Mechanical methods – Foley catheter
- Mechanical methods – Double balloon or Cook's catheter

Therefore, sensitivity analyses were undertaken to allow for the potentially higher inpatient costs associated with other methods of induction of labour. The cost of outpatient administration was estimated from the NHS Reference Costs of an outpatient obstetric appointment. Inpatient administration was estimated from the cost of an excess bed-day for vaginal birth with epidural or induction of labour. The additional cost of inpatient

administration was determined as the difference between the two and, in the sensitivity analysis, this additional cost was added to the costs listed in Table 33 for those induction methods not available on an outpatient basis. The costs used to derive the additional costs of inpatient administration are described in Table 34.

Table 34: Cost data used to estimate the additional costs of inpatient administration of induction of labour

Variable	Cost	Source
Outpatient administration	£172	National Schedule of NHS Costs 2018/19, WF01B Non-Admitted Face-to-Face Attendance, First (Consultant led)
Inpatient administration	£569	NHS Reference Costs 2017/18, NZ31C Normal Delivery, with Epidural or Induction, with CC Score 0 (Excess bed days) and updated for inflation by a multiplier of 1.036[a]
Additional cost of inpatient administration	£397	Calculated[b]

(a) Equivalent National Schedule of NHS Costs data was not available for excess bed days in 2018/19 and therefore the cost was increased in line with the percentage increase in costs of outpatient administration costs over that time
(b) Calculated as the difference in cost between inpatient and outpatient administration

b) Outcome costs

In addition to the costs of intervention the model also included the costs associated with mode of birth and NICU admission. The unit costs for these inputs are shown in Table 35.

Table 35: Cost of model outcomes

Outcome	Cost	Standard Error [a]	Distribution	Source
Vaginal birth within 24 hours	£1,820	£58.50	Normal	National Schedule of NHS Costs 2018/19, NZ31C Normal Delivery, with Epidural or Induction, with CC Score 0 (Non-elective short stay)
Vaginal birth after 24 hours	£3,225	£76.09	Normal	National Schedule of NHS Costs 2018/19, NZ31C Normal Delivery, with Epidural or Induction, with CC Score 0 (Non-elective long stay)
Excess bed-day for vaginal birth after 24 hours	£569	£2.88 [b]	Normal	NHS Reference Costs 2017/18, NZ31C Normal Delivery, with Epidural or Induction, with CC Score 0 (Excess bed days) and updated for inflation by multiplier of 1.036
Caesarean birth	£5,128	£117.06	Normal	National Schedule of NHS Costs 2018/19, NZ51C Emergency Caesarean Section with CC Score 0-1 (Non-elective long stay)
NICU admission – transitional care	£466	£55.98	Normal	National Schedule of NHS Costs 2018/19, XA05Z Neonatal Critical Care, Normal Care

Outcome	Cost	Standard Error [a]	Distribution	Source
NICU admission – high dependency unit	£1,007	£112.90	Normal	National Schedule of NHS Costs 2018/19, XA02Z Neonatal Critical Care, High Dependency
NICU admission – intensive care unit	£1,200	£273.26	Normal	National Schedule of NHS Costs 2018/19, XA01Z Neonatal Critical Care, Intensive Care

(a) Standard errors were estimated from the organisation level source data available as part of the National Cost Collection for the NHS (https://www.england.nhs.uk/national-cost-collection /)
(b) Organisation level source data was not available in the 2018/19 National Schedule of NHS Reference Costs. In this case the standard error was estimated from the interquartile range in the 2017/18 National Schedule of NHS Reference Costs using the method outlined in https://www.nice.org.uk/guidance/ng3/evidence/full-guideline-pdf-3784285 (page 575). This was then uprated for inflation

The unit cost of vaginal birth after 24 hours is based on a maximum expected length of stay. However, some women have a longer length of stay than this expected amount and the NHS Reference Costs include data providing a per diem cost for these 'excess' bed-days to account for this. Therefore, the total cost of vaginal births after 24 hours includes the cost of these excess bed-days. The additional mean cost of excess bed-days per vaginal birth after 24 hours was calculated as follows:

Mean cost of excess bed-days per birth = cost of excess bed day x no. excess bed-days ÷ no. of births

For PSA the number of excess bed-days per birth was sampled using a beta distribution.

The NICU unit costs listed in Table 35 are per diem. Therefore, the total costs of NICU admission also has to include the mean length of stay for an admission, which was estimated from data in 100 term NICU admissions at Liverpool Women's NHS Foundation Trust in 2014. NICU length of stay was handled deterministically as there was no quantification of the uncertainty around the point estimate. The additional resource unit data needed to calculate the costs associated with mode of birth and NICU admission are given in Table 36.

Table 36: Resource use variable accounted for in the analysis

Variable	Value	Source
Number of vaginal births after 24 hours	34,277	NHS Reference Costs 2017/18, NZ31C Normal Delivery, with Epidural or Induction, with CC Score 0 (Non-elective short stay)
Number of excess bed-days for vaginal births after 24 hours	9,590	NHS Reference Costs 2017/18, NZ31C Normal Delivery, with Epidural or Induction, with CC Score 0 (Excess bed days)
NICU admission – transitional care length of stay	2.0 days	UK HTA evaluation 2016 (Liverpool Women's NHS Foundation Trust)
NICU admission – high dependency unit length of stay	1.5 days	UK HTA evaluation 2016 (Liverpool Women's NHS Foundation Trust)
NICU admission – intensive care length of stay	2.0 days	UK HTA evaluation 2016 (Liverpool Women's NHS Foundation Trust)

QALYs

No data was found subsequent to the HTA evaluation to derive health state utilities using the EQ-5D. Therefore, we utilised the health state utilities (HSU) reported in the HTA report as shown in Table 37. We assumed a uniform distribution between specified ranges when sampling utility values for PSA.

Table 37: Health state utilities for model outcomes

Outcome	Health state utility	Range
Vaginal birth	0.92	0.72 – 1.00
Caesarean birth	0.59	0.25 – 0.95
NICU –transitional care	0.99	0.99 – 1.00
NICU – high dependency unit	0.845	0.70 – 0.99
NICU – intensive care unit	0.70	0.05 – 0.99

The final health state utilities, from a mother and baby perspective, reflected the combination of mode of birth and any NICU admission as outlined in Table 38.

Table 38: Health state utilities combining mode of birth and NICU admission

Mode of birth	HSU	NICU admission	HSU	Combined HSU
Vaginal birth	0.92	No NICU	1.00	0.92 x 1.00 = 0.92
		Transitional care	0.99	0.92 x 0.99 = 0.91
		High dependency unit	0.845	0.92 x 0.845 = 0.78
		Intensive care unit	0.70	0.92 x 0.70 = 0.64
Caesarean birth	0.59	No NICU	1.00	0.59 x 1.00 = 0.59
		Transitional care	0.99	0.59 x 0.99 = 0.58
		High dependency unit	0.845	0.59 x 0.845 = 0.50
		Intensive care unit	0.70	0.59 x 0.70 = 0.41

However, our approach diverged from the HTA economic evaluation as this analysis used those health state utilities to estimate QALYs for the different model outcomes. This was done in order to provide consistency with the cost-effectiveness threshold approach to decision making in NICE guidelines.

In order to derive QALYs a time horizon of 4 days was assumed for the model which was based on the time from birth to the maximum time to discharge. In order to determine the time to discharge associated with each of the outcomes in the decision tree (Figure 112), a duration was assigned to particular modes of birth using the assumptions outlined in Table 39 which was combined with assumptions about NICU length of stay given in Table 36. It was additionally assumed that all NICU admission occurred on the day of birth. The time to discharge for any decision tree outcome would then be determined either by the length of stay by mode of birth where there was no NICU admission, or according to the longest length of stay resulting from NICU admission or mode of birth. A return to full health was assumed following discharge. The general approach is illustrated in Figure 113 and the time to discharge for each decision tree outcome and the QALY derivation is shown in Table 40.

Table 39: Model inputs for length of stay by mode of birth

Outcome	Days [a]	Source
Vaginal birth within 24 hours	1.0	NHS Reference Costs 2017/18, NZ31C Normal Delivery, with Epidural or Induction, with CC Score 0 (Non-elective short stay)
Vaginal birth after 24 hours	3.0	NHS Reference Costs 2017/18, NZ31C Normal Delivery, with Epidural or Induction, with CC Score 0 (Non-elective long stay)
Caesarean birth	4.0	NHS Reference Costs 2017/18, NZ51C Emergency Caesarean Section with CC Score 0-1 (Non-elective long stay)
Model time horizon	4.0	Assumption

(a) Days to discharge in the event there is no NICU admission

Figure 113: Chart to illustrate QALY estimation using the example of vaginal birth within 24 hours with NICU admission (high dependency unit)

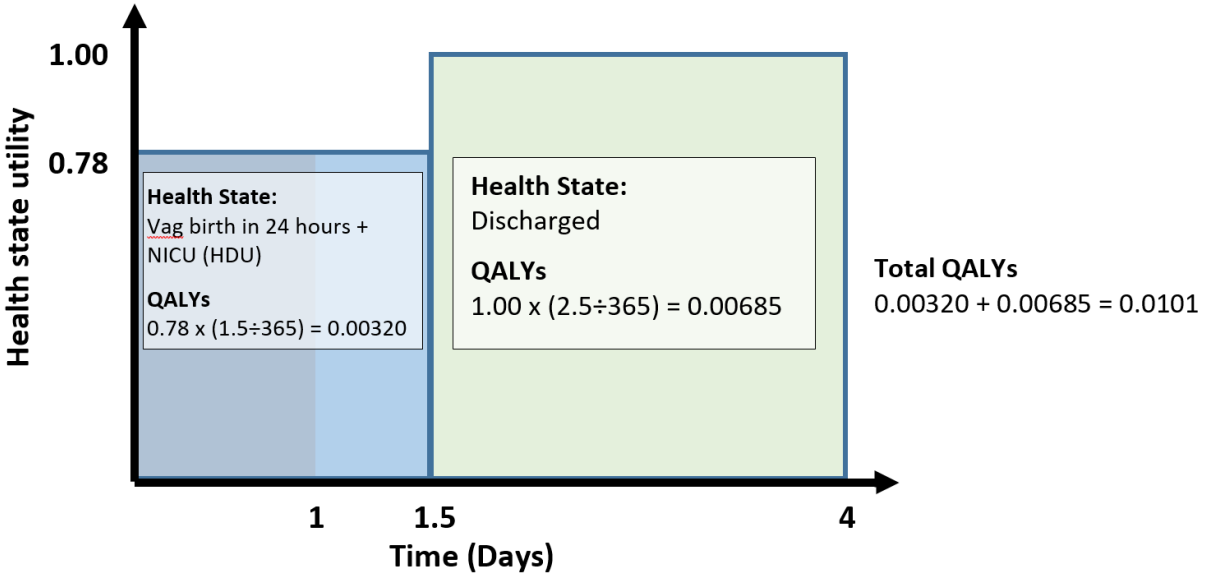


Table 40: Time to discharge (days) and QALYs for each outcome in the decision tree

Mode of birth outcome	NICU outcome	Time to discharge (days)	QALYs
Vaginal birth within 24 hours	No NICU admission	1.0	0.0107
Vaginal birth within 24 hours	Transitional care	2.0	0.0105
Vaginal birth within 24 hours	High dependency unit	1.5	0.0101
Vaginal birth within 24 hours	Intensive care unit	2.0	0.0090
Vaginal birth after 24 hours	No NICU admission	3.3[b]	0.0102
Vaginal birth after 24 hours	Transitional care	3.3[b]	0.0101
Vaginal birth after 24 hours	High dependency unit	3.3[b]	0.0090
Vaginal birth after 24 hours	Intensive care unit	3.3[b]	0.0077
Caesarean birth	No NICU admission	4.0	0.0065

Mode of birth outcome	NICU outcome	Time to discharge (days)	QALYs
Caesarean birth	Transitional care	4.0	0.0064
Caesarean birth	High dependency unit	4.0	0.0055
Caesarean birth	Intensive care unit	4.0	0.0045

(a) Values based on model point estimates
(b) Includes excess bed days associated with a longer inpatient stay

Sensitivity analysis

All results are presented using PSA so as to reflect uncertainty with respect to the precise value of model parameters. This involved running a total of 10,000 Monte Carlo simulations where, with the exception of a small number of deterministic parameters, model inputs are sampled from a probability distribution. In each simulation the costs and QALYs are calculated for each induction of labour method, relative to no treatment, which can be used to generate an incremental net monetary benefit (iNMB) based on a cost-effectiveness threshold of £20,000 per QALY:

NMB = QALYs x £20,000 – costs

By assessing which induction of labour method is the most cost-effective in each simulation it is possible to generate the probability each particular method is the most cost-effective. A summary measure of cost-effectiveness is provided by calculating the mean incremental NMB for each intervention across the 10,000 iterations of the model.

Simulations of relative treatment effectiveness were undertaken using Bayesian Markov chain Monte Carlo (MCMC) simulation, which sampled directly from the joint posterior distribution from the NMAs, thereby maintaining any correlation between them, in the WinBugs® package. The results output (CODA) was then imported into the Microsoft Excel® spreadsheet model. When running the simulations in Excel a random number was used to select a row of data (reflecting a single WinBugs® simulation) so that any correlation between the LORs would be preserved.

However, in addition to the base case and subgroup analysis additional sensitivity analyses were undertaken, in each case the results are presented from a PSA. The various sensitivity analyses are listed below:

1. Base case analysis but with amniotomy and IV oxytocin plus amniotomy additionally included as treatment options
2. Induction of labour in all women but with certain methods of induction of labour administered on an outpatient basis
3. Induction of labour in women with a Bishop score of 6 or less and with certain methods of induction of labour administered on an outpatient basis
4. Induction of labour in all women but with certain methods of induction of labour administered on an outpatient basis and with amniotomy and IV oxytocin plus amniotomy additionally included as treatment options

The reporting of admission to NICU was reported variably in the evidence, and therefore all neonatal admissions were classified for the NMA as admission to NICU. Therefore, as some admissions may have been to a lower intensity care setting the overall NICU admission rate may have been over estimated. Therefore, a sensitivity analysis was taken in which the

baseline NICU admission rate was reduced by 50%. Although not formally presented in the results below, this sensitivity analysis did not substantially alter the results or conclusions of the model.

It should be noted that the threshold analysis, reported in Appendix Q, is a distinct piece of work and not connected to the sensitivity analysis undertaken for this economic analysis.

Results

a) Base case analysis

The results for the base case analysis are summarised in Table 41, Figure 114, Figure 115, Figure 116 and Figure 117. The cost-effectiveness planes (Figure 114 and Figure 115) show a plot of incremental costs and QALYs compared to no treatment for each Monte Carlo simulation. The cost effectiveness acceptability curve (CEAC) in Figure 116 illustrates the probability of an induction of labour method being cost-effective when the cost-effectiveness threshold is varied. The 95% credible intervals for the mean iNMB relative to no treatment are presented graphically in Figure 117.

As Table 41 shows, all induction of labour methods are cost-effective when compared with no treatment as indicated by a positive mean iNMB. Furthermore, it shows that they are all cost saving relative to no treatment with the “downstream” savings from lower rates of caesarean birth and NICU admissions more than offsetting any treatment costs.

The ‘vaginal PGE2 pessary (normal release)’ is the most cost-effective with a mean iNMB of £821 with a vast majority of that accounted for by mean cost savings of £809. It also had the highest probability (33%) of being the most cost-effective intervention.

The low monetary valuation of QALY gains is reflected in the CEAC depicted in Figure 116, which show there is very limited impact of the size of the cost-effectiveness threshold on the probability of any given induction of labour method being cost-effective.

Table 41: Results of base case analysis for all women offered induction of labour

Treatment	Mean incremental cost	Mean incremental QALY	Mean iNMB (95% credible intervals)	Probability cost-effective
Vaginal PGE_2 pessary (normal release)	-£809	0.0006	£821 (£424 to £1,251)	0.333
Titrated (low dose) oral misoprostol	-£781	0.0006	£793 (£441 to £1,186)	0.144
Vaginal misoprostol (dose <50mcg)	-£757	0.0006	£768 (£457 to £1,136)	0.064
Oral misoprostol (dose <50mcg)	-£746	0.0007	£758 (£329 to £1,232)	0.194
Vaginal misoprostol (dose >50mcg)	-£702	0.0005	£711 (£369 to £1,081)	0.018
Buccal/sublingual misoprostol	-£684	0.0005	£694 (£326 to £1,095)	0.047
Sustained release misoprostol	-£673	0.0005	£684 (£190 to £1,1194)	0.126

Treatment	Mean incremental cost	Mean incremental QALY	Mean iNMB (95% credible intervals)	Probability cost-effective
Vaginal PGE_2 gel	-£610	0.0005	£619 (£286 to £988)	0.002
Oral misoprostol (dose >50mcg)	-£553	0.0005	£562 (£248 to £917)	0.000
Intracervical PGE2	-£545	0.0005	£553 (£264 to £894)	0.000
Vaginal PGE2 pessary (slow release)	-£542	0.0005	£550 (£229 to £930)	0.000
Vaginal PGE_2 tablet	-£475	0.0004	£483 (£170 to £833)	0.001
Foley catheter	-£471	0.0003	£478 (£139 to £857)	0.000
Double balloon or Cook's catheter	-£464	0.0003	£470 (£47 to £913)	0.003
Mifepristone	-£429	0.0005	£438 (£18 to £989)	0.056
Nitric oxide	-£417	0.0003	£423 (£81 to £825)	0.003
IV oxytocin	-£333	0.0002	£337 (-£102 to £775)	0.000
Extra-amniotic PGE_2	-£62	-0.0001	£59 (-£728 to £822)	0.010
Placebo	-£12	0.0000	£12 (-£56 to £107)	0.000
No treatment	-	-	-	0.000

Figure 114: Cost-effectiveness plane for base case analysis

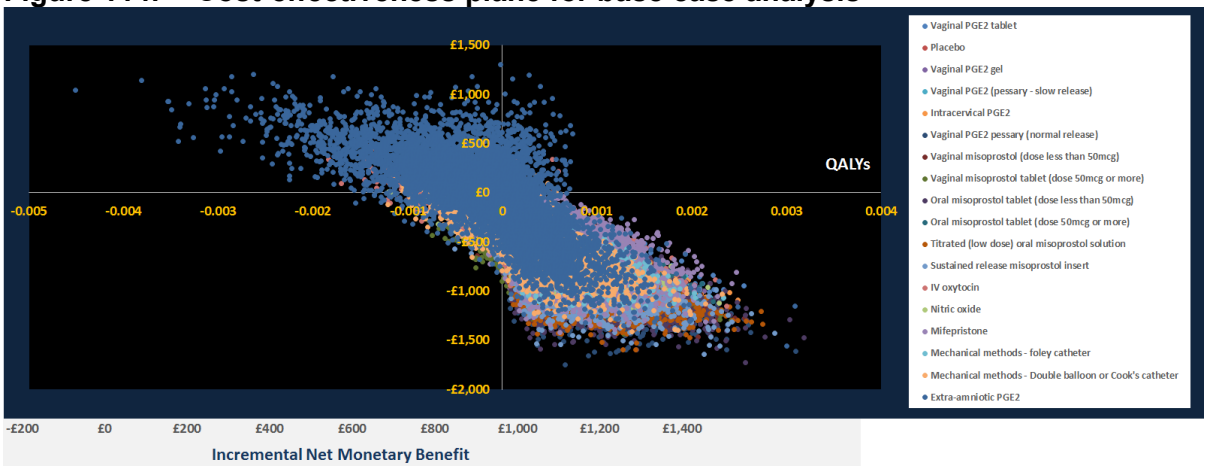


Figure 115: Cost-effectiveness plane for base case analysis (restricted to a comparison of vaginal PGE2 pessary (normal release) versus no treatment)

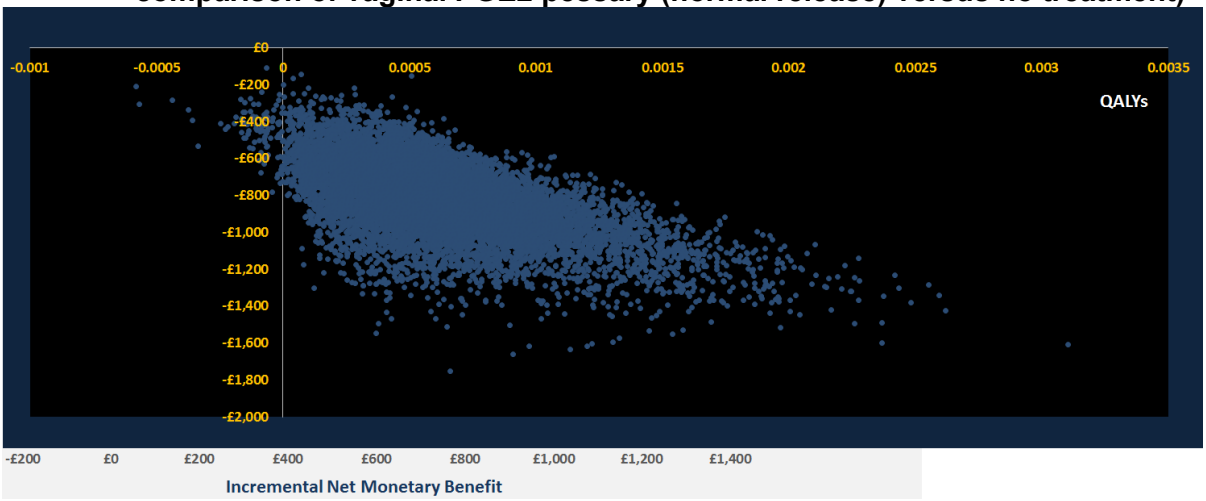
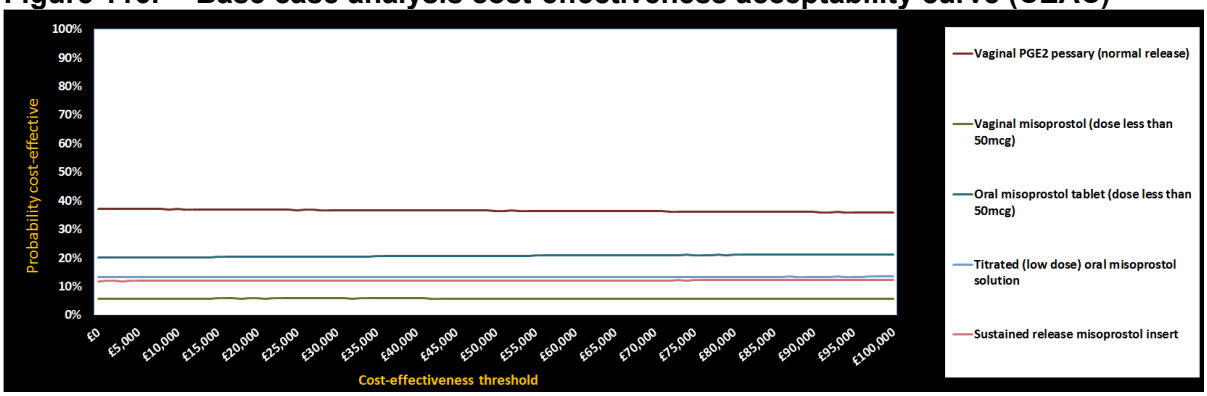
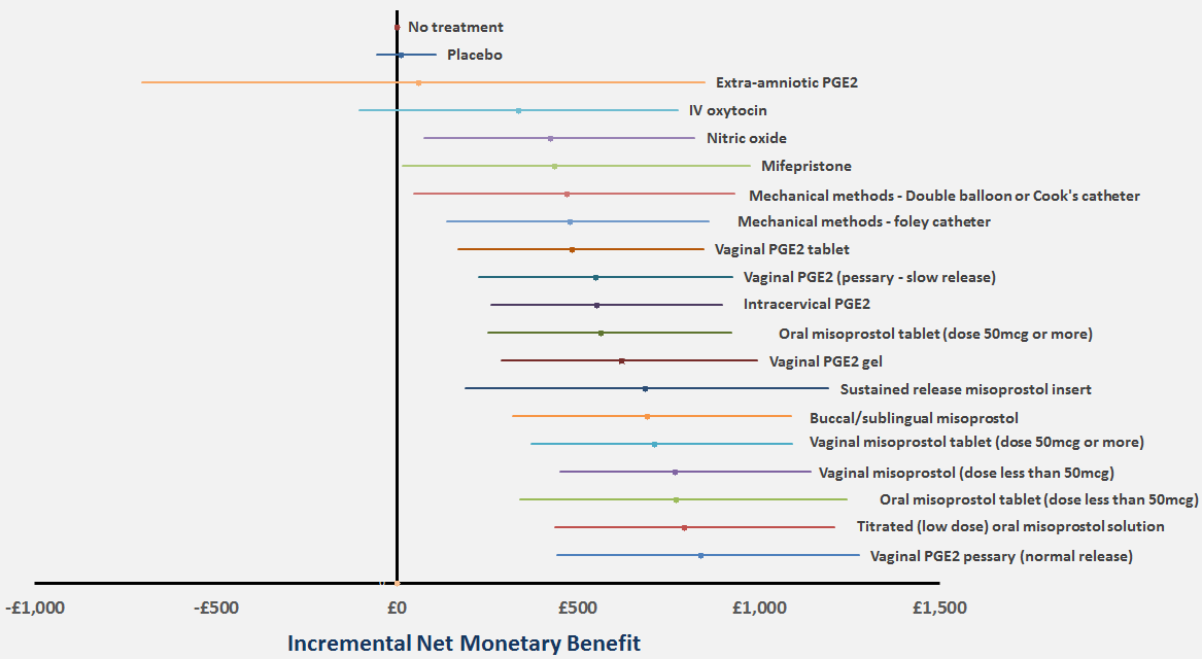


Figure 116: Base case analysis cost-effectiveness acceptability curve (CEAC)



The treatments shown are limited to those with a greater than 5% probability of being cost-effective at a cost-effectiveness threshold of £20,000 per QALY

Figure 117: 95% credible intervals for base case analysis



b) Subgroup analysis for women with a Bishop score ≤6

The results for the subgroup analysis for women with a Bishop score ≤6 are summarised in Table 42, Figure 118, Figure 119, Figure 120 and Figure 121.

Table 42 shows that ranking by mean iNMB is almost identical to ranking by mean incremental cost saving. It shows that 'vaginal PGE_2 pessary (normal release)' is most cost-effective with a mean iNMB of £792 and a 28% probability of being the most cost-effective. All induction of labour methods were cost-effective relative to no treatment.

The CEAC shown in Figure 120 indicates that the value of the cost-effectiveness threshold has very limited impact on the probability of any given induction of labour method being cost-effective. Figure 121 graphs the 95% credible intervals for the mean iNMB relative to no treatment.

Table 42: Results of subgroup analysis for women with a Bishop score of 6 or less on vaginal examination

Treatment	Mean incremental cost	Mean incremental QALY	Mean iNMB (95% credible intervals)	Probability cost-effective
Vaginal PGE2 pessary (normal release)	-£781	0.0006	£792 (£379 to £1,283)	0.278
Vaginal misoprostol (dose <50mcg)	-£756	0.0006	£767 (£416 to £1,159)	0.068
Titrated (low dose) oral misoprostol	-£756	0.0006	£767 (£367 to £1,209)	0.124

Treatment	Mean incremental cost	Mean incremental QALY	Mean iNMB (95% credible intervals)	Probability cost-effective
Buccal/sublingual misoprostol	-£736	0.0005	£746 (£336 to £1,190)	0.140
Oral misoprostol (dose <50mcg)	-£710	0.0006	£699 (£242 to £1,216)	0..156
Vaginal misoprostol (dose >50mcg)	-£690	0.0004	£701 (£334 to £1,097)	0.014
Sustained release misoprostol insert	-£661	0.0005	£671 (£142 to £1,205)	0.129
Vaginal PGE_2 gel	-£566	0.0004	£573 (£196 to £979)	0.001
Vaginal PGE_2 pessary (slow release)	-£528	0.0004	£536 (£154 to £957)	0.001
Oral misoprostol (dose >50mcg)	-£516	0.0004	£524 (£155 to £920)	0.000
Intracervical PGE_2	-£504	0.0004	£511 (£168 to £883)	0.000
Mifepristone	-£454	0.0005	£463 (-£15 to £1,029)	0.079
Double balloon or Cook's catheter	-£453	0.0003	£458 (-£26 to £967)	0.008
Foley catheter	-£444	0.0003	£449 (£56 to £862)	0.000
Nitric oxide	-£408	0.0003	£414 (£24 to £842)	0.002
Vaginal PGE_2 tablet	-£381	0.0003	£386 (-£6 to £800)	0.001
IV oxytocin	-£317	0.0003	£322 (-£125 to £786)	0.000
Placebo	-£35	0.0000	£35 (-£40 to £189)	0.000
No treatment	-	-	-	0.000

Figure 118: Cost-effectiveness plane for subgroup analysis

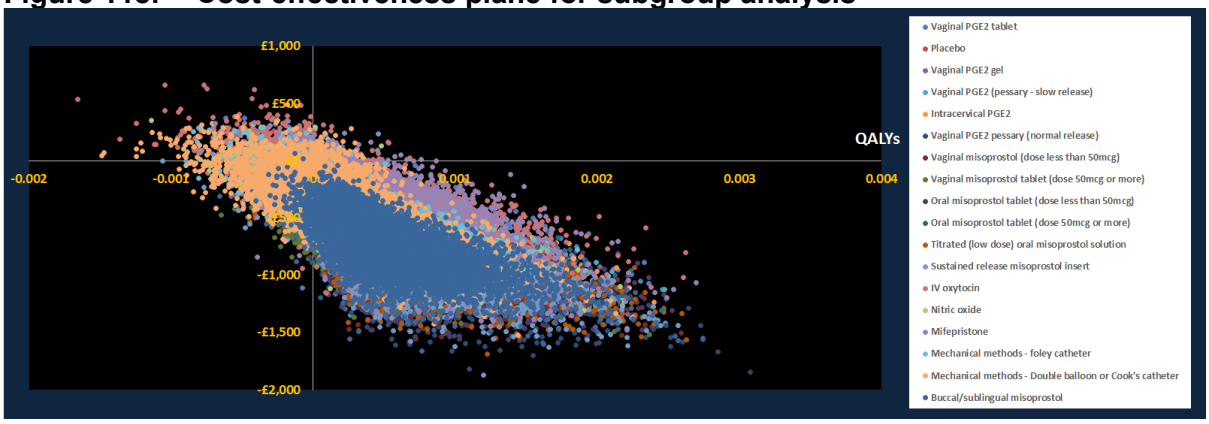


Figure 119: Cost-effectiveness plane for subgroup analysis (restricted to a comparison of vaginal PGE2 pessary (normal release) versus no treatment)

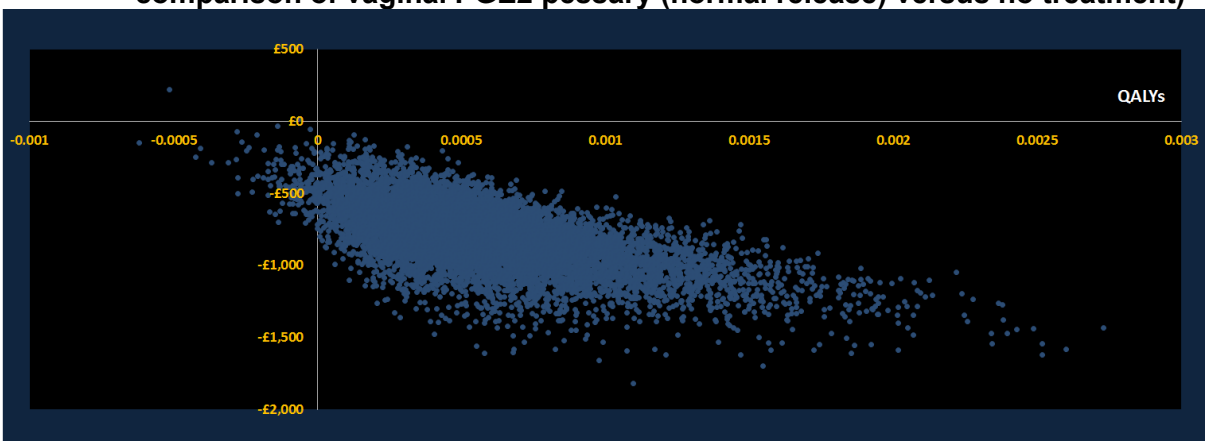
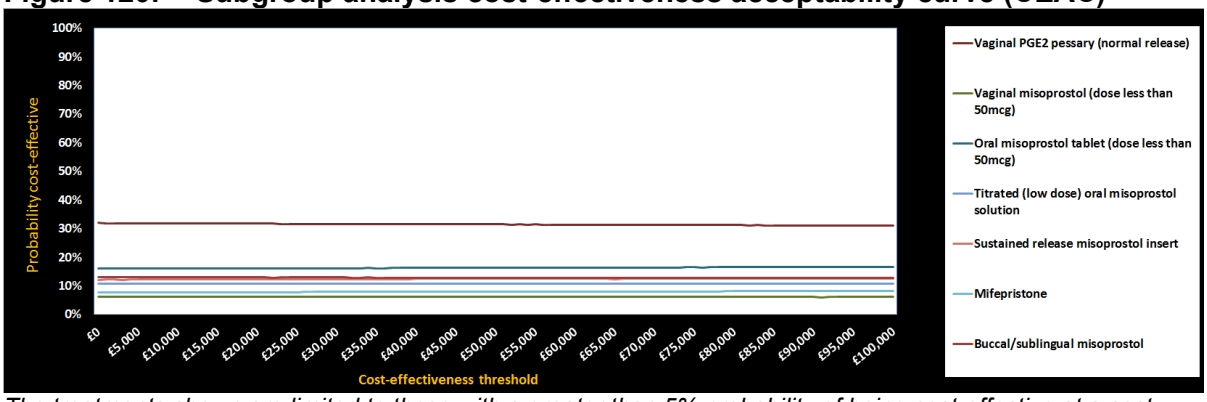
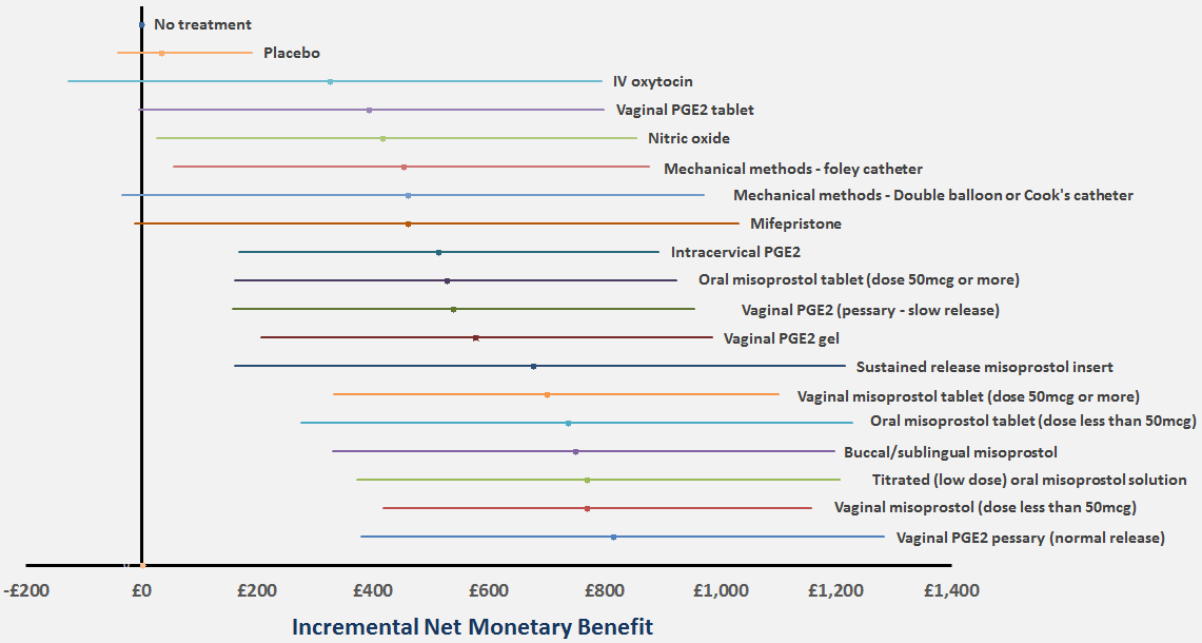


Figure 120: Subgroup analysis cost-effectiveness acceptability curve (CEAC)



The treatments shown are limited to those with a greater than 5% probability of being cost-effective at a cost-effectiveness threshold of £20,000 per QALY

Figure 121: 95% credible intervals for sub-group analysis for women with a Bishop score of 6 or less on vaginal examination



c) Sensitivity analysis 1: Base case analysis for induction of labour but with amniotomy alone and IV oxytocin plus amniotomy additionally included as treatment options

The results for this sensitivity analysis are shown in Table 43, Figure 122, Figure 123, Figure 124 and Figure 125.

Table 43 indicates that 'IV oxytocin plus amniotomy' was the cost-effective treatment with a substantially higher mean iNMB of £1,003 than the other induction of labour methods and a 63% probability of being the most cost-effective, much higher than for any other method. It produced the highest mean incremental savings relative to 'no treatment' and the highest mean incremental QALY, which would lead us to conclude that it dominated the other treatment alternatives. Given this dominance it is not surprising that the CEAC in Figure 124 shows that the cost-effectiveness threshold has a negligible bearing on the probability of 'IV oxytocin plus amniotomy' being the most cost-effective treatment. The 95% credible intervals for the mean iNMB relative to no treatment for this sensitivity analysis are shown diagrametically in Figure 125.

Table 43: Results of sensitivity analysis 1 with amniotomy alone and IV oxytocin plus amniotomy added to the available treatment options

Treatment	Mean incremental cost	Mean incremental QALY	Mean iNMB (95% credible intervals)	Probability cost-effective
IV oxytocin plus amniotomy	-£987	0.0008	£1,003 (£370 to £1,590)	0.625

Treatment	Mean incremental cost	Mean incremental QALY	Mean iNMB (95% credible intervals)	Probability cost-effective
Vaginal PGE_2 pessary (normal release)	-£811	0.0006	£823 (£439 to £1,253)	0.127
Titrated (low dose) oral misoprostol	-£782	0.0006	£794 (£440 to £1,205)	0.050
Vaginal misoprostol (dose <50mcg)	-£758	0.0006	£769 (£458 to £1,143)	0.015
Oral misoprostol (dose <50mcg)	-£746	0.0007	£759 (£332 to £1,231)	0.080
Vaginal misoprostol (dose >50mcg)	-£704	00005	£713 (£373 to £1,088)	0.004
Buccal/sublingual misoprostol	-£685	0.0005	£695 (£321 to £1,106)	0.010
Sustained release misoprostol	-£675	0.0005	£685 (£194 to £1,194)	0.055
Vaginal PGE_2 gel	-£612	0.0005	£621 (£303 to £997)	0.000
Oral misoprostol (dose >50mcg)	-£556	0.0005	£565 (£248 to £925)	0.000
Intracervical PGE2	-£545	0.0005	£554 (£266 to £897)	0.000
Vaginal PGE2 pessary (slow release)	-£541	0.0005	£550 (£223 to £923)	0.000
Amniotomy	-£492	0.0003	£498 (£56 to £961)	0.003
Vaginal PGE2 tablet	-£478	0.0004	£486 (£171 to £847)	0.000
Foley catheter	-£473	0.0004	£480 (£140 to £860)	0.000
Double balloon or Cook's catheter	-£466	0.0003	£472 (£52 to £930)	0.000
Mifepristone	-£426	0.0005	£435 (£1 to £981)	0.025
Nitric oxide	-£420	0.0003	£426 (£70 to £817)	0.001
IV oxytocin	-£337	0.0002	£341 (-£94 to £784)	0.000
Extra-amniotic PGE_2	-£64	-0.0001	£61 (-£713 to £847)	0.004
Placebo	-£12	0.0000	£12 (-£53 to £107)	0.000
No treatment	-	-	-	0.000

Figure 122: Cost-effectiveness plane for sensitivity analysis 1 with amniotomy alone and IV oxytocin plus amniotomy added to the available treatment options

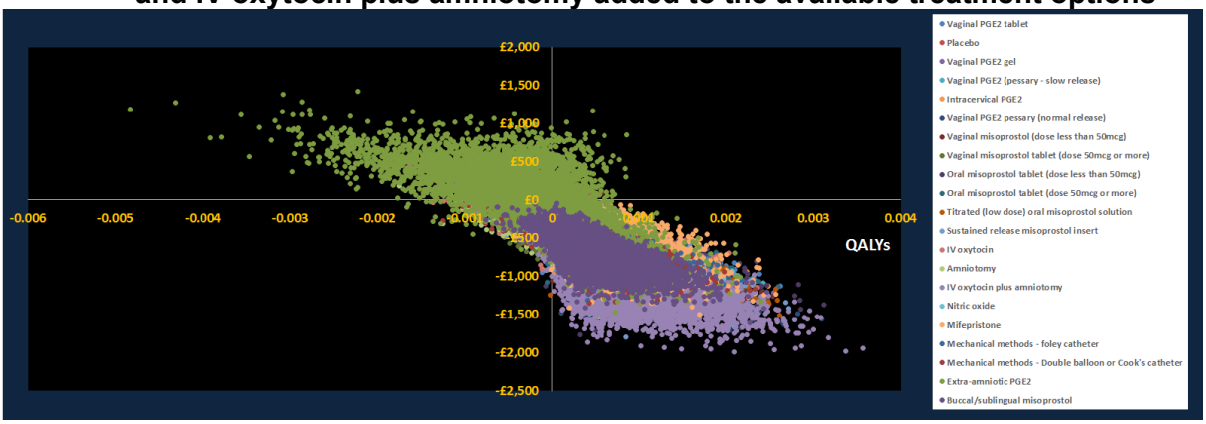


Figure 123: Cost-effectiveness plane for sensitivity analysis 1 (restricted to a comparison of IV oxytocin plus amniotomy versus no treatment)

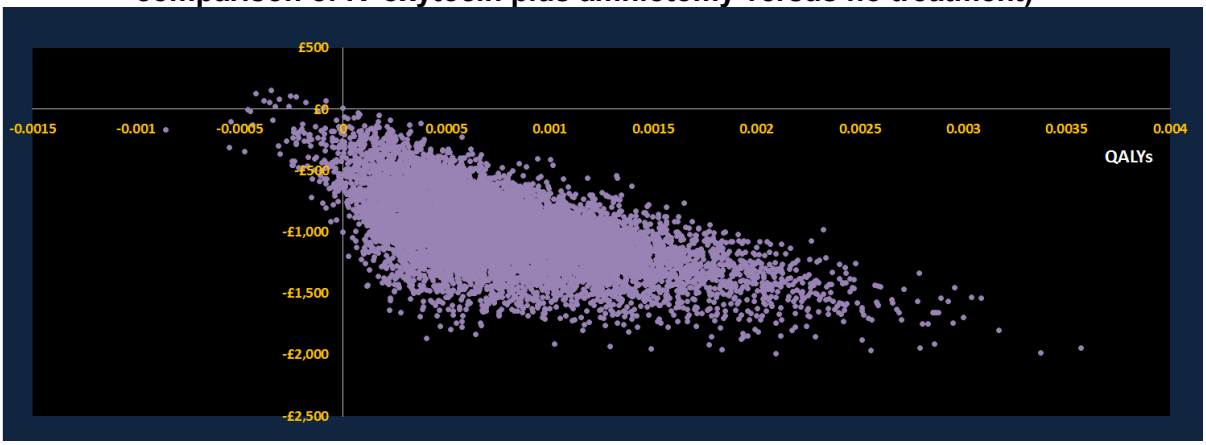
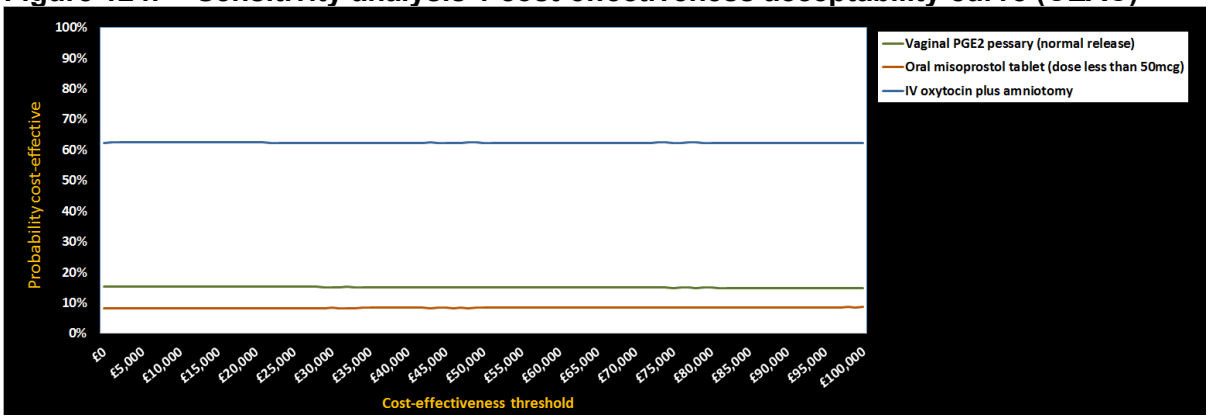
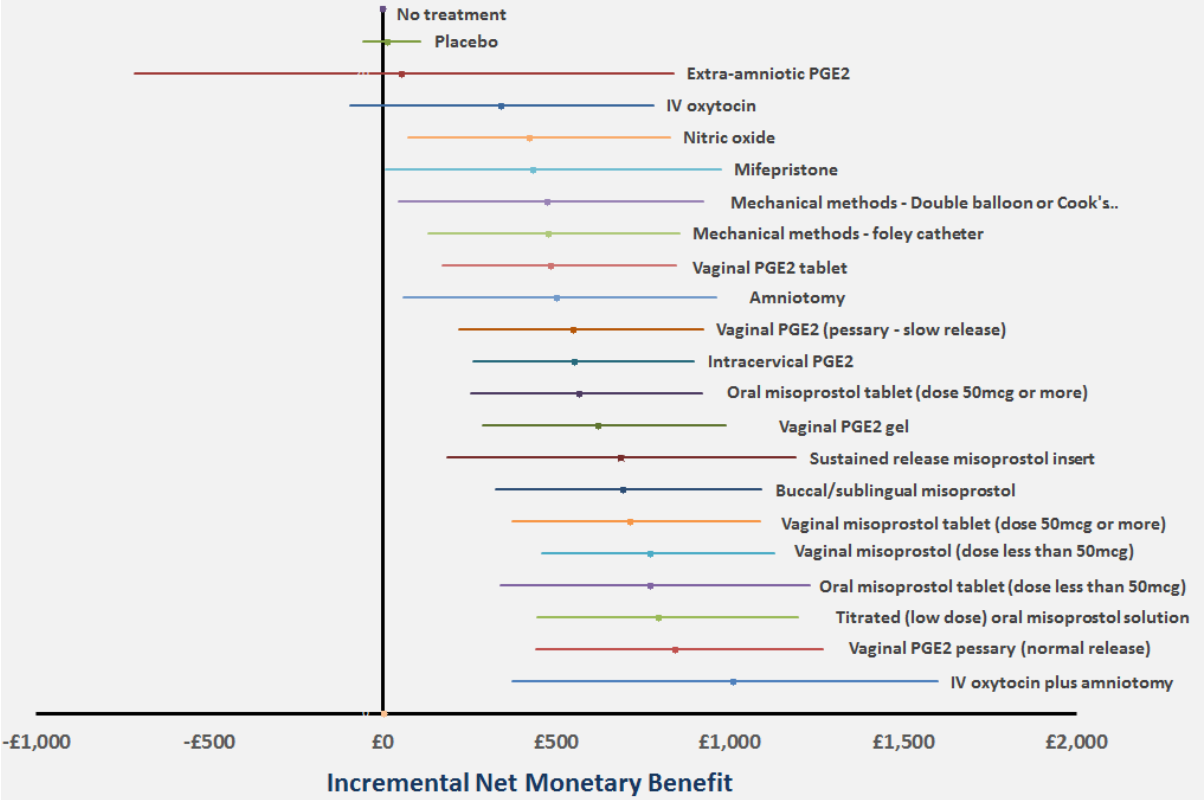


Figure 124: Sensitivity analysis 1 cost-effectiveness acceptability curve (CEAC)



The treatments shown are limited to those with a greater than 5% probability of being cost-effective at a cost-effectiveness threshold of £20,000 per QALY

Figure 125: 95% credible intervals for sensitivity analysis 1 with amniotomy alone and IV oxytocin plus amniotomy added to the available treatment options



d) Sensitivity analysis 2: Base case analysis for induction of labour in women but with certain methods of induction of labour administered on an outpatient basis

Table 44, Figure 126, Figure 127, Figure 128 and Figure 129 provide a summary of the results obtained from this analysis. In Table 44 it can be seen that the 'vaginal PGE_2 gel' is the most cost-effective with a mean iNMB of £621 and a 47% probability of being the most cost-effective treatment. Between them the 3 prostaglandin methods offered on an outpatient basis account for 70% of cost-effective simulations.

Introducing a distinction between much cheaper induction of labour methods because of outpatient administration means that the correlation between cost saving rank and effectiveness rank, as measured by QALYs, is less. The most cost-effective treatments are no longer the most effective and therefore as shown by the CEAC in Figure 128 the probability of 'vaginal PGE2 gel' does fall slightly with an increasing cost-effectiveness threshold caused by its cost-effectiveness falling relatively to methods with a higher incremental QALY gain. The 95% credible intervals for the mean iNMB relative to no treatment are plotted in Figure 129.

Nearly all treatments remained more cost-effective than no treatment even when additional inpatient costs were assumed.

Table 44: Results of sensitivity analysis 2 with the base case analysis adapted to allow outpatient induction of labour for certain methods

Treatment	Mean incremental cost	Mean incremental QALY	Mean iNMB (95% credible intervals)	Probability cost-effective
Vaginal PGE_2 gel	-£612	0.0005	£621 (£294 to £989)	0.473
Vaginal PGE_2 pessary (slow release)	-£544	0.0005	£553 (£232 to £919)	0.144
Vaginal PGE_2 tablet	-£478	0.0004	£486 (£174 to £832)	0.084
Foley catheter	-£475	0.0004	£481 (£142 to £864)	0.044
Double balloon or Cook's catheter	-£469	0.0003	£475 (£46 to £931)	0.129
Vaginal PGE_2 pessary (normal release)	-£415	0.0006	£428 (£40 to £854)	0.047
Titrated (low dose) oral misoprostol	-£387	0.0006	£399 (£40 to £801)	0.006
Vaginal misoprostol (dose <50mcg)	-£363	0.0006	£374 (£66 to £737)	0.000
Oral misoprostol (dose <50mcg)	-£353	0.0007	£366 (-£60 to £837)	0.032
Vaginal misoprostol (dose >50mcg)	-£307	0.0005	£316 (-£17 to £690)	0.000
Buccal/sublingual misoprostol	-£288	0.0005	£298 (-£74 to £705)	0.001
Sustained release misoprostol	-£279	0.0005	£290 (-£200 to £774)	0.021
Oral misoprostol (dose >50mcg)	-£161	0.0005	£170 (-£136 to £530)	0.000
Intracervical PGE_2	-£149	0.0005	£158 (-£130 to £491)	0.000
Mifepristone	-£32	0.0005	£41 (-£386to £598)	0.017
Nitric oxide	-£20	0.0003	£26 (-£330 to £423)	0.000
No treatment	-	-	-	0.000
IV oxytocin	£59	0.0002	-£55 (-£490 to £389)	0.000
Extra-amniotic PGE_2	£347	-0.0001	-£350 (-£1,113 to £427)	0.002
Placebo	£385	0.0000	-£386 (-£455 to -£289)	0.000

Figure 126: Cost-effectiveness plane for sensitivity analysis 2 with certain induction of labour methods administered on an outpatient basis

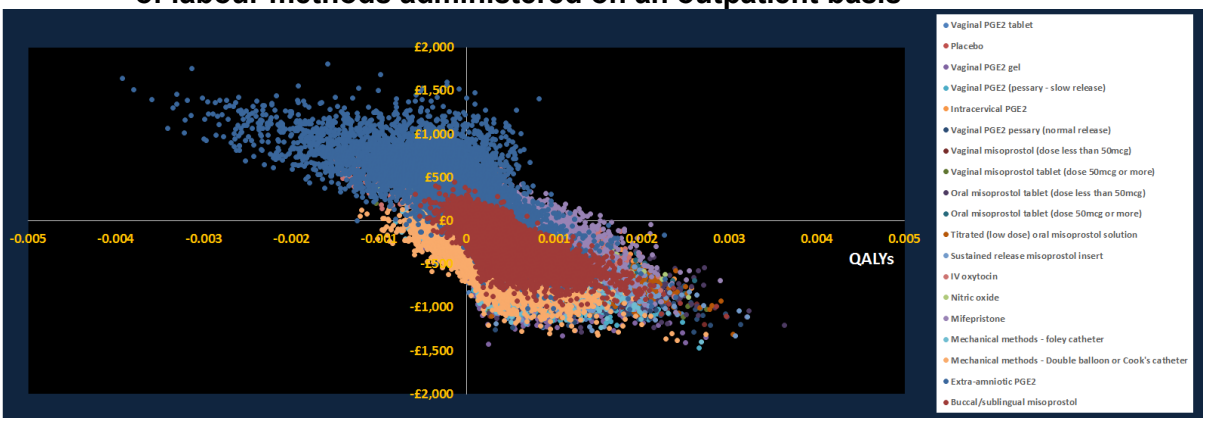


Figure 127: Cost-effectiveness plane for sensitivity analysis 2 (restricted to a comparison of vaginal PGE2 gel versus no treatment)

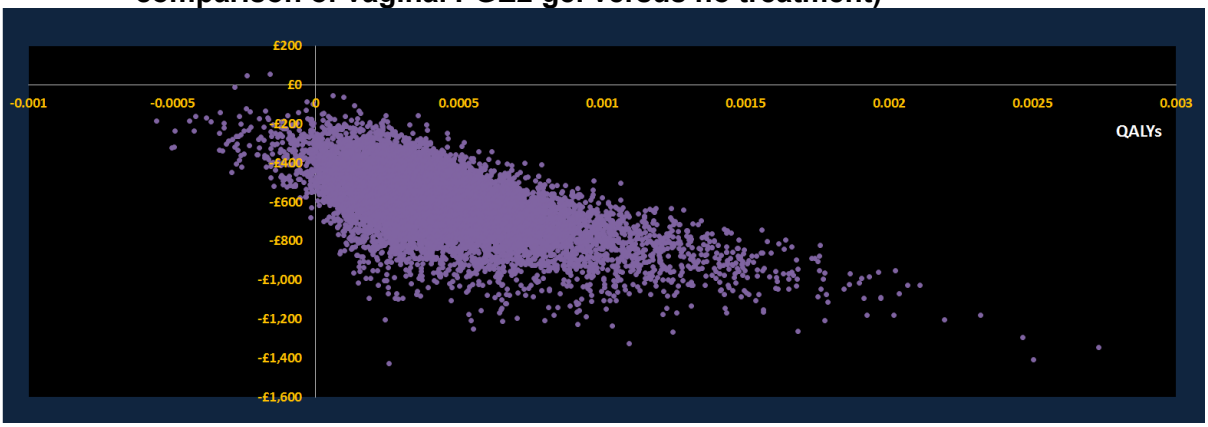
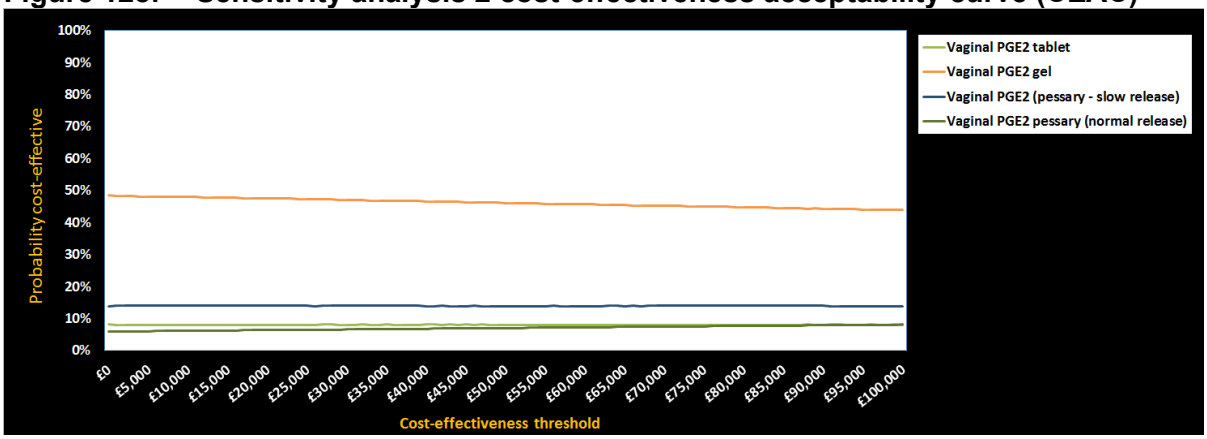
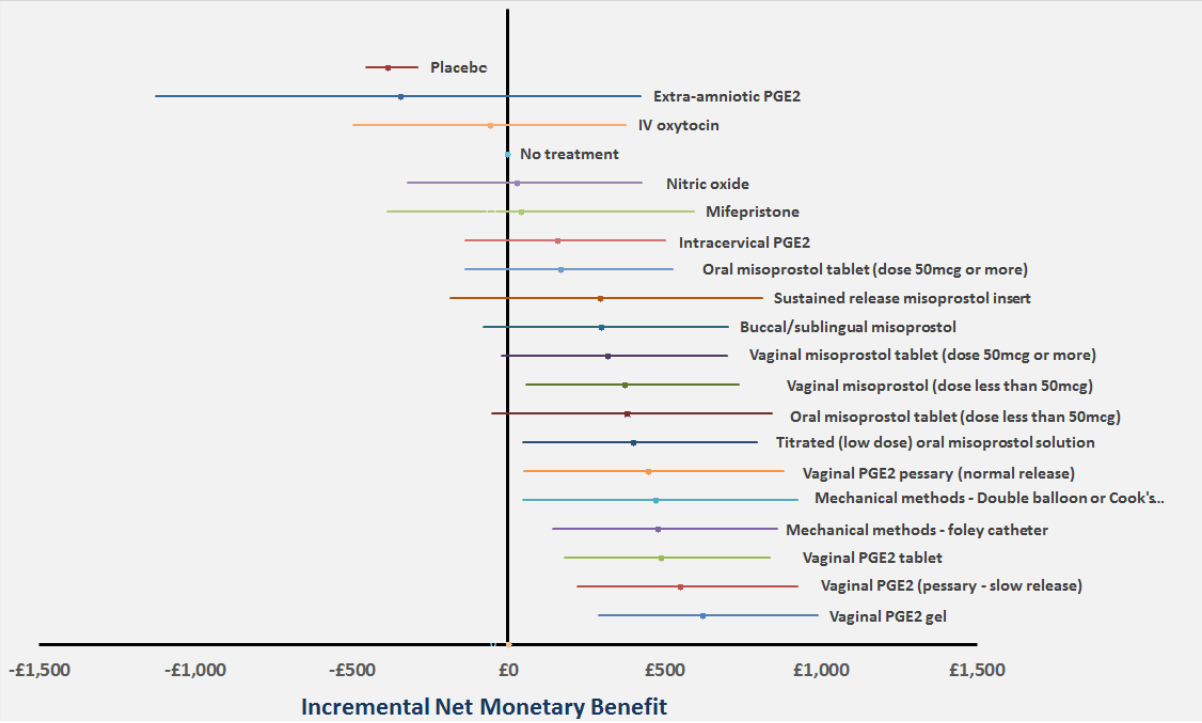


Figure 128: Sensitivity analysis 2 cost-effectiveness acceptability curve (CEAC)



The treatments shown are limited to those with a greater than 5% probability of being cost-effective at a cost-effectiveness threshold of £20,000 per QALY

Figure 129: 95% credible intervals for sensitivity analysis 2 with the base case analysis adapted to allow outpatient induction of labour for certain methods



e) Sensitivity analysis 3: Subgroup analysis for induction of labour in women with a Bishop score ≤6 but with certain methods of induction of labour administered on an outpatient basis

Table 45 indicates that 'vaginal PGE_2 gel' is the most cost-effective treatment with a mean iNMB of £575 and a 36% probability of being cost-effective. 'Vaginal PGE_2 gel' did not have the greatest mean incremental QALYs but did produce the greatest mean incremental cost saving when compared with other methods of induction of labour in this sub-group. As the CEAC shows in Figure 132, the probability of that 'vaginal PGE_2 gel' (and other methods used in an outpatient setting) was cost-effective did decline slightly at higher cost-effectiveness threshold levels. As Table 45 also shows, most induction of labour methods remained cost-effective relative to no treatment.

Figure 133 illustrates the 95% credible intervals for mean iNMB relative to no treatment for each induction of labour method.

Table 45: Results of sensitivity analysis 3 showing the subgroup analysis (Bishop score 6 or less) adapted to allow outpatient induction of labour for certain methods

Treatment	Mean incremental cost	Mean incremental QALY	Mean iNMB (95% credible intervals)	Probability cost-effective
Vaginal PGE_2 gel	-£568	0.0004	£575 (£198 to £977)	0.364

Treatment	Mean incremental cost	Mean incremental QALY	Mean iNMB (95% credible intervals)	Probability cost-effective
Vaginal PGE_2 pessary (slow release)	-£529	0.0004	£538 (£151 to £958)	0.214
Double balloon or Cook's catheter	-£454	0.0003	£460 (-£40 to £983)	0.171
Foley catheter	-£448	0.0003	£453 (£53 to £882)	0.048
Vaginal PGE2 pessary (normal release)	-£386	0.0006	£397 (-£35 to £868)	0.044
Vaginal PGE2 tablet	-£382	0.0003	£388 (-£4 to £793)	0.061
Titrated (low dose) oral misoprostol	-£359	0.0006	£371 (-£25 to £808)	0.007
Vaginal misoprostol (dose <50mcg)	-£359	0.0006	£370 (£14 to £769)	0.001
Buccal/sublingual misoprostol	-£336	0.0005	£346 (-£68 to £794)	0.014
Oral misoprostol (dose <50mcg)	-£316	0.0006	£328 (-£129 to £819)	0.025
Vaginal misoprostol (dose >50mcg)	-£293	0.0005	£301 (-£61 to £707)	0.000
Sustained release misoprostol	-£264	0.0005	£274 (-£259 to £804)	0.020
Oral misoprostol (dose >50mcg)	-£119	0.0004	£127 (-£242 to £538)	0.000
Intracervical PGE_2	-£108	0.0004	£116 (-£231 to £501)	0.000
Mifepristone	-£54	0.0005	£63 (-£410 to £623)	0.033
Nitric oxide	-£12	0.0003	£17 (-£376 to £457)	0.000
No treatment	-	-	-	0.000
IV oxytocin	£77	0.0003	-£71 (-£524 to £394)	0.000
Placebo	£362	0.0000	-£362 (-£436 to -£213)	0.000

Figure 130: Cost-effectiveness plane for sensitivity analysis 3 with certain induction of labour methods administered on an outpatient basis in a subgroup of women with a Bishop score of 6 or less

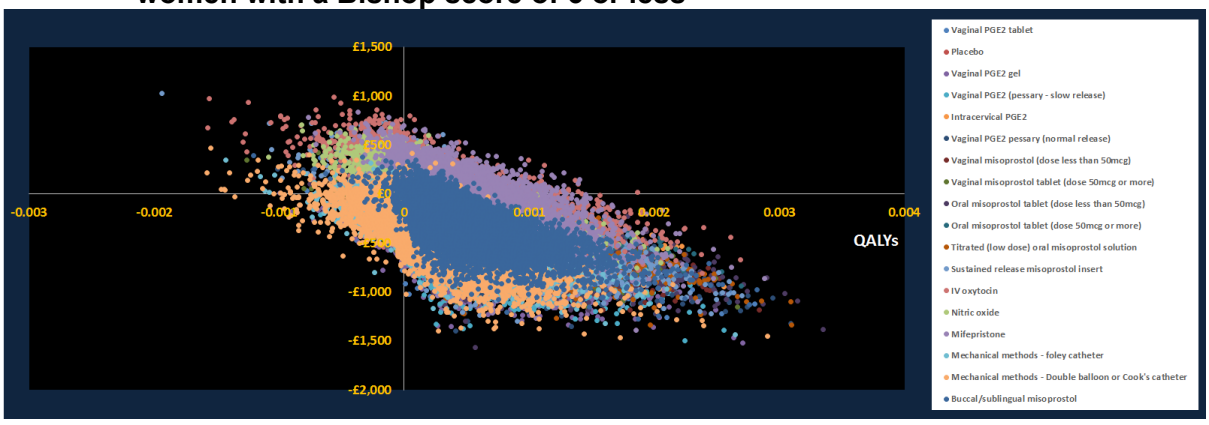


Figure 131: Cost-effectiveness plane for sensitivity analysis 3 (restricted to a comparison of vaginal PGE2 gel versus no treatment)

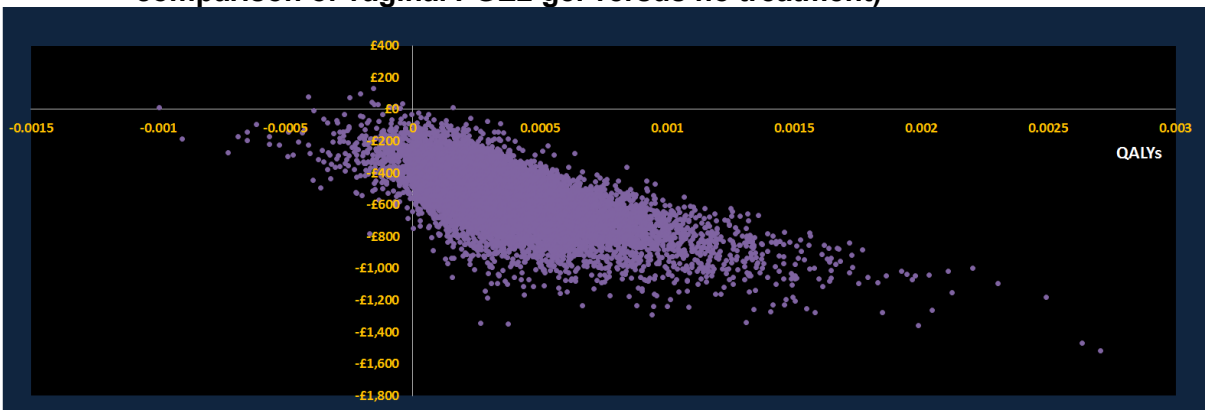
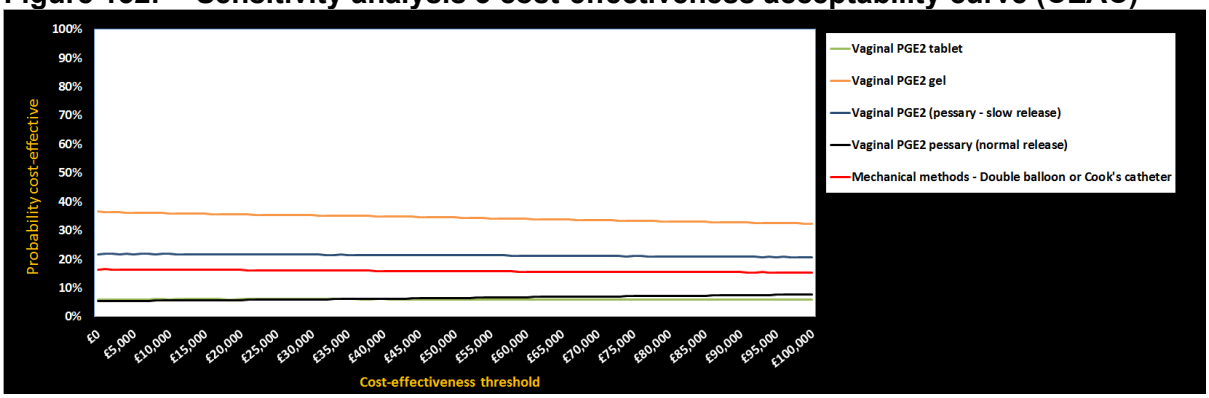
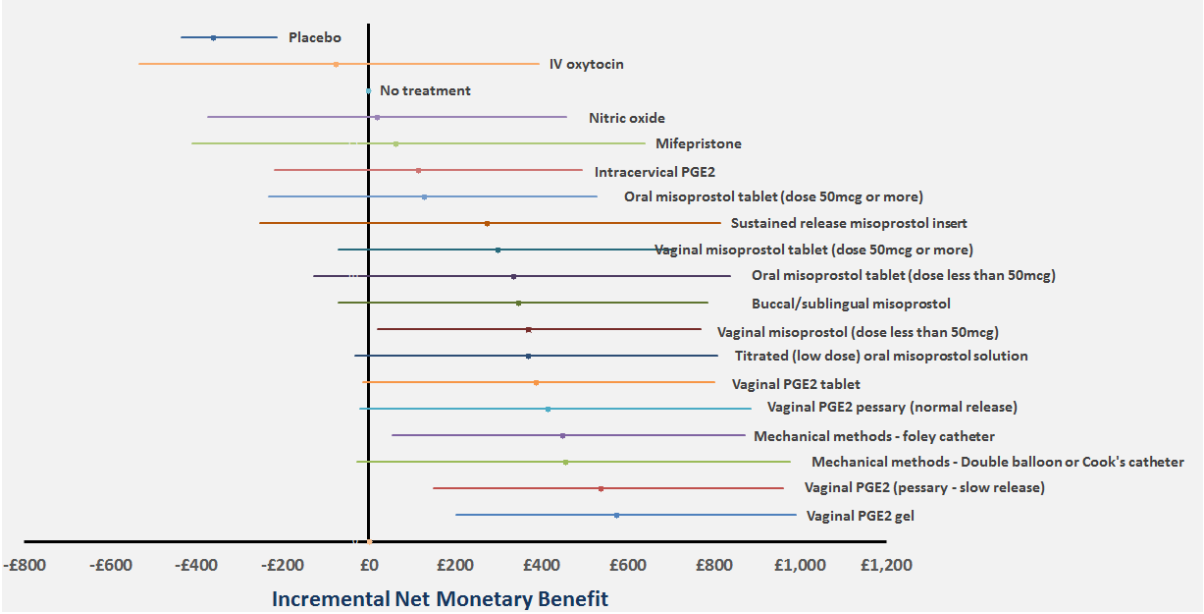


Figure 132: Sensitivity analysis 3 cost-effectiveness acceptability curve (CEAC)



The treatments shown are limited to those with a greater than 5% probability of being cost-effective at a cost-effectiveness threshold of £20,000 per QALY

Figure 133: 95% credible intervals for sensitivity analysis 3 showing the subgroup analysis (Bishop score 6 or less) adapted to allow outpatient induction of labour for certain methods



f) Sensitivity analysis 4: Induction of labour in all women but with certain methods of induction of labour administered on an outpatient basis and with amniotomy and IV oxytocin plus amniotomy additionally included as treatment options

Table 46 indicates that 'vaginal PGE2 gel' was the most cost-effective treatment in this sensitivity analysis as measured by mean iNMB. However, IV oxytocin plus amniotomy had the highest probability of being cost-effective even though it was a treatment administered on an inpatient basis. It has a mean iNMB of £607 and a 43% probability of being cost-effective. 'Vaginal PGE_2 gel' had a mean iNMB of £623 but a much lower (27%) probability of being cost-effective. The lower monetary value of its benefits in incremental mean QALYs compared to 'IV oxytocin plus amniotomy' just being more than offset by its greater incremental mean cost saving. The greater effectiveness of 'IV oxytocin plus amniotomy' is reflected in an increasing probability of being cost-effective at higher cost-effectiveness threshold levels as indicated by Figure 136. The 95% credible intervals for the mean iNMB of the different methods of induction relative to no treatment are illustrated in Figure 137.

Table 46: Results of sensitivity analysis 4 for induction of labour in all women but with certain methods of induction of labour administered on an outpatient basis and with amniotomy and IV oxytocin plus amniotomy additionally included as treatment options

Treatment	Mean incremental cost	Mean incremental QALY	Mean iNMB (95% credible intervals)	Probability cost-effective
Vaginal PGE2 gel	-£614	0.0005	£623 (£295 to £992)	0.271

Treatment	Mean incremental cost	Mean incremental QALY	Mean iNMB (95% credible intervals)	Probability cost-effective
IV oxytocin plus amniotomy	-£591	0.0008	£607 (-£42 to £1,202)	0.426
Vaginal PGE_2 pessary (slow release)	-£542	0.0005	£551 (£212 to £923)	0.082
Vaginal PGE_2 tablet	-£479	0.0004	£486 (£172 to £839)	0.033
Foley catheter	-£473	0.0004	£480 (£141 to £862)	0.023
Double balloon or Cook's catheter	-£469	0.0003	£475 (£47 to £931)	0.087
Vaginal PGE_2 pessary (normal release)	-£435	0.0006	£447 (£44 to £877)	0.033
Titrated (low dose) oral misoprostol	-£388	0.0006	£400 (£39 to £795)	0.002
Oral misoprostol (dose <50mcg)	-£362	0.0007	£375 (-£59 to £837)	0.020
Vaginal misoprostol (dose <50mcg)	-£362	0.0006	£374 (£55 to £732)	0.000
Vaginal misoprostol (dose >50mcg)	-£308	00005	£317 (-£24 to £692)	0.000
Buccal/sublingual misoprostol	-£289	0.0005	£299 (-£74 to £704)	0.001
Sustained release misoprostol	-£283	0.0006	£293 (-£194 to £797)	0.011
Oral misoprostol (dose >50mcg)	-£159	0.0005	£168 (-£146 to £522)	0.000
Intracervical PGE_2	-£149	0.0005	£158 (-£137 to £501)	0.000
Amniotomy	-£98	0.0003	£103 (-£352 to £576)	0.000
Mifepristone	-£32	0.0005	£41 (-£384 to £581)	0.011
Nitric oxide	-£21	0.0003	£27 (-£322 to £434)	0.000
No treatment	-	-	-	0.000
IV oxytocin	£57	0.0002	-£53 (-£496 to £386)	0.000
Extra-amniotic PGE_2	£338	-0.0001	-£341 (-£1,106 to £443)	0.002
Placebo	£386	0.0000	-£386 (-£454 to -£291)	0.000

Figure 134: Cost-effectiveness plane for sensitivity analysis 4 with certain induction of labour methods administered on an outpatient basis and with amniotomy alone and IV oxytocin plus amniotomy included in the analysis

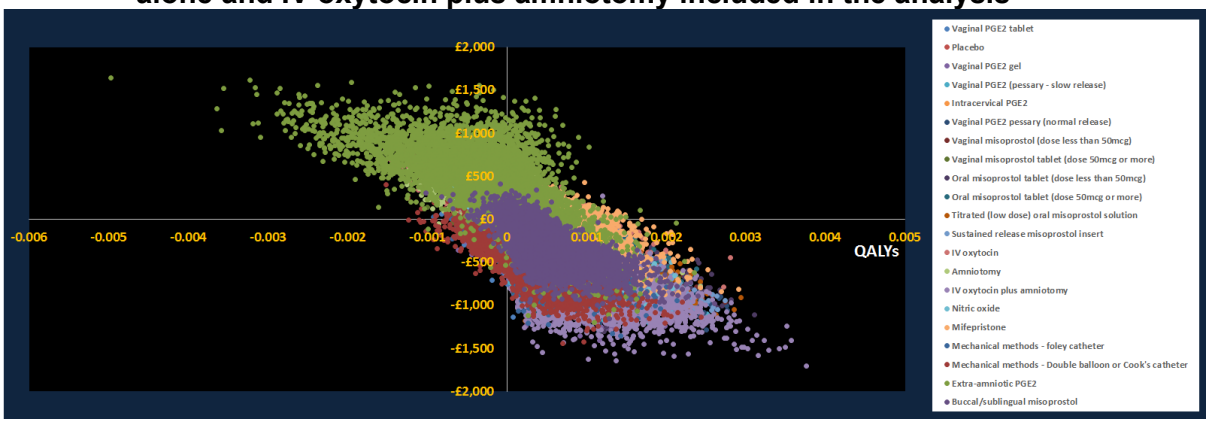


Figure 135: Cost-effectiveness plane for sensitivity analysis 4 (restricted to a comparison of vaginal PGE2 gel versus no treatment)

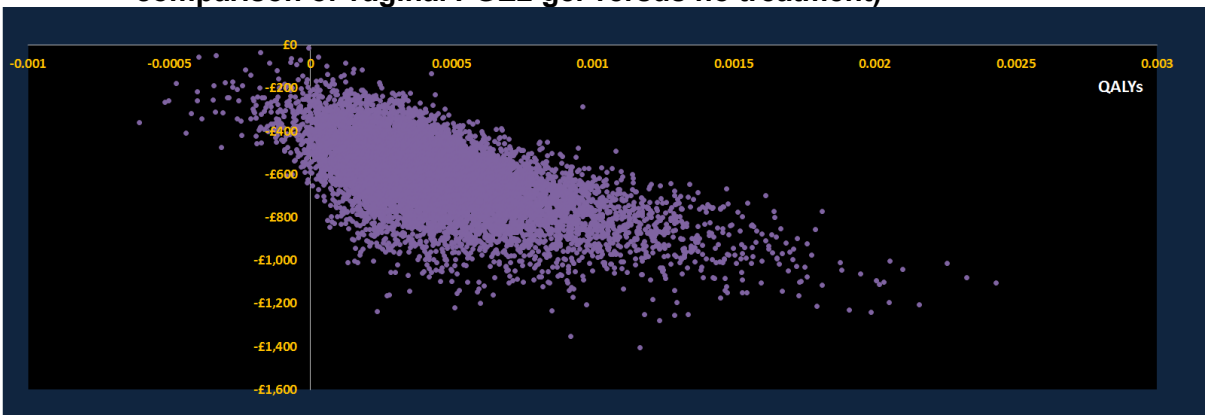
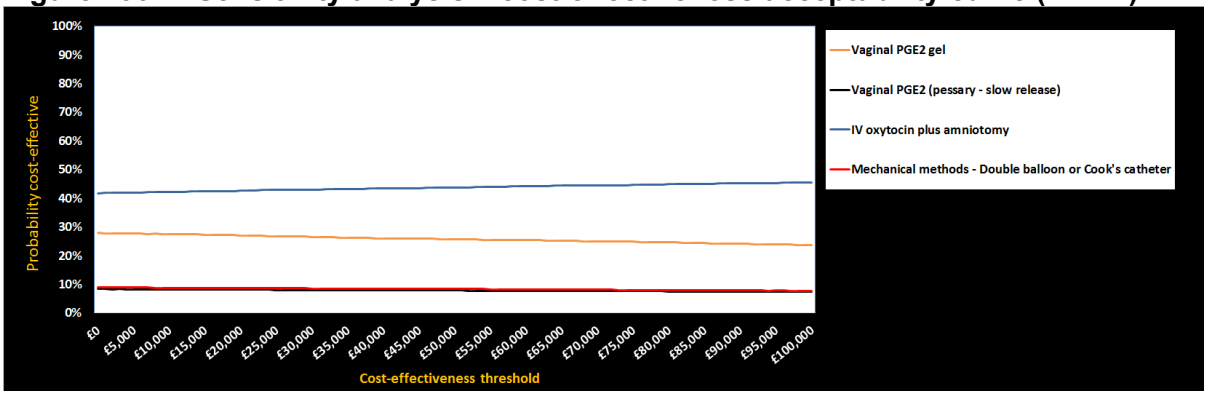
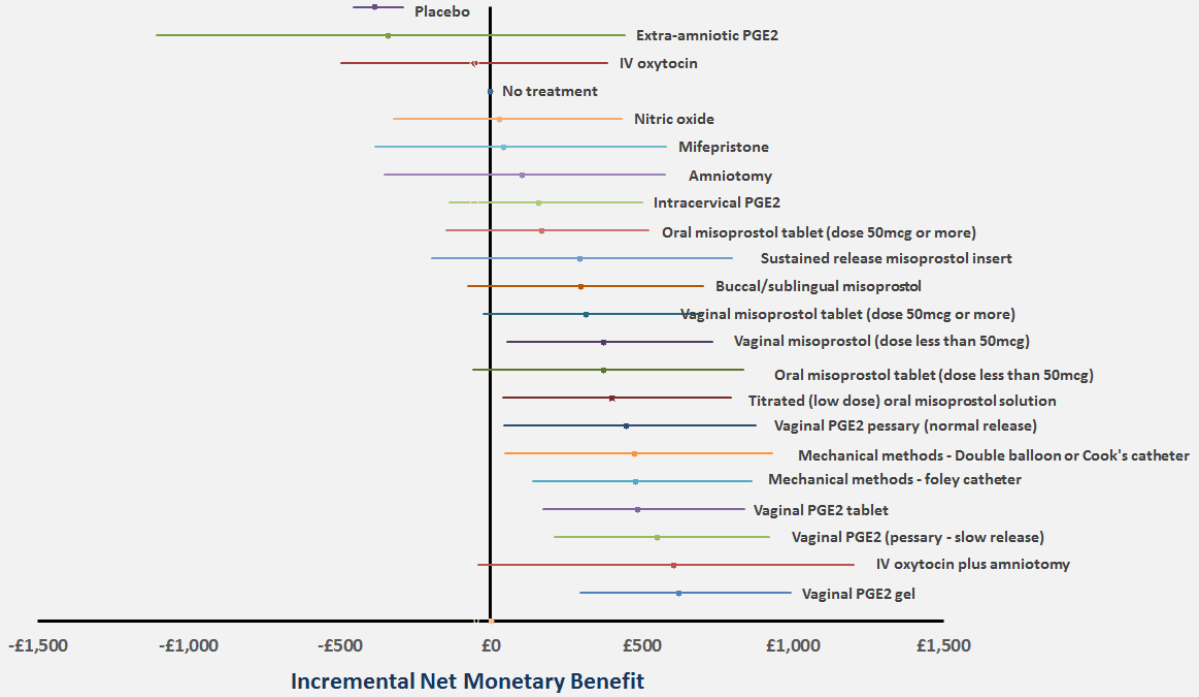


Figure 136: Sensitivity analysis 4 cost-effectiveness acceptability curve (CEAC)



The treatments shown are limited to those with a greater than 5% probability of being cost-effective at a cost-effectiveness threshold of £20,000 per QALY

Figure 137: 95% credible intervals for sensitivity analysis 4 for induction of labour in all women but with certain methods of induction of labour administered on an outpatient basis and with amniotomy and IV oxytocin plus amniotomy additionally included as treatment options



Discussion

The results very strongly suggest that induction of labour is cost-effective although they present a less clear picture with respect to the optimal method. The strongest evidence of cost-effectiveness, in a population of all pregnant women offered induction of labour, is 'IV oxytocin plus amniotomy'. Although not included in the base case analysis as there was no relative treatment effectiveness evidence for NICU admission, sensitivity analysis suggested that there was a 63% probability that it was the most cost-effective treatment when all induction of labour was undertaken on an inpatient basis. Even in a sensitivity analysis which allowed for the possibility of outpatient (cheaper) induction of labour for some methods, 'IV oxytocin plus amniotomy' was still found to have the highest probability of being the most cost-effective method, albeit without quite achieving the highest mean iNMB. Driving the cost-effectiveness of 'IV oxytocin plus amniotomy' was its best relative treatment effectiveness for achieving a vaginal birth within 24 hours, which is the birth outcome associated with the cheapest mode of birth and the least QALY loss. Although, there was no NICU admission relative effectiveness data for 'IV oxytocin plus amniotomy' there is little grounds to suppose it would differ from 'IV oxytocin' which was used to impute relative treatment effectiveness for this outcome. 'IV oxytocin plus amniotomy' did not feature in the subgroup analysis for women with a Bishop score ≤6 as there was no NMA data which reflects that this method is not generally appropriate in that sub-group. It is therefore reasonable to infer that the NMA data for 'IV oxytocin plus amniotomy' in the population level analysis will reflect a population with a Bishop score >6.

The sensitivity analysis, which accounted for the fact that outpatient induction of labour may be undertaken for some methods, suggested that this could have an important effect on the relative treatment cost-effectiveness. As expected, this favoured those methods of induction that were undertaken on an outpatient basis, with 3 methods of prostaglandin administration being the most cost-effective method in 70% of simulations. It should be noted that this analysis assumes that outpatient administration itself has no impact on mode of birth or NICU admission, which is not assessed by the evidence presented in this review.

In the subgroup of women with a Bishop score ≤6 the cost-effectiveness of different methods of induction of labour was less clear cut. In the base case subgroup analysis, the most cost-effective treatment was 'vaginal PGE_2 normal release pessary' with a 28% probability of being cost-effective, although this preparation of vaginal dinoprostone (PGE2) is not available in the UK. In the sensitivity analysis with some methods of induction administered as an outpatient procedure, 'vaginal PGE_2 gel' and the 'vaginal PGE_2 slow release pessary' were the most cost-effective with a mean iNMB of £575 and £538 respectively. The 'vaginal PGE_2 gel' had a 36% probability of being cost-effective with the corresponding value being 21% for the 'vaginal PGE_2 slow release pessary'.

There are a number of limitations with this analysis. Many of those limitations are discussed in more detail in the UK HTA: Which method is best for the induction? (2016) which reported the original economic model. These limitations included restricting the analysis to those interventions for which there was sufficient evidence for them to be included within the NMA. However, where there was partial NMA data for an induction of labour we were able to mitigate this limitation by imputing relative treatment effect from an intervention considered likely to have similar effectiveness for the missing outcome.

Furthermore, the model did not include all outcomes of interest. In the case of postpartum haemorrhage, this reflected a lack of evidence due to limited reporting of this outcome in clinical studies. For outcomes, such as hyperstimulation, it was considered that this would be captured to some extent in other outcomes, such as NICU admission. The model may have underestimated some pharmacological treatment costs as the treatment cost was based on the initial dose and subsequent doses will often be administered if labour is not initiated. So, for example, up to 8 tablets of the newly licensed 25mcg oral misoprostol tablet can be administered in a 24 hour period which would imply a treatment cost of £83.14 rather than the £10.39 used in the analysis. In practice the mean treatment cost will lie somewhere between these 2 values. However, these costs are generally very small when compared to the outcome related costs and therefore are unlikely to have an important bearing on model results. In the case of the 25mcg oral misoprostol treatment the difference in iNMB would only differ by £73 between an analysis based on the initial and analysis based on the maximum dose.

The UK HTA report documented the limitations with respect to the health state utility and we did not find any evidence to suggest that better estimates were available for this update of the original model. Therefore, the same utility estimates and assumptions were used to inform this analysis. However, additional assumptions were made in order to derive a QALY estimate which could be used in a way consistent with NICE assessment of cost-effectiveness. It should be noted that these assumptions were fairly crude, in the absence of evidence, in limiting any loss in health state utility to a very limited duration, namely the time to discharge. However, it should be noted that this assumption is not an important driver of the cost-effectiveness conclusions reached, although it may cause the overall cost-effectiveness of all effective induction of labour methods to be under-estimated if differences in health related quality of life persist after hospital discharge. This is because treatment

costs are small in relation to the costs associated with model outcomes and because cost savings arising from earlier birth, averted caesarean birth and averted NICU admission are positively correlated with the small QALY gains from treatment. The most cost-effective methods of induction of labour tend to be those which produce the greatest cost saving when compared to no treatment with the saving generally more than compensating for any additional treatment costs. As the time horizon of the model is limited to time to discharge, the differences in QALYs between the different methods of induction is very small, and consequently so is the monetary evaluation placed on benefits in the iNMB formula. The limited importance of the QALYs to the cost-effectiveness conclusion is also demonstrated by the very flat CEACs, which show that a very large increase in the cost-effectiveness threshold, or 'willingness-to-pay' for a QALY, has a negligible impact on the probability of an intervention being cost-effective. This is because even if a method has a greater QALY gain, the absolute difference is small and even with a large cost-effectiveness threshold this has only a limited impact on the monetary quantification of benefit and this remains small relative to the cost savings. If a longer time frame was considered, then those methods which had the greatest cost saving would generally have a larger QALY gain associated with them and this would be reflected in greater mean iNMB.

Conclusion

The model provided strong evidence that induction of labour was cost-effective relative to no treatment with most methods having a positive iNMB even when induction of labour is offered as an additional inpatient intervention. Despite considerable uncertainty across the analyses the model suggested that the probability of no treatment being cost-effective was 0%.

The analysis provided good evidence that 'IV oxytocin plus amniotomy' is cost-effective and thus supports the offer recommendation made for women with a Bishop score >6, with the method not suitable for women with a Bishop score ≤6.

For women with a Bishop score ≤6 the cost-effectiveness of the various methods was less clear cut. There was cost-effectiveness evidence to support the use of induction of labour with vaginal PGE_2 as tablet, gel or controlled release pessary particularly when administered as an outpatient procedure. There was also some evidence from the cost-effectiveness analysis to support the use of mechanical methods (such as balloon catheters) although these interventions were likely to be less cost-effective than vaginal PGE_2 methods. Various misoprostol preparations and modes of administration also had relatively good cost-effectiveness in this subgroup and the committee recommended the newly licensed low dose (25 microgram) oral misoprostol tablets. However, the committee had some concerns about higher dose misoprostol with respect to hyperstimulation, noting that this outcome was not reflected in the economic model.

Acknowledgements

This analysis was adapted from a previous model developed by Edna Keeney and Nicky Welton (University of Bristol) for a NHS National Institute of Health Research Health Technology Assessment - UK HTA: Which method is best for the induction? (2016).

Appendix K – Excluded studies

Excluded clinical and economic studies for review question: What are the benefits and harms of pharmacological and mechanical methods in induction of labour?

Clinical studies

Table 47: Excluded studies and reasons for their exclusion. From the update search

Study	Reason for Exclusion
Elective induction of labor compared with expectant management of nulliparous women at 39 weeks of gestation: a randomized controlled trial: editorial comment, Obstetrical and gynecological survey. 71 (4) (pp 197-198), 2016. Date of publication: 2016., 2016	Editorial comment only, no relevant data
Individual and combined administration of intravaginal misoprostol and transcervical foley catheter in cervical ripening in nulliparous women, Iranian journal of obstetrics, gynecology and infertility, 21, 16â□□22, 2018	Study in Arabic
Abraham, Cynthia, Outpatient Foley Catheter for Induction of Labor in Parous Women: A Randomized Controlled Trial, Obstetrics and Gynecology, 132, 1062-1063, 2018	Editorial comment only, no relevant data
Agboghoroma, C. O., Ngonadi, N., A randomized controlled study comparing Prostaglandin E2 vaginal suppository with intra-cervical Foleys catheter balloon for preinduction cervical ripening at term, West African journal of medicine, 34, 77-82, 2015	Unavailable
Agrawal, M., Acharya, N., Joshi, K., Shrivastava, D., Effectiveness of isosorbide mononitrate in cervical ripening before induction of labor in full-term antenatal patients, Journal of SAFOG, 11, 96â□□99, 2019	No relevant outcomes were reported
Akbari, M., Javadnoori, M., Siahpoosh, A., Afshari, P., Haghighi, M. H., Lake, E., Comparison the effect of Anethum graveolens and oxytocin on induction of labor in term pregnancy: A randomized clinical trial, Jundishapur Journal of Natural Pharmaceutical Products, 11, e27876, 2016	No relevant outcomes were reported
Alberico, S., Erenbourg, A., Hod, M., Yogev, Y., Hadar, E., Neri, F., Ronfani, L., Maso, G., Ginexmal Group, Immediate delivery or expectant management in gestational diabetes at term: the GINEXMAL randomised controlled trial, BJOG : an international journal of obstetrics and gynaecology, 124, 669-677, 2017	Women in the experimental group were offered induction of labour with different interventions, depending on clinical presentation
Alcoseba-Lim W, Famador-Juario H, Stripping of membranes to induce labor at term, Philippine J Surg Surg Special, 47, 139â□“42, 1992	Included in HTA (already included)
Alfirevic,Zarko, Aflaifel,Nasreen, Weeks,Andrew, Oral misoprostol for induction of labour, Cochrane Database of Systematic Reviews, - , 2014	Systematic review, references checked for inclusion
Al-Harmi, J., Chibber, R., Fouda, M., Mohammed, K. Z., El-Saleh, E., Tasneem, A., Is membrane sweeping beneficial at the initiation of labor induction?, Journal of Maternal-Fetal and Neonatal Medicine, 28, 1214-1218, 2015	Complex intervention (sweep plus oxytocin/PGE)

Study	Reason for Exclusion
Al-Ibraheemi, Z., Brustman, L., Bimson, B., Porat, N., Rosenn, B., Misoprostol with foley bulb vs. Misoprostol alone for cervical ripening: A randomized controlled trial, American Journal of Obstetrics and Gynecology, 216, S473, 2017	Complex intervention (misoprostol plus Foley bulb)
Al-Shaikh, Ghadeer, Al-Mandeel, Hazem, The outcomes of trial of labour after cesarean section following induction of labour compared to spontaneous labour, Archives of Gynecology and Obstetrics, 287, 1099-103, 2013	Observational study; all women had ruptured membranes
Anabusi, Saja, Mei-Dan, Elad, Hallak, Mordechai, Walfisch, Asnat, Mechanical labor induction in the obese population: a secondary analysis of a prospective randomized trial, Archives of Gynecology and Obstetrics, 293, 75-80, 2016	Results reported by BMI and not by treatment group; secondary analysis of 2 studies included in Alfirevic 2015
Anastasio, H. B., Ward, A., Berghella, V., St Marie, P., Hoffman, M. K., Sciscione, A., Schoen, C., Association between timing of rupture of membranes and length of labor induction: Secondary analysis of a randomized controlled trial, American journal of obstetrics and gynecology, 218 (1 Supplement 1), S249, 2018	Complex intervention (Foley catheter plus oxytocin)
Anjanappa, B., Sreeelatha,, Ramaiah, R., Comparison of sublingual versus vaginal misoprostol for the induction of labour at term:A randomised study, BJOG: An International Journal of Obstetrics and Gynaecology, 2), 89-90, 2014	No relevant outcomes were reported
Anjum, S., Sharma, R., Oral misoprostol vs intravenous oxytocin infusion for induction of labor in prelabor rupture of membranes, Journal of SAFOG, 8, 4-7, 2016	All women had ruptured membranes
Anonymous,, Erratum: Comparative Evaluation of 50 Microgram Oral Misoprostol and 25 Microgram Intravaginal Misoprostol for Induction of Labour at Term: A Randomized Trial (Journal of Obstetrics and Gynaecology Canada (2013) 35(5) (408-416)(S1701216315309312)(10.1016/S1701-2163(15)30931-2), Journal of Obstetrics and Gynaecology Canada, 39, 66, 2017	Erratum of a study included in Alfirevic 2016
Antonazzo, P., Laoreti, A., Personeni, C., Grossi, E., Martinelli, A., Cetin, I., A randomized prospective study: Intravenous oxytocin compared to vaginal dinoprostone for labor induction in patients non responders to a first dose of dinoprostone, Reproductive Sciences, 21, 77A, 2014	Complex intervention (dinoprostone plus oxytocin)
Arshad, A. H., Zainuddin, A. A., Ghani, N. A. A., Ali, A., The efficiency of laminaria as an adjunct to induction of labour with prostin: A randomised controlled trial, BJOG: An International Journal of Obstetrics and Gynaecology, 123, 156, 2016	Complex intervention (laminaria plus prostin)
Attanayake, K., Goonewardene, M., Cervical ripening with self administered iso sorbide mononitrate vaginally, in uncomplicated singleton pregnancies at 39 weeks gestation: a double blind randomised controlled trial, The Ceylon medical journal, 61, 142-148, 2016	No relevant comparison (pyridoxine)
Austin, K, Chambers, Gm, Abreu, Lourenco R, Madan, A, Susic, D, Henry, A, Cost-effectiveness of term induction of labour using inpatient prostaglandin gel versus outpatient Foley catheter, Australian & New Zealand journal of obstetrics & gynaecology, 55, 440-445, 2015	No relevant outcomes were reported

Study	Reason for Exclusion
Avdiyovski, Helen, Haith-Cooper, Melanie, Scally, Andrew, Membrane sweeping at term to promote spontaneous labour and reduce the likelihood of a formal induction of labour for postmaturity: a systematic review and meta-analysis, Journal of obstetrics and gynaecology : the journal of the Institute of Obstetrics and Gynaecology, 39, 54-62, 2019	Systematic review, references checked for inclusion
Ayachi, A., Bouchahda, R., Derouich, S., Mkaouer, L., Mourali, M., Labor induction: Why complicate things when they can be simple? a randomized controlled clinical trial, Gazzetta Medica Italiana Archivio per le Scienze Mediche, 176, 419-423, 2017	Study in Italian
Ayati, S., Vahidroodsari, F., Farshidi, F., Shahabian, M., Aghaeed, M. A., Vaginal versus sublingual misoprostol for labor induction at term and post term: A randomized prospective study, Iranian journal of pharmaceutical research, 13, 299-304, 2014	More than 1/3 of the population had ruptured membranes
Baev, O., Rumyantseva, V., Tysyachnyu, O., Randomized trial of labour preinduction with mifepristone versus expectant management, International Journal of Gynecology and Obstetrics, 143 (Supplement 3), 277, 2018	Abstract of Baev 2017
Baev, Oleg R., Rumyantseva, Valentina P., Tysyachnyu, Oleg V., Kozlova, Olga A., Sukhikh, Gennady T., Outcomes of mifepristone usage for cervical ripening and induction of labour in full-term pregnancy. Randomized controlled trial, European journal of obstetrics, gynecology, and reproductive biology, 217, 144-149, 2017	Some women received a complex intervention (mifepristone in combination with dinoprostone/ amniotomy)
Bapoo, S., Shukla, M., Abbasi, N., D'Souza, R., Induction of labour in low-risk pregnancies before 40 weeks of gestation: A systematic review and meta-analysis, Obstetrics and Gynecology, 131, 176S, 2018	Systematic review, references checked for inclusion
Battarbee, A. N., Sandoval, G., Grobman, W. A., Reddy, U. M., Tita, A. T. N., Silver, R. M., El-Sayed, Y. Y., Wapner, R. J., Rouse, D. J., Saade, G. R., Chauhan, S. P., Iams, J. D., Chien, E. K., Casey, B. M., Gibbs, R. S., Srinivas, S. K., Swamy, G. K., Simhan, H. N., Maternal and Neonatal Outcomes Associated with Amniotomy among Nulliparous Women Undergoing Labor Induction at Term, American Journal of Perinatology, 2020	Study compared women who did not receive amniotomy to women who received amniotomy in combination with oxytocin at different time points, however the timing of administration of oxytocin was not randomised
Beckmann, M, Thompson, R, Miller, Y, Prosser, Sj, Flenady, V, Kumar, S, Measuring women's experience of induction of labor using prostaglandin vaginal gel, European journal of obstetrics, gynecology, and reproductive biology, 210, 189-195, 2017	All women received prostaglandin gel (then randomised to amniotomy or repeat gel)
Beckmann, M., Acreman, M., Schmidt, E., Merollini, K. M. D., Miller, Y., Women's experience of induction of labor using PGE2 as an inpatient versus balloon catheter as an outpatient, European Journal of Obstetrics and Gynecology and Reproductive Biology, 249, 1-6, 2020	The intervention group received 2 different formulations of prostaglandin (gel, sustained release) and results have not been reported separately
Beckmann, M., Gibbons, K., Flenady, V., Kumar, S., Induction of labour using prostaglandin E2 as an inpatient versus balloon catheter as an outpatient: a multicentre randomised controlled trial, BJOG: An International Journal of Obstetrics and Gynaecology, 127, 571-579, 2020	The intervention group received 2 different formulations of prostaglandin (gel, sustained

Study	Reason for Exclusion
	release) and results have not been reported separately
Bernardes, T. P., Broekhuijsen, K., Koopmans, C. M., Boers, K. E., van Wyk, L., Tajik, P., van Pampus, M. G., Scherjon, S. A., Mol, B. W., Franssen, M. T., van den Berg, P. P., Groen, H., Caesarean section rates and adverse neonatal outcomes after induction of labour versus expectant management in women with an unripe cervix: a secondary analysis of the HYPITAT and DIGITAT trials, BJOG: An International Journal of Obstetrics and Gynaecology, 123, 1501-1508, 2016	Women in the experimental group were offered induction of labour with different interventions, depending on clinical presentation
Biesty, Linda M, Egan, Aoife M, Dunne, Fidelma, Dempsey, Eugene, Meskell, Pauline, Smith, Valerie, Ni, Bhuinneain G Meabh, Devane, Declan, Planned birth at or near term for improving health outcomes for pregnant women with gestational diabetes and their infants, Cochrane Database of Systematic Reviews, 2018	Systematic review, references checked for inclusion
Bleicher, Inna, Dikopoltsev, Elena, Kadour-Ferro, Einav, Sammour, Rami, Gonen, Ron, Sagi, Shlomi, Eshel, Aya, Nussam, Liraz, Vitner, Dana, Double-Balloon Device for 6 Compared With 12 Hours for Cervical Ripening: A Randomized Controlled Trial, Obstetrics and Gynecology, 135, 1153-1160, 2020	Study compared 2 variants of the same intervention from this review's protocol
Blue, N. R., Holbrook, B. D., Weinberg, D., Rayburn, W., Reported experience with intracervical ripening bulb for outpatient induction of labor at term, Obstetrics and Gynecology, 127, 78S, 2016	Systematic review, references checked for inclusion
Boers, K. E., Thornton, J. G., Scherjon, S. A., Neonatal morbidity after induction versus expectant monitoring in intrauterine growth restriction at term, Archives of Disease in Childhood: Fetal and Neonatal Edition, 97, A7, 2012	Women in the experimental group were offered induction of labour with different interventions, depending on clinical presentation
Boie, S., Glavind, J., Uldbjerg, N., Bakker, J. J. H., van der Post, J. A. M., Steer, P. J., Bor, P., CONDISOX- continued versus discontinued oxytocin stimulation of induced labour in a double-blind randomised controlled trial, BMC Pregnancy and Childbirth, 19, 320, 2019	Study protocol
Bond, D. M., Gordon, A., Hyett, J., de Vries, B., Carberry, A. E., Morris, J., Planned early delivery versus expectant management of the term suspected compromised baby for improving outcomes, Cochrane Database of Systematic Reviews, 11, CD009433, 2015	Systematic review, references checked for inclusion
Bond, Dm, Middleton, P, Levett, Km, Ham, Dp, Crowther, Ca, Buchanan, Sl, Morris, J, Planned early birth versus expectant management for women with preterm prelabour rupture of membranes prior to 37 weeks' gestation for improving pregnancy outcome, Cochrane database of systematic reviews (Online), 2017, 2017	Systematic review, references checked for inclusion
Bostanci, E., Kilicci, C., Ozkaya, E., Abide Yayla, C., Eroglu, M., Continuous oxytocin versus intermittent oxytocin for induction of labor: a randomized study, Journal of Maternal-Fetal and Neonatal Medicine, 33, 651-656, 2020	Study compared 2 variants of the same intervention from this review's protocol
Boulton, A., Chong, G., Smith, T., Best, E., Woods, A., Murray, H., Symonds, I., Cervical ripening-one size may not fit all-cervical ripening using misoprostol versus dinoprostone vaginal insert in very	Study protocol

Study	Reason for Exclusion
unfavourable primiparous women (CRUMD study): protocol and preliminary results, BJOG, 126, 136â□□137, 2019	
Boulvain, M., Senat, M. V., Perrotin, F., Winer, N., Beucher, G., Subtil, D., Bretelle, F., Azria, E., Hejaiej, D., Vendittelli, F., Capelle, M., Langer, B., Matis, R., Connan, L., Gillard, P., Kirkpatrick, C., Ceysens, G., Faron, G., Irion, O., Rozenberg, P., Induction of labour versus expectant management for large-for-date fetuses: A randomised controlled trial, The Lancet., 2015	Women in the experimental group were offered induction of labour with different interventions, depending on clinical presentation
Boulvain, Michel, Irion, Olivier, Dowswell, Therese, Thornton, Jim G., Induction of labour at or near term for suspected fetal macrosomia, The Cochrane database of systematic reviews, CD000938, 2016	Systematic review, references checked for inclusion
Bracken, H., Mundle, S., Faragher, B., Easterling, T., Haycox, A., Turner, M., Alfirevic, Z., Winikoff, B., Weeks, A., Induction of labour in pre-eclamptic women: A randomised trial comparing the Foley balloon catheter with oral misoprostol, BMC Pregnancy and Childbirth, 1-5, 2015	Study protocol
Bräne, E, Olsson, A, Andolf, E, A randomized controlled trial on early induction compared to expectant management of nulliparous women with prolonged latent phases, Acta Obstetricia et Gynecologica Scandinavica, 93, 1042-1049, 2014	Women in the experimental group were offered induction of labour with different interventions, depending on clinical presentation
Broekhuijsen, K., Van Baaren, G. J., Van Pampus, M. G., Ganzevoort, W., Sikkema, J. M., Woiski, M. D., Oudijk, M. A., Bloemenkamp, K. W. M., Scheepers, H. C. J., Bremer, H. A., Rijnders, R. J. P., Van Loon, A. J., Perquin, D. A. M., Sporken, J. M. J., Papatsonis, D. N. M., Van Huizen, M. E., Vredevoogd, C. B., Brons, J. T. J., Kaplan, M., Van Kaam, A. H., Groen, H., Porath, M. M., Van Den Berg, P. P., Mol, B. W. J., Franssen, M. T. M., Langenveld, J., Immediate delivery versus expectant monitoring for hypertensive disorders of pregnancy between 34 and 37 weeks of gestation (HYPITAT-II): An open-label, randomised controlled trial, The Lancet, 385, 2492-2501, 2015	Women in the experimental group were offered induction of labour with different interventions, depending on clinical presentation
Carbone, L., De Vivo, V., Saccone, G., D'Antonio, F., Mercorio, A., Raffone, A., Arduino, B., D'Alessandro, P., Sarno, L., Conforti, A., Maruotti, G. M., Alviggi, C., Zullo, F., Sexual Intercourse for Induction of Spontaneous Onset of Labor: A Systematic Review and Meta-Analysis of Randomized Controlled Trials, Journal of Sexual Medicine, 16, 1787-1795, 2019	Systematic review, references checked for inclusion
Caughey, A. B., Systematic review and meta-analysis: Elective induction of labour is associated with decreased perinatal mortality and lower odds of caesarean section at 40 and 41 weeks, Evidence-Based Medicine, 19, 236, 2014	Systematic review, references checked for inclusion
Cecatti JG, Aquino MMA, Garcia GM, Rodrigues TMC, Misoprostol Versus Oxytocin for Labor Induction: Randomized Controlled Trial, Book 4, 28	Included in HTA (already included)
Chanrachakul B, Punyavachira P, Preechapornprasert D, Srilar A, Promsonthi P, Randomized comparison of sublingual and vaginal misoprostol for cervical ripening at term, Reprod Sci, 17, A352â□“3, 2010	Included in HTA (already included)

Study	Reason for Exclusion
Charoenkul S, Sripramote M, A randomized comparison of one single dose of vaginal 50 microg misoprostol with 3 mg dinoprostone in pre-induction cervical ripening, J Med Assoc Thai, 83, 1026â□“34, 2000	Included in HTA (already included)
Chau, C. T., Eakin, C., Ehrenberg, S., Rugarn, O., Tipping, D., Powers, B., Wing, D. A., Effect on labor induction outcomes with the dinoprostone vaginal insert in patients with diabetes, Reproductive Sciences, 1), 214A, 2016	Results reported by the presence/absence of diabetes
Chen, Da-Chung, Yuan, Shyng-Shiou F., Su, Her-Young, Lo, Shin-Chieh, Ren, Shin-Sia, Wu, Gwo-Jang, Urinary cyclic guanosine 3',5'-monophosphate and cyclic adenosine 3',5'-monophosphate changes in spontaneous and induced onset active labor, Acta Obstetricia et Gynecologica Scandinavica, 84, 1081-6, 2005	All women had ruptured membranes
Chen, V., Sheehan, P., Outpatient versus inpatient catheter balloon cervical ripening-A randomised trial, Australian and New Zealand Journal of Obstetrics and Gynaecology, 59, 39-40, 2019	Conference poster
Chen, W., Xue, J., Peprah, M. K., Wen, S. W., Walker, M., Gao, Y., Tang, Y., A systematic review and network meta-analysis comparing the use of Foley catheters, misoprostol, and dinoprostone for cervical ripening in the induction of labour, BJOG: An International Journal of Obstetrics and Gynaecology, 123, 346-354, 2016	Systematic review, references checked for inclusion
Chowdhary, A., Bagga, R., Jasvinder, Kalra, Jain, V., Saha, S. C., Kumar, P., Comparison of intracervical Foley catheter used alone or combined with a single dose of dinoprostone gel for cervical ripening: a randomised study, Journal of Obstetrics and Gynaecology, 2019	Complex intervention (Foley/dinoprostone)
Connolly, Katherine A., Kohari, Katherine S., Factor, Stephanie H., Rekawek, Patricia, Miller, Meredith R., Smilen, Brooke S., Stone, Joanne L., Bianco, Angela T., A Randomized Trial of Foley Balloon Induction of Labor Trial in Multiparas (FIAT-M), American Journal of Perinatology, 34, 1108-1114, 2017	Study compared 2 variants of the same intervention from this review's protocol
Ctri,, Clinical trial to study different methods of induction agents to induce labour, http://www.who.int/trialsearch/Trial2.aspx?TrialID=CTRI/2019/06/019614, 2019	Study registry
Ctri,, "SAFETY AND EFFICACY OF ORAL AND VAGINAL MISOPROSTOL FOR INDUCTION OF LABOUR IN TERM PREGNANCIESÃ¢??- A RANDOMISED CONTROLLED TRIAL IN A TERTIARY HEALTH CENTRE, http://www.who.int/trialsearch/Trial2.aspx?TrialID=CTRI/2019/09/021130, 2019	Study registry
Ctri,, Role of tablet misoprostol in inducing labour in pregnant female and which route is more effective whether sublingual or pervaginal in terms of time interval, http://www.who.int/trialsearch/Trial2.aspx?TrialID=CTRI/2019/03/018335, 2019	Study registry
Ctri,, Comparison of two methods for labour induction in women with pregnancy hypertension, http://www.who.int/trialsearch/Trial2.aspx?TrialID=CTRI/2019/04/018827, 2019	Study registry

Study	Reason for Exclusion
Ctri,, A trial to study the usefulness of an already marketed tablet Mifepristone 200 mg as compared to other methods in preparing the reproductive tract for delivery in term pregnancy, http://www.who.int/trialsearch/Trial2.aspx?TrialID=CTRI/2019/06/019821, 2019	Study registry
Ctri,, induction of labour with foleys catheter placed intracervically, http://www.who.int/trialsearch/Trial2.aspx?TrialID=CTRI/2019/05/019282, 2019	Study registry
Ctri,, comparative study of onset of labour using 2 forms of prostaglandins, http://www.who.int/trialsearch/Trial2.aspx?TrialID=CTRI/2019/08/020771, 2019	Study registry
Danesh-Shaharaki, A, Biranvand-Heidari, K, Comparison of the effect of misoprostol and double-balloon catheter in preinduction of cervical ripening among postterm women, Journal of isfahan medical school, 35, 1707-1713, 2018	Unavailable
Danesh-Shaharaki, A., Biranvand-Heidari, K., Comparison of the effect of misoprostol and double-balloon catheter in preinduction of cervical ripening among postterm women, Journal of isfahan medical school, 35, 1707â□□1713, 2018	Unavailable
Danilack, V. A., Phipps, M. G., Kimmel, H., Trikalinos, T. A., 386: A network meta-analysis of cervical ripening interventions, American Journal of Obstetrics and Gynecology, 220, S263-S264, 2019	Systematic review, references checked for inclusion
De Bonrostro Torralba, C., Tejero Cabrejas, E. L., Cotaina Gracia, L., Lazaro Garcia, V. E., Moreno Perez, R., Agustin Oliva, A., Franco Royo, M. J., Envid Lazaro, B., Roca Aquillue, M., Hernandez Pimenta, J. V., Diaz Rabasa, B., Migdan, C. M., Campillos Maza, J. M., Vaginal misoprostol and dinoprostone for pre-induction of labour at term, Journal of Perinatal Medicine, 43, 2015	Abstract of a study already included (De Bonrostro Torralba 2019)
De Los Reyes, S. X., Sheffield, J. S., Eke, A. C., Single versus Double-Balloon Transcervical Catheter for Labor Induction: A Systematic Review and Meta-Analysis, American Journal of Perinatology, 36, 790-797, 2019	Systematic review, references checked for inclusion
de Los Reyes, Samantha X., Sheffield, Jeanne S., Eke, Ahizechukwu C., Single versus Double-Balloon Transcervical Catheter for Labor Induction: A Systematic Review and Meta-Analysis, American Journal of Perinatology, 2018	Systematic review, references checked for inclusion
de Vaan, M. D. T., ten Eikelder, M. L. G., Jozwiak, M., Palmer, K. R., Daviesâ□□Tuck, M., Bloemenkamp, K. W. M., Mol, B. W. J., Boulvain, M., Mechanical methods for induction of labour, Cochrane Database of Systematic Reviews, 2019	Systematic review, references checked for inclusion
De Vivo, V., Carbone, L., Saccone, G., Magoga, G., De Vivo, G., Locci, M., Zullo, F., Berghella, V., Early amniotomy after cervical ripening for induction of labor: a systematic review and meta-analysis of randomized controlled trials, American Journal of Obstetrics and Gynecology, 222, 320-329, 2020	Systematic review, references checked for inclusion
Deo, S., Preinduction cervical ripening: A prospective randomised comparison of intracervical foley catheter versus PGE2 gel, International Journal of Gynecology and Obstetrics, 131, E113, 2015	No relevant outcomes were reported
Deshmukh, Varsha Laxmikant, Yelikar, Kanan Avinash, Waso, Vandana, Comparative study of efficacy and safety of oral versus	Included in HTA (already included)

Study	Reason for Exclusion
vaginal misoprostol for induction or labour, Journal of obstetrics and gynaecology of India, 63, 321-4, 2013	
Diederen, M., Gommers, J. S. M., Wilkinson, C., Turnbull, D., Mol, B. W. J., Safety of the balloon catheter for cervical ripening in outpatient care: complications during the period from insertion to expulsion of a balloon catheter in the process of labour induction: a systematic review, BJOG: An International Journal of Obstetrics and Gynaecology, 125, 1086-1095, 2018	Systematic review, references checked for inclusion
Diederen, M., Gommers, Jsm, Wilkinson, C., Turnbull, D., Mol, Bwj, Safety of the balloon catheter for cervical ripening in outpatient care: complications during the period from insertion to expulsion of a balloon catheter in the process of labour induction: a systematic review, BJOG : an international journal of obstetrics and gynaecology, 125, 1086-1095, 2018	Systematic review, references checked for inclusion
Diguisto, C., Gouge, A. L., Giraudeau, B., Perrotin, F., Mechanical cervicAl ripeninG for women with PrOlongedPregnancies (MAGPOP): Protocol for a randomised controlled trial of a silicone double balloon catheter versus the Propess system for the slow release of dinoprostone for cervical ripening of prolonged pregnancies, BMJ Open, 7, e016069, 2017	Study protocol
Diguisto, Caroline, Le Gouge, Amelie, Giraudeau, Bruno, Perrotin, Franck, Mechanical cervicAl ripeninG for women with PrOlongedPregnancies (MAGPOP): protocol for a randomised controlled trial of a silicone double balloon catheter versus the Propess system for the slow release of dinoprostone for cervical ripening of prolonged pregnancies, BMJ Open, 7, e016069, 2017	Study protocol
Dixi, M. S., Somalwar, S. A., Tathe, G. R., Effectiveness of isosorbide mononitrate vs prostaglandin E2 gel for cervical ripening: A study, Journal of SAFOG, 11, 288-291, 2019	No relevant outcomes were reported
Dodd, Jodie M., Deussen, Andrea R., Grivell, Rosalie M., Crowther, Caroline A., Elective birth at 37 weeks' gestation for women with an uncomplicated twin pregnancy, Cochrane Database of Systematic Reviews, 2014	Systematic review, references checked for inclusion
Du, Chuying, Liu, Yukun, Liu, Yinglin, Ding, Hong, Zhang, Rui, Tan, Jianping, Double-balloon catheter vs. dinoprostone vaginal insert for induction of labor with an unfavorable cervix, Archives of Gynecology and Obstetrics, 291, 1221-7, 2015	Non randomised trial (women self-selected treatment)
Du, Y. M., Zhu, L. Y., Cui, L. N., Jin, B. H., Ou, J. L., Double-balloon catheter versus prostaglandin E2 for cervical ripening and labour induction: a systematic review and meta-analysis of randomised controlled trials, BJOG: An International Journal of Obstetrics and Gynaecology, 124, 891-899, 2017	Systematic review, references checked for inclusion
Duro Gomez, J., Garrido Oyarzun, M. F., Rodriguez Marin, A. B., de la Torre Gonzalez, A. J., Arjona Berral, J. E., Castelo-Branco, C., Vaginal misoprostol and cervical ripening balloon for induction of labor in late-term pregnancies, Journal of Obstetrics & Gynaecology Research, 43, 87-91, 2017	Observational study
Edwards, R. K., Norris, M. L., West, M. D., Zornes, C., Loeffler, K. A., Peck, J. D., Controlled Release Dinoprostone Insert and Foley Compared to Foley Alone: A Randomized Pilot Trial, American Journal of Perinatology, 2020	Complex intervention (dinoprostone/Foley)

Study	Reason for Exclusion
Edwards, R., Szychowski, J., Berger, J., Petersen, M., Ingersoll, M., Braescu, A. B., Lin, M., Effect of parity on duration and outcome of labor inductions with either Foley catheter or the prostaglandin E2 vaginal insert, American Journal of Obstetrics and Gynecology, 210, S292, 2014	Included in HTA (already included)
Edwards, R., Szychowski, J., Braescu, A. B., Biggio, J., Lin, M., Potential barriers to adopting foley catheter for induction of labor in women with an unfavorable cervix: Does the labor curve differ?, American journal of obstetrics and gynecology, 1), S413-S414, 2015	No relevant outcomes were reported
Edwards, Rk, Szychowski, Jm, Berger, Jl, Petersen, M, Ingersoll, M, Bodea-Braescu, Av, Lin, Mg, Foley catheter compared with the controlled-release dinoprostone insert: a randomized controlled trial, Obstetrics and Gynecology, 123, 1280-1287, 2014	Included in HTA (already included)
Edwards,R., Szychowski,J., Berger,J., Petersen,M., Ingersoll,M., Braescu,A.B., Lin,M., Randomized trial comparing Foley catheter to the prostaglandin E2 vaginal insert for induction of labor, American Journal of Obstetrics and Gynecology, 210, S39-S40, 2014	Included in HTA (already included)
Ekabua, J., Odusolu, P., Njoku, C., Iklaki, C., Comparative study of pregnancy outcomes of two different methods of cervical ripening for induction of labour, International Journal of Gynecology and Obstetrics, 131, E225, 2015	Misoprostol intervention just states â□œmisoprostolâ□□ no information on route of administration, or dosage
El Khouly, Nabih I., A prospective randomized trial comparing Foley catheter, oxytocin, and combination Foley catheter-oxytocin for labour induction with unfavourable cervix, Journal of obstetrics and gynaecology : the journal of the Institute of Obstetrics and Gynaecology, 37, 309-314, 2017	Complex intervention (Foley catheter plus oxytocin)
El-Din NMN, El-Moghazt DAM, Cervical Ripening and Induction of Labour with Misoprostol, Prostaglandin E2 or Prostaglandin E2 gel: A Randomized Comparative Clinical Trial, abstract no 329	Included in HTA (already included)
El-Khayat, Waleed, Alelaiw, Heba, El-kateb, Abdallah, Elsemary, Ali, Comparing vaginal misoprostol versus Foley catheter plus vaginal isosorbide mononitrate for labor induction, The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians, 29, 487-92, 2016	Complex intervention (Foley catheter plus vaginal IMN)
Eser, A., Ozkaya, E., Abide, C. Y., Eser, T., Eser, G. Y., Abike, F., Tayyar, A. T., Eroglu, M., Transcervical Foley balloon catheter and vaginal prostaglandin E2 insert combination vs. vaginal prostaglandin E2 insert only for induction of labor at term: a randomized clinical trial, Archives of Gynecology and Obstetrics, 299, 451â□□457, 2019	Complex intervention (Foley/prostaglandin)
Euctr, A. T., Comparison of patient satisfaction between two methods of induction of labour: use of a balloon catheter on an outpatient basis compared to an inpatient treatment with the medication "Propess", http://www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2017-002978-39-AT, 2019	Study registry
Euctr, S. E., A Study to Evaluate the Efficacy, Safety, Tolerability and dose response of Subcutaneously Administered Tafoxiparin to induce labor in Term Pregnant, Nulliparous Women with an unripe	Study registry

Study	Reason for Exclusion
cervix, http://www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2019-000620-17-SE, 2019	
Finucane, E. M., Murphy, D. J., Biesty, L. M., Gyte, G. M. L., Cotter, A. M., Ryan, E. M., Boulvain, M., Devane, D., Membrane sweeping for induction of labour, Cochrane Database of Systematic Reviews, 2020	Systematic review, references checked for inclusion
Fuks, Am, Robinson, Jv, Rothschild, Tj, Akinnawonu, Kf, Salafia, C, Mechanical labor induction using the foley catheter balloon compared with the cook cervical balloon, Obstetrics and gynecology., 125, 37s, 2015	Observational study
Garba, I, Muhammed, As, Muhammad, Z, Galadanci, Hs, Ayyuba, R, Abubakar, Is, Induction to delivery interval using transcervical Foley catheter plus oxytocin and vaginal misoprostol: a comparative study at Aminu Kano Teaching Hospital, Kano, Nigeria, Annals of african medicine, 15, 114-119, 2016	Complex intervention (Foley catheter plus oxytocin)
Gattas, D. S. M. B., Da Silva Junior, J. R., Souza, A. S. R., Feitosa, F. E., De Amorim, M. M. R., Misoprostol administered sublingually at a dose of 12.5 mug versus vaginally at a dose of 25 mug for the induction of full-term labor: A randomized controlled trial protocol, Reproductive health, 15 (1) (no pagination), 2018	Study protocol
Gattas, Dsmb, Silva, Junior Jr, Souza, Asr, Feitosa, Fe, Amorim, Mmr, Misoprostol administered sublingually at a dose of 12.5 mug versus vaginally at a dose of 25 mug for the induction of full-term labor: a randomized controlled trial protocol, Reproductive health, 15, 2018	Study protocol
Gaudineau, A, Vayssiere, C, Cervical ripening with misoprostol with a live fetus (Provisional abstract), Database of Abstracts of Reviews of Effects, 169-178, 2014	Study in French
Ghafarzadeh, Masoomeh, Moeininasab, Samira, Namdari, Mehrdad, Effect of early amniotomy on dystocia risk and cesarean delivery in nulliparous women: a randomized clinical trial, Archives of Gynecology and Obstetrics, 292, 321-5, 2015	Participants were in spontaneous labour, not attending for induction.
Gholami, F., Samani, L. N., Kashanian, M., Naseri, M., Hosseini, A. F., Nejad, S. A. H., Onset of labor in post-term pregnancy by chamomile, Iranian Red Crescent Medical Journal, 18, e19871, 2016	No relevant outcomes were reported
Ghosh, Arpita, Lattey, Katherine R., Kelly, Anthony J., Nitric oxide donors for cervical ripening and induction of labour, The Cochrane database of systematic reviews, 12, CD006901, 2016	Systematic review review, studies checked
Gilson, G. J., A randomized control trial of low dose oral liquid misoprostol versus foley balloon-oxytocin for induction of labor, American Journal of Obstetrics and Gynecology, 216, S511, 2017	Complex intervention (Foley catheter plus oxytocin)
Goel G, Shirazee HH, Phadikar A, Saha SK, Sublingual versus Vaginal Misoprostol Induction of Labour and its Fetomaternal Outcome, abstract no 160	Included in HTA (already included)
Gommers, Jip S. M., Diederen, Milou, Wilkinson, Chris, Turnbull, Deborah, Mol, Ben W. J., Risk of maternal, fetal and neonatal complications associated with the use of the transcervical balloon catheter in induction of labour: A systematic review, European	Systematic review, references checked for inclusion

Study	Reason for Exclusion
journal of obstetrics, gynecology, and reproductive biology, 218, 73-84, 2017	
Greenberg, Victoria, Khalifeh, Adeeb, Intracervical Foley balloon catheter for cervical ripening and labor induction: A review, Seminars in perinatology, 39, 441-3, 2015	Systematic review, references checked for inclusion
Greer IA, Calder AA, Pre-induction cervical ripening with extra-amniotic and vaginal prostaglandin E2, J Obstet Gynaecol, 10, 18â□“22, 1989	Included in HTA (already included)
Grimm, B., Wilson-Liverman, A., Bennett, K., Randomized comparison of misoprostol and oxytocin for labor induction in multiparous women, American Journal of Obstetrics and Gynecology, 1), S376, 2015	No relevant outcomes were reported
Grivell, R., Systematic review with meta-analysis: Induction of labour decreases a woman's chance of caesarean delivery when compared with expectant management, Evidence-Based Medicine, 19, 217, 2014	Systematic review, references checked for inclusion
Grobman, W., A randomized trial of elective induction of labor at 39 weeks compared with expectant management of low-risk nulliparous women, American Journal of Obstetrics and Gynecology, 218, S601, 2018	Author did not report which method was used for inducing labour
Grobman, W. A., 2: Resource utilization among low-risk nulliparas randomized to elective induction at 39 weeks or expectant management, American Journal of Obstetrics and Gynecology, 220, S2-S3, 2019	Author did not report which method was used for inducing labour
Grobman, W. A., Caughey, A. B., Elective induction of labor at 39 weeks compared with expectant management: a meta-analysis of cohort studies, American Journal of Obstetrics and Gynecology, 2019	Systematic review, references checked for inclusion
Grobman, W. A., Rice, M. M., Reddy, U. M., Tita, A. T. N., Silver, R. M., Mallett, G., Hill, K., Thom, E. A., El-Sayed, Y. Y., Perez-Delboy, A., Rouse, D. J., Saade, G. R., Boggess, K. A., Chauhan, S. P., Iams, J. D., Chien, E. K., Casey, B. M., Gibbs, R. S., Srinivas, S. K., Swamy, G. K., Simhan, H. N., MacOnes, G. A., Labor induction versus expectant management in low-risk nulliparous women, New England Journal of Medicine, 379, 513-523, 2018	Women in the experimental group were offered induction of labour with different interventions, depending on clinical presentation
Grobman, W. A., Sandoval, G., Reddy, U. M., Tita, A. T. N., Silver, R. M., Mallett, G., Hill, K., Rice, M. M., El-Sayed, Y. Y., Wapner, R. J., Rouse, D. J., Saade, G. R., Thorp, J. M., Chauhan, S. P., Iams, J. D., Chien, E. K., Casey, B. M., Gibbs, R. S., Srinivas, S. K., Swamy, G. K., Simhan, H. N., Macones, G. A., Peaceman, A., Plunkett, B., Paycheck, K., Dinsmoor, M., Harris, S., Sheppard, J., Biggio, J., Harper, L., Longo, S., Servay, C., Varner, M., Sowles, A., Coleman, K., Atkinson, D., Stratford, J., Dellermann, S., Meadows, C., Esplin, S., Martin, C., Peterson, K., Stradling, S., Willson, C., Lyell, D., Girsen, A., Knapp, R., Gyamfi, C., Bousleiman, S., Perez-Delboy, A., Talucci, M., Carmona, V., Plante, L., Tocci, C., Leopanto, B., Hoffman, M., Dill-Grant, L., Palomares, K., Otarola, S., Skupski, D., Chan, R., Allard, D., Gelsomino, T., Rousseau, J., Beati, L., Milano, J., Werner, E., Salazar, A., Costantine, M., Chiossi, G., Pacheco, L., Saad, A., Munn, M., Jain, S., Clark, S., Clark, K., Boggess, K., Timlin, S., Eichelberger, K., Moore, A., Beamon, C., Byers, H., Ortiz, F., Garcia, L., Sibai, B., Bartholomew,	No relevant outcomes were reported

Study	Reason for Exclusion
A., Buhimschi, C., Landon, M., Johnson, F., Webb, L., McKenna, D., Fennig, K., Snow, K., Habli, M., McClellan, M., Lindeman, C., Dalton, W., Hackney, D., Cozart, H., Mayle, A., Mercer, B., Moseley, L., Gerald, J., Fay-Randall, L., Garcia, M., Sias, A., Price, J., Hale, K., Phipers, J., Heyborne, K., Craig, J., Parry, S., Sehdev, H., Bishop, T., Ferrara, J., Bickus, M., Caritis, S., Thom, E., Doherty, L., de Voest, J., Health resource utilization of labor induction versus expectant management, American Journal of Obstetrics and Gynecology, 222, 369.e1-369.e11, 2020	
Gulersen, M., Bornstein, E., Baum, S. R., Krantz, D., Minior, V., Divon, M., Does labor induction in nulliparous, term, singleton and vertex pregnancies increase the risk of cesarean delivery?, Obstetrics and Gynecology, 131, 121S-122S, 2018	Systematic review, references checked for inclusion
Haghighi, L., Homam, H., Raoofi, Z., Najmi, Z., Intravaginal isosorbide dinitrate or misoprostol for cervical ripening prior to induction of labour: a randomised controlled trial, Journal of Obstetrics & Gynaecology, 33, 272-6, 2013	Included in HTA (already included)
Hales KA, Rayburn WF, Turnbull GL, Christensen HD, Patatanian E, Double-blind comparison of intracervical and intravaginal prostaglandin E2 for cervical ripening and induction of labor, Am J Obstet Gynecol, 171, 1087â□“91, 1994	Included in HTA (already included)
Hamed, H. O., Alsheeha, M. A., Abu-Elhasan, A. M., Abd Elmoniem, A. E., Kamal, M. M., Pregnancy outcomes of expectant management of stable mild to moderate chronic hypertension as compared with planned delivery, International Journal of Gynecology and Obstetrics, 127, 15-20, 2014	Women in the experimental group were offered induction of labour with different interventions, depending on clinical presentation
Hay D, Robinson G, Filshie M, James D, Cervical ripening with prostaglandin E2 gel and hygroscopic cervical dilators, abstract no 480	Included in HTA (already included)
Hekmatzadeh, S. F., Bazarganipour, F., Malekzadeh, J., Goodarzi, F., Aramesh, S., A randomized clinical trial of the efficacy of applying a simple protocol of boiled Anethum Graveolens seeds on pain intensity and duration of labor stages, Complementary Therapies in Medicine, 22, 970-976, 2014	No relevant outcomes reported
Herabutya Y, O-Prasertsawat P, A comparison of oral and intracervical prostaglandin E2 for ripening of the unfavourable cervix prior to induction of labour, J Med Assoc Thai, 71, 269â□“73, 1988	Included in HTA (already included)
Herabutya Y, O-Prasertsawat P, Ripening of the unfavorable cervix with prostaglandin E2: intracervical versus intravaginal route, J Med Assoc Thai, 76, 63â□“8, 1993	Included in HTA (already included)
Hill, K., Mallett, G. L., 95: Maternal characteristics, delivery outcomes and self-reported perceived control during childbirth in low-risk nulliparous women, American Journal of Obstetrics and Gynecology, 220, S76-S77, 2019	Author did not report which method was used for inducing labour
Hoppe,K., Schiff,M., Peterson,S., Gravett,M., Randomized controlled trial: Comparing 80mL double versus 30mL single balloon catheters for pre-induction cervical ripening, American Journal of Obstetrics and Gynecology, 210, S326-, 2014	Abstract of Hoppe 2016
Howard, Kirsten, Gerard, Karen, Adelson, Pamela, Bryce, Robert, Wilkinson, Chris, Turnbull, Deborah, Women's preferences for	All women received the same intervention (prostaglandin)

Study	Reason for Exclusion
inpatient and outpatient priming for labour induction: a discrete choice experiment, BMC health services research, 14, 330, 2014	
Hutchon DJ, Geirsson R, Patel NB, A double-blind controlled trial of PGE2 gel in cervical ripening, Int J Gynaecol Obstet, 17, 604â□“7, 1980	Included in HTA (already included)
Irct20191115045453N,, Comparing the Effects of Vaginal Misoprostol, Vaginal Trinitroglycerin (TNG) and oral Evening Primrose Oil in Cervical Ripening at term pregnancy, http://www.who.int/trialsearch/Trial2.aspx?TrialID=IRCT20191115045453N1, 2019	Protocol registry
Iskander MN, A comparison of the efficacy and safety of extra-amniotic prostaglandin E2 and intravenous prostaglandin E2 for the induction of labour in patients with unripe cervices, J Int Med Res, 6, 144â□“6, 1978	Included in HTA (already included)
Jahdi, F., Kalati, M., Kashanian, M., Naseri, M., Haghani, H., Effect of oral evening primrose capsules on ripening of the cervix in nulliparous Iranian pregnant women (A randomized trial), Acta Medica Mediterranea, 32, 1273-1279, 2016	No relevant outcomes were reported
Jahromi, Bn, Poorgholam, F, Yousefi, G, Salarian, L, Sublingual versus vaginal misoprostol for the induction of labor at term: a randomized, triple-blind, placebo-controlled clinical trial, Iranian journal of medical sciences, 41, 79-85, 2016	>1/3 population had ruptured membranes
Javadnoori, M., Akbari, M., Afshari, P., Siahpoosh, A., Lak, E., Comparison of the effect of anethum graveolens (dill) seeds with oxytocin on induction of labor in term pregnancy: A randomized clinical trial, International Journal of Gynecology and Obstetrics, 131, E595, 2015	No relevant outcomes were reported
Johnson IR, Macpherson MB, Welch CC, Filshie GM, A comparison of Lamicel and prostaglandin E2 vaginal gel for cervical ripening before induction of labor, Am J Obstet Gynecol, 151, 604â□“7, 1985	Included in HTA (already included)
Jozwiak, M., Ten Eikelder, M., Rengerink, K. O., De Groot, C., Feitsma, H., Spaanderman, M., Van Pampus, M., De Leeuw, J. W., Mol, B. W., Bloemenkamp, K., Foley catheter versus vaginal misoprostol: Randomized controlled trial (PROBAAT-M Study) and systematic review and meta-analysis of literature, American journal of perinatology, 31, 145-155, 2014	Included in HTA (already included)
Jozwiak, Marta, Oude Rengerink, Katrien, Ten Eikelder, Mieke L. G., van Pampus, Maria G., Dijksterhuis, Marja G. K., de Graaf, Irene M., van der Post, Joris A. M., van der Salm, Paulien, Scheepers, Hubertina C. J., Schuitemaker, Nico, de Leeuw, Jan Willem, Mol, Ben W. J., Bloemenkamp, Kitty W. M., Foley catheter or prostaglandin E2 inserts for induction of labour at term: an open-label randomized controlled trial (PROBAAT-P trial) and systematic review of literature, European journal of obstetrics, gynecology, and reproductive biology, 170, 137-45, 2013	Included in HTA (already included)
Jyotsna, T., Seema, S., Eena, S., Sameet, M., A randomized clinical study to evaluate the effect of Sukhprasavkar lepa, Matra vasti and Yoni pichu on ameliorating the process of labour, International Journal of Research in Ayurveda and Pharmacy, 9, 101-112, 2018	No relevant intervention - compares a paste applied to naval to reduce pain. The enema (intervention of interest) and tampon are in both groups

Study	Reason for Exclusion
Kalati, Mahnaz, Kashanian, Maryam, Jahdi, Fereshteh, Naseri, Mohsen, Haghani, Hamid, Sheikhansari, Narges, Evening primrose oil and labour, is it effective? A randomised clinical trial, Journal of obstetrics and gynaecology : the journal of the Institute of Obstetrics and Gynaecology, 38, 488-492, 2018	No relevant outcomes were reported
Katukuri, V., Blue, N. R., Holbrook, B. D., Chao, C. R., Rayburn, W. F., Blackstone, J. A., Mozurkewich, E. L., Double balloon is not superior to single balloon trans-cervical catheter for induction of labor: A meta-analysis, American Journal of Obstetrics and Gynecology, 216, S434, 2017	Systematic review, references checked for inclusion
Ke, X-Y, Chen, B-Y, Xu, H-F, Li, D-C, Li, Y-F, Sun, X, Clinical study of Jiawei Bazhen decoction combined with oxytocin for cervical ripening of qi and blood deficiency type of pregnant women, Zhongguo zhongyao zazhi, 40, 1821-1824, 2015	Study in Chinese
Keeney, E., Alfirevic, Z., Caldwell, D. M., Dowswell, T., Dias, S., Jones, L., Navaratnam, K., Welton, N. J., Labour induction with prostaglandins: What works best? A systematic review, network meta-analysis and cost-effectiveness analysis, Value in Health, 17 (7), A505-A506, 2014	Systematic review, references checked for inclusion
Kellie, F. J., Amniotomy plus intravenous oxytocin for induction of labour, Cochrane Database of Systematic Reviews, 2017, CD009821, 2017	Systematic review, references checked for inclusion
Kelly, A. J., Kavanagh, J., Thomas, J., Castor oil, bath and/or enema for cervical priming and induction of labour, Cochrane Database of Systematic Reviews, 7, CD003099, 2013	Systematic review, references checked for inclusion
Kelly,Anthony J., Alfirevic,Zarko, Ghosh,Arpita, Outpatient versus inpatient induction of labour for improving birth outcomes, Cochrane Database of Systematic Reviews, -, 2013	Systematic review, references checked for inclusion
Keskin, Huseyin Levent, Kabacaoglu, Gokalp, Secen, Elcin Islek, Ustuner, Isik, Yegin, Gulin, Avsar, Ayse Filiz, Effects of intravaginally inserted controlled-release dinoprostone and oxytocin for labor induction on umbilical cord blood gas parameters, Journal of the Turkish German Gynecological Association, 13, 257-60, 2012	No relevant outcomes were reported
Khan, O. Z., Khan, M. H., Batool, S., Akhtar, R., Comparing the efficacy of sublingual misoprostol and vaginal misoprostol for induction of labor at term live pregnancy, Rawal medical journal, 43, 444â□□447, 2018	No relevant outcomes were reported
Kim JH, Yang HS, A comparison of intravaginal misoprostol and dinoprostone for cervical ripening and labor inducton in term pregnancy with unfavorable cervix, Korean J Obstet Gynecol, 43, 243â□“7, 2000	Included in HTA (already included)
Kortekaas, J. C., Bruinsma, A., Keulen, J. K. J., van Dillen, J., Oudijk, M. A., Zwart, J. J., Bakker, J. J. H., de Bont, D., Nieuwenhuijze, M., Offerhaus, P. M., van Kaam, A. H., Vandenbussche, F., Mol, B. W. J., de Miranda, E., Effects of induction of labour versus expectant management in women with impending post-term pregnancies: The 41 week - 42 week dilemma, BMC Pregnancy and Childbirth, 1-7, 2015	Study protocol
Kulkarni, V. G., Kulkarni, J. V., Sreekantha,, Yogesh, B., The study of comparision of sublinguinal versus vaginal 25 micro gram of	Unavailable

Study	Reason for Exclusion
misoprostol in the induction of labour at term, International Journal of Pharma and Bio Sciences, 5, P1-P13, 2014	
Lackritz R, Gibson M, Frigoletto FD, Preinduction use of laminaria for the unripe cervix, Am J Obstet Gynecol, 134, 349â□“50, 1979	Included in HTA (already included)
Lajusticia, H., Martinez-Dominguez, S. J., Perez-Roncero, G. R., Chedraui, P., Perez-Lopez, F. R., Single versus double-balloon catheters for the induction of labor of singleton pregnancies: a meta-analysis of randomized and quasi-randomized controlled trials, Archives of Gynecology and Obstetrics, 297, 1089-1100, 2018	Systematic review, references checked for inclusion
Lajusticia, Hector, Martinez-Dominguez, Samuel J., Perez-Roncero, Gonzalo R., Chedraui, Peter, Perez-Lopez, Faustino R., Health, Outcomes, Systematic Analyses, Project, Single versus double-balloon catheters for the induction of labor of singleton pregnancies: a meta-analysis of randomized and quasi-randomized controlled trials, Archives of gynecology and obstetrics, 297, 1089-1100, 2018	Systematic review, references checked for inclusion
Lapuente-Ocamica, O., Ugarte, L., Lopez-Picado, A., Sanchez-Refoyo, F., Lasa, I. L., Echevarria, O., Alvarez-Sala, J., Farinas, A., Bilbao, I., Barbero, L., Vicarregui, J., Hernanz Chaves, R., Paz Corral, D., Lopez-Lopez, J. A., Efficacy and safety of administering oral misoprostol by titration compared to vaginal misoprostol and dinoprostone for cervical ripening and induction of labour: Study protocol for a randomised clinical trial, BMC Pregnancy and Childbirth, 19, 14, 2019	Study protocol
Leigh, S., Granby, P., Haycox, A., Mundle, S., Bracken, H., Khedikar, V., Mulik, J., Faragher, B., Easterling, T., Turner, M. A., Alfirevic, Z., Winikoff, B., Weeks, A. D., Foley catheter vs. oral misoprostol to induce labour among hypertensive women in India: a cost-consequence analysis alongside a clinical trial, BJOG : an international journal of obstetrics and gynaecology, 2018	Same as Mundle 2018
Levine, L. D., Sammel, M. D., Parry, S., Williams, C. T., Elovitz, M. A., Srinivas, S. K., Foley or misoprostol for the management of induction (The 'FOR MOMI' trial): A four-arm randomized clinical trial, American Journal of Obstetrics and Gynecology, 214, S4, 2016	Abstract of Levine 2016
Lewis GJ, Cervical ripening before induction of labour with prostaglandin E2 pessaries or a Foleyâ□™s catheter, J Obstet Gynaecol, 3, 173â□“6, 1983	Included in HTA (already included)
Li, Y., He, Z., Song, L., Zhang, J., Wang, J., Cheng, J., Foley catheter balloon versus prostaglandins for cervical ripening and labor induction: A systematic review and meta-analysis, International Journal of Clinical and Experimental Medicine, 9, 7573-7584, 2016	Systematic review, references checked for inclusion
Liu, Aihai, Lv, Jieqiang, Hu, Yue, Lang, Junzhe, Ma, Luhang, Chen, Wenbing, Efficacy and safety of intravaginal misoprostol versus intracervical dinoprostone for labor induction at term: a systematic review and meta-analysis, The journal of obstetrics and gynaecology research, 40, 897-906, 2014	Systematic review, references checked for inclusion
Liu, X., Wang, Y., Zhang, F., Zhong, X., Ou, R., Luo, X., Qi, H., Double- versus single-balloon catheters for labour induction and cervical ripening: A meta-analysis, BMC Pregnancy and Childbirth, 19, 358, 2019	Systematic review, references checked for inclusion

Study	Reason for Exclusion
Liu, Yi-Ran, Pu, Cai-Xiu, Wang, Xiao-Yan, Wang, Xue-Yan, Double-balloon catheter versus dinoprostone insert for labour induction: a meta-analysis, Archives of Gynecology and Obstetrics, 299, 7-12, 2019	Systematic review, references checked for inclusion
Lopes P, Besse O, Sagot P, Dantal F, De Morel P, Panel N, et al, Induction of labour with vaginal prostaglandin E2 with a â˜Spongelâ™ Results of a prospective randomised study taking into account Bishopâ™s score and the dose of PGE2 used, J Gynecol Obstet Biol Reprod, 19, 505, 1990	Not English
Lopes P, Besse O, Sagot P, Dantal F, De Morel P, Panel N, et al/, PGE2 Application on a Biodegradable Support for Cervix Ripening and Induction of Labour. , Proceedings of 2nd European Congress on Prostaglandins in Reproduction, 30 Aprilâ“3 May 1991, The Hague, The Netherlands, Abstract no. 147., 1991	Included in HTA (already included)
Mahacakri, E. P., Bernolian, N., Theodorus, W. T. P., A comparitive study of titrated oral misoprostol in solution versus vaginal misoprostol for labour induction, Journal of Perinatal Medicine, 45 (Supplement 2), 363, 2017	Abstract of Mahacakri 2018
Majeed, A., Kundu, S., Singh, P., Study on induction of labour versus expectant management in gestational hypertension or mild preeclampsia after 36 weeks of gestation, BJOG: An International Journal of Obstetrics and Gynaecology, 121, 118, 2014	Method of induction was not specified
Manandhar, R., Saha, R., Bajracharya, J., Malla, R., Mifepristone versus oxytocin for cervical ripening prior to induction of labor, Journal of Obstetrics and Gynaecology Research, 43, 189-190, 2017	Abstract only, full text available
Martin, J. N., Jr., Owens, M. Y., Thigpen, B., Parrish, M. R., Keiser, S. D., Wallace, K., OS011. Management of late preterm pregnancy complicated by mildpreeclampsia: A prospective randomized trial, Pregnancy hypertension, 2, 180, 2012	Method for induction was not reported
McKenzie, I., Davis, D., Ferguson, S., Induction of labour versus expectant management for well women and babies in pregnancies extending beyond 41 weeks: A systematic review and meta-analysis, Women and Birth, 31, S36, 2018	Systematic review, references checked for inclusion
McMaster, K., Sanchez-Ramos, L., Kaunitz, A. M., Balancing the efficacy and safety of misoprostol: a meta-analysis comparing 25 versus 50 micrograms of intravaginal misoprostol for the induction of labour, BJOG: An International Journal of Obstetrics & Gynaecology, 122, 468-76, 2015	Systematic review, references checked for inclusion
McMaster, Kristen, Sanchez-Ramos, Luis, Kaunitz, Andrew M., Evaluation of a Transcervical Foley Catheter as a Source of Infection: A Systematic Review and Meta-analysis, Obstetrics and Gynecology, 126, 539-51, 2015	Systematic review, references checked for inclusion
Middleton, P., Shepherd, E., Crowther, C. A., Induction of labour for improving birth outcomes for women at or beyond term, Cochrane Database of Systematic Reviews, 2018 (5) (no pagination), 2018	Systematic review, references checked for inclusion
Miller, H, Goetzl, L, Wing, Da, Powers, B, Rugarn, O, Optimising daytime deliveries when inducing labour using prostaglandin vaginal inserts, Journal of maternal-fetal & neonatal medicine, 29, 517-522, 2016	Same trial as Wing 2013

Study	Reason for Exclusion
Miller, H., Billips, B., Dutia, R., Raymond, K., Powers, B., Safety and efficacy of dinoprostone and misoprostol vaginal inserts for labor induction, Obstetrics and Gynecology, 129, 84S-85S, 2017	Pooled analysis, references not reported
Miller, H., Billips, B., Dutia, R., Soskin, L., Raymond, K., Powers, B., Does gestational age affect efficacy and safety of induction of labor?, American Journal of Obstetrics and Gynecology, 218, S230-S231, 2018	No relevant outcomes were reported
Miller, N. R., Cypher, R. L., Foglia, L. M., Pates, J. A., Nielsen, P. E., Elective induction of nulliparous labor at 39 weeks of gestation: A randomized clinical trial, Obstetrics and Gynecology, 123, 72S, 2014	Women in the intervention arm received different interventions, depending on clinical presentation
Miller, Nr, Cypher, Rl, Foglia, Lm, Pates, Ja, Nielsen, Pe, Elective Induction of Labor Compared With Expectant Management of Nulliparous Women at 39 Weeks of Gestation: a Randomized Controlled Trial, Obstetrics and Gynecology, 126, 1258-1264, 2015	Women in the intervention arm received different interventions, depending on clinical presentation
Mirteimouri, M., Pourali, L., Najaf Najafi, M., Ghaffarian Omid, M., Intravaginal administration of isosorbide mononitrate for cervical ripening in prolonged pregnancy: a randomised clinical trial, Journal of Obstetrics and Gynaecology, 2019	Complex intervention (misoprostol/IMN)
Mishanina, Ekaterina, Rogozinska, Ewelina, Thatthi, Tej, Uddin-Khan, Rehan, Khan, Khalid S., Meads, Catherine, Use of labour induction and risk of cesarean delivery: a systematic review and meta-analysis, CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne, 186, 665-73, 2014	Systematic review, references checked for inclusion
Moeini, A., Aalami-Harandi, R., Karamali, M., Induction of labor with titrated oral misoprostol solution versus oxytocin in term pregnancy: Randomized controlled trial, Revista brasileira de ginecologia e obstetricia, 35, 60-65, 2013	Included in HTA (already included)
Mollart, Lyndall J., Adam, Jon, Foureur, Maralyn, Impact of acupressure on onset of labour and labour duration: A systematic review, Women and birth : journal of the Australian College of Midwives, 28, 199-206, 2015	Systematic review, references checked for inclusion
Moukhah, S, Ahmadi, F, Preinduction cervical ripening using oral and vaginal isosorbide dinitrate in patients with term pregnancy: a randomized clinical trial, Koomesh, 17, 863-870, 2016	Different preparations of the same intervention were used (isosorbide dinitrate)
Mundle, S., Bracken, H., Faragher, B., Alfirevic, Z., Winikoff, B., Weeks, A., Induction of labour in hypertensive women in India: A randomised trial comparing the Foley catheter with oral misoprostol, BJOG: An International Journal of Obstetrics and Gynaecology, 123, 8, 2016	Abstract of Mundle 2018
Mundle, S., Bracken, H., Faragher, B., Easterling, T., Winikoff, B., Weeks, A., Induction of labor in preeclamptic women in India: A randomized trial comparing foley catheter with oral misoprostol, Obstetrics and Gynecology, 127, 75S, 2016	Abstract of Mundle 2018
Nager CW, Key TC, Moore TR, Cervical ripening and labor outcome with preinduction intracervical prostaglandin E2 (Prepidil) gel, J Perinatol, 7, 189â□“93, 1987	Included in HTA (already included)
Namavar Jahromi, B., Poorgholam, F., Yousefi, G., Salarian, L., Sublingual versus vaginal misoprostol for induction of labor at term: A randomized triple-blind placebo controlled clinical trial, International journal of gynaecology and obstetrics, 131, 2015	>1/3 population had ruptured membranes

Study	Reason for Exclusion
Nct,, Misoprostol Labour Induction Study, Https://clinicaltrials.gov/show/nct03489928, 2018	Not published
Nct,, A Trial of Prostaglandin E2 Tablets Versus Foley Catheter for Labor Induction, Https://clinicaltrials.gov/show/nct02486679, 2015	Not published
Nct,, Tearing of Membranes Before Birth - a Comparison Between Two Ways of Induction of Labor Pitocin Opposite Prostaglandin, Https://clinicaltrials.gov/show/nct02720978, 2016	Not published
Nct,, Continuous Versus Intermittent Oxytocin Infusion for Induction of Labor, https://clinicaltrials.gov/show/NCT04017247, 2019	Protocol registry
Nct,, Oral Misoprostol Solution in Labor Induction, https://clinicaltrials.gov/show/NCT03927807, 2019	Protocol registry
Nct,, Induction of Labor in Term Pregnancies With Unfavourable Cervix, https://clinicaltrials.gov/show/NCT04280874, 2020	Protocol registry
Neiger R, Greaves PC, Comparison between vaginal misoprostol and cervical dinoprostone for cervical ripening and labor induction, Tenn Med, 94, 25â□“7, 2001	Included in HTA (already included)
Neri, I, Monari, F, Midwife, Cs, Facchinetti, F, Acupuncture in post-date pregnancy: a pilot study, Journal of maternal-fetal & neonatal medicine, 27, 874-878, 2014	No denominator data was reported; pilot study Neri 2018
Neri, I., Pignatti, L., Fontanesi, F., Facchinetti, F., Acupuncture in Postdate Pregnancy Management, JAMS Journal of Acupuncture and Meridian Studies, 2018	Not randomised - patient-selected group allocation
Nigam A, Madan M, Puri M, Agarwal S, Trivedi SS, Labour induction with 25 micrograms versus 50 micrograms intravaginal misoprostol in full term pregnancies, Trop Doct, 40, 53â□“5, 2010	Included in HTA (already included)
Ntsaluba A, The use of an indwelling catheter compared to intracervical prostaglandin gel for cervical ripening prior to induction of labour, O&G Forum, 17â□“21, 1997	Included in HTA (already included)
Nuutila M, Kajanoja P, Cervical ripening prior to labor induction with intracervical prostaglandin E2 gel in patients with preeclampsia: a placebo-controlled study, Hypertens Pregn, 14, 313â□“17, 1995	Included in HTA (already included)
Okon, Okon Asuquo, Ekabua, John Egede, Postpartum Vaginal Blood Loss following Two Different Methods of Cervical Ripening, Obstetrics and gynecology international, 2017, 1678265, 2017	Serial doses of misoprostol were provided
Olmo I, Rodenas JJ, Bou J, Jaca A, Moraga R, Monleon J, Labour induction Oxytocin ev vs dinoprostone (PGE2) vaginal propess, J Perinatal Med, 29, 14, 2001	Included in HTA (already included)
Ophir E, Haj N, Korenblum R, Oettinger M, Cervical ripening before induction of labor: comparison of an intracervical Foley catheter and prostaglandin E2 vaginal tablets, Int J Feto-Maternal Med, 5, 101â□“6, 1992	Included in HTA (already included)
Owen J, Winkler CL, Harris BA, Hauth JC, Smith MC, A randomized, double-blind trial of prostaglandin E2 gel for cervical ripening and meta-analysis, Am J Obstet Gynecol, 165, 991â□“6, 1991	Included in HTA (already included)
Owens, M. Y., Thigpen, B., Parrish, M. R., Keiser, S. D., Sawardecker, S., Wallace, K., Martin Jr, J. N., Management of preeclampsia when diagnosed between 34-37 weeks gestation: deliver now or deliberate until 37 weeks?, Journal of the Mississippi State Medical Association, 55, 208-211, 2014	Method for induction of labour was not reported

Study	Reason for Exclusion
Padayachee, L., Kale, M., Mannerfeldt, J., Metcalfe, A., Oral Misoprostol for Induction of Labour in Term PROM: A Systematic Review, Journal of Obstetrics and Gynaecology Canada, 2020	Systematic review, references checked for inclusion
Paisarntantiwong R, Getgan M, A comparison between single dose of 50 microg oral misoprostol and 25 microg vaginal misoprostol for labor induction, J Med Assoc Thai, 88, 56â□“62, 2005	Included in HTA (already included)
Parewijck W, Thiery M, Cervical Ripening: Randomized Comparative Study of Extra-amniotic vs Intracervical PGE2 Gel, abstract no 165	Included in HTA (already included)
Patil PK, Swamy MK, Rao Radhika K, Oral misoprostol vs intra-cervical dinoprostone for cervical ripening and labour induction, J Obstet Gynaecol India, 55, 128â□“31, 2005	Included in HTA (already included)
Pimentel, V. M., Arabkhazaeli, M., Moon, J. Y., Wang, A., Kapedani, A., Bernstein, P. S., Tropper, P., Is more than one dose of misoprostol needed to expedite vaginal delivery in a patient with an unripe cervix? - A randomized controlled study, American journal of obstetrics and gynecology, 218 (1 Supplement 1), S74-S75, 2018	Abstract of Pimentel 2018
Pimentel, V. M., Arabkhazaeli, M., Moon, J. Y., Wang, A., Kapedani, A., Bernstein, P. S., Tropper, P. J., Induction of labor using one dose vs multiple doses of misoprostol: a randomized controlled trial, American journal of obstetrics and gynecology, 218, 614.e1-614.e8, 2018	Same intervention in both arms, just single versus multiple doses; not relevant to protocol
Pineda, M. E. S., Effectiveness of intravaginal evening primrose oil as a cervical ripening agent in nulliparous women: A double blinded randomized controlled clinical trial, Journal of Obstetrics and Gynaecology Research, 43, 39, 2017	No relevant outcomes were reported
Poulsen HK, Müller LK, Westergaard JG, Thomsen SG, Giersson RT, Arngrìmsson R, Open randomized comparison of prostaglandin E2 given by intracervical gel or vagitory for preinduction cervical ripening and induction of labor, Acta Obstet Gynecol Scand, 70, 549â□“53, 1991	Included in HTA (already included)
Prameela,, Sharma, Kavya D., Comparison Between Use of Oral Misoprostol Versus Vaginal Misoprostol for Induction of Labour at Term, Journal of obstetrics and gynaecology of India, 68, 88-92, 2018	>1/3 population had ruptured membranes
Pulle C, Granese D, Panama S, Celona A, Cervical ripening and induction of labour by single intracervical PGE2-gel application, Acta Ther, 5â□“12, 1986	Included in HTA (already included)
Ren, H, Fan, J-H, Zhang, L, Yang, Z-J, Clinical study of double-balloon catheter in full-term pregnancy to promote cevical maturity, Journal of shanghai jiaotong university (medical science), 37, 80-84, 2017	Study in Chinese
Richardson CJ, Evans JF, Meisel RL, Duration of intracervical prostaglandin and Cesarean section, Am J Obstet Gynecol, 164, 403, 1991	Included in HTA (already included)
Rivera, L., Garcia, M., Comparison of intravenous oxytocin infusion versus intracervical dinoprostone followed after 6 hours by intravenous oxytocin infusion for labor induction in prelabor rupture of membranes a randomized controlled trial, Journal of perinatal medicine, 47, eA202â□□eA203, 2019	Complex intervention (dinoprostone/oxytocin)

Study	Reason for Exclusion
Roberts WE, North DH, Speed JE, Martin JN, Palmer SM, Morrison JC, Comparative study of prostaglandin, laminaria, and minidose oxytocin for ripening of the unfavorable cervix prior to induction of labor, J Perinatol, 6, 16â□“19, 1986	Included in HTA (already included)
Roztocil A, Pilka L, JelÌnek J, Koudelka M, Miklica J, A comparison of three preinduction cervical priming methods: prostaglandin E2 gel, Dilapan S rods and Estradiol gel, Ceska Gynekol, 63, 3â□“9, 1998	Not English
Rugarn, O., Tipping, D., Powers, B., Wing, D. A., Induction of labour with retrievable prostaglandin vaginal inserts: outcomes following retrieval due to an intrapartum adverse event, BJOG: An International Journal of Obstetrics and Gynaecology, 124, 796-803, 2017	No relevant data
Sabzposh, N., Baghel, K., Pathak, S., Manazir Ali, S., Evaluation of sublingual misoprostol for induction of labor at term, International Journal of Gynecology and Obstetrics, 131, E496, 2015	No relevant outcomes were reported
Saccone, G., Della Corte, L., Maruotti, G. M., Quist-Nelson, J., Raffone, A., De Vivo, V., Esposito, G., Zullo, F., Berghella, V., Induction of labor at full-term in pregnant women with uncomplicated singleton pregnancy: A systematic review and meta-analysis of randomized trials, Acta Obstetricia et Gynecologica Scandinavica, 98, 958-966, 2019	Systematic review, references checked for inclusion
Saccone, Gabriele, Berghella, Vincenzo, Induction of labor at full term in uncomplicated singleton gestations: a systematic review and metaanalysis of randomized controlled trials, American Journal of Obstetrics and Gynecology, 213, 629-36, 2015	Systematic review, references checked for inclusion
Saggaf A, Rouzi AA, Radhan B, Alshehry S, Yamani T, Abduljabbar H, Misoprostol for preinduction cervical ripening and induction of labour: a randomized controlled trial, Saudi J Obstet Gynecol, 1, 89â□“93, 2001	Included in HTA (already included)
Saleem S, Efficacy of dinoprostone, intracervical foleys and misoprostol in labor induction, J Coll Physicians Surg Pak, 16, 276â□“9, 2006	Included in HTA (already included)
Salim, Raed, Schwartz, Naama, Zafran, Noah, Zuarez-Easton, Sivan, Garmi, Gali, Romano, Shabtai, Comparison of single- and double-balloon catheters for labor induction: a systematic review and meta-analysis of randomized controlled trials, Journal of perinatology : official journal of the California Perinatal Association, 38, 217-225, 2018	Systematic review, references checked for inclusion
Sanchez-Ramos L, Kaunitz AM, Connor PM, Hygroscopic cervical dilators and prostaglandin E2 gel for preinduction cervical ripening A randomized, prospective comparison, J Reprod Med, 37, 355â□“9, 1992	Included in HTA (already included)
Sanu, Olaleye, Outpatient cervical ripening by nitric oxide donors for prolonged pregnancy: a randomized controlled trial, Obstetrics and Gynecology, 125, 741-2, 2015	No relevant data, editorial comment only
Sargunam, P. N., Bak, L. L. M., Tan, P. C., Vallikkannu, N., Noor Azmi, M. A., Zaidi, S. N., Win, S. T., Omar, S. Z., Induction of labor compared to expectant management in term nulliparas with a latent phase of labor of more than 8 hours: a randomized trial, BMC Pregnancy and Childbirth, 19, 493, 2019	Women in the experimental group were offered induction of labour with different interventions, depending on clinical presentation

Study	Reason for Exclusion
Sayed Ahmed, W. A., Ahmed, M. R., Madny, E. H., Mohamed, R. M., Elshahat, A. M., A comparison between two different doses of vaginal isosorbide mononitrate versus misoprostol in preinduction cervical ripening at term: A randomized controlled study, Journal of Maternal-Fetal and Neonatal Medicine, 27, 150, 2014	No relevant outcomes were reported
Schmitz,T., Closset,E., Fuchs,F., Maillard,F., Rozenberg,P., Anselem,O., Winer,N., Perrotin,F., Verspyck,E., Azria,E., Carbonne,B., Lepercq,J., Goffinet,F., Outpatient cervical ripening with nitric oxide (NO) donors for prolonged pregnancy in nullipara: the NOCETER randomized, multicentre, double-blind, placebo-controlled trial, American Journal of Obstetrics and Gynecology, 210, S19-, 2014	Abstract of Schmitz 2014
Selin, L., Wennerholm, U. B., Jonsson, M., Dencker, A., Wallin, G., Wiberg-Itzel, E., Almstrom, E., Petzold, M., Berg, M., High-dose versus low-dose of oxytocin for labour augmentation: a randomised controlled trial, Women and Birth, 32, 356-363, 2019	Study compared 2 variants of the same intervention from this review's protocol
Smith, Caroline A., Armour, Mike, Dahlen, Hannah G., Acupuncture or acupressure for induction of labour, The Cochrane database of systematic reviews, 10, CD002962, 2017	Systematic review, references checked for inclusion
Smith,Caroline A., Crowther,Caroline A., Grant,Suzanne J., Acupuncture for induction of labour, Cochrane Database of Systematic Reviews, -, 2013	Systematic review, references checked for inclusion
Sotiriadis, A., Petousis, S., Thilaganathan, B., Figueras, F., Martins, W. P., Odibo, A. O., Dinas, K., Hyett, J., Maternal and perinatal outcomes after elective induction of labor at 39 weeks in uncomplicated singleton pregnancy: a meta-analysis, Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology, 53, 26-35, 2019	Systematic review, references checked for inclusion
Souza, Alex S. R., Feitosa, Francisco E. L., Costa, Aurelio A. R., Pereira, Ana P. R., Carvalho, Andreza S., Paixao, Renata M., Katz, Leila, Amorim, Melania M. R., Titrated oral misoprostol solution versus vaginal misoprostol for labor induction, International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics, 123, 207-12, 2013	Included in HTA (already included)
Srisomboon J, Singchai S, A comparison between 25 micrograms and 50 micrograms of intravaginal misoprostol for labor induction, J Med Assoc Thai, 81, 779â□“83, 1998	Included in HTA (already included)
Srisomboon J, Tongsong T, Tosiri V, Preinduction cervical ripening with intravaginal prostaglandin E1 methyl analogue misoprostol: a randomized controlled trial, J Obstet Gynaecol Res, 22, 119â□“24, 1996	Included in HTA (already included)
Stewart P, Kennedy JH, Hillan E, Calder AA, The unripe cervix: management with vaginal or extra-amniotic prostaglandin E2, J Obstet Gynaecol, 4, 90â□“3, 1983	Included in HTA (already included)
Strandberg, M., Wallstrom, T., Itzel, E., Women's experiences of labor induction, International journal of gynecology and obstetrics. Conference: 22nd FIGO world congress of gynecology and obstetrics. Brazil, 143, 302, 2018	No relevant data was reported
Sutton, A. L., Mele, L., Landon, M. B., Ramin, S. M., Varner, M. W., Thorp Jr, J. M., Sciscione, A., Catalano, P., Harper, M., Saade, G.,	No relevant outcomes were reported

Study	Reason for Exclusion
Caritis, S. N., Sorokin, Y., Grobman, W. A., Delivery timing and cesarean delivery risk in women with mild gestational diabetes mellitus, American Journal of Obstetrics and Gynecology, 211, 244, 2014	
Suvobrata S, Shyamal D, A Comparative Study of Sublingual Misoprostol and Oxytocin Infusion in Induction of Labor in Nulliparous Women at Term, abstract no 83	Included in HTA (already included)
Tabatabie, R. S., Dehghani Firouzabadi, R., Farajkhoda, T., Comparative analysis of effects of vaginal isosorbide mononitrate pill and low-dose syntocinon for cervical ripening in childbirth, Iranian Journal of Reproductive Medicine, 11, 56-57, 2013	No relevant outcomes were reported
Tajik, P, Wyk, L, Boers, Ke, Cessie, S, Zafarmand, Mh, Roumen, F, Post, Ja, Porath, M, Pampus, Mg, Spaanderdam, Me, Kwee, A, Duvekot, Jj, Bremer, Ha, Delemarre, Fm, Bloemenkamp, Kw, Groot, Cj, Willekes, C, Lith, Jm, Bossuyt, Pm, Mol, Bw, Scherjon, Sa, Which intrauterine growth restricted fetuses at term benefit from early labour induction? A secondary analysis of the DIGITAT randomised trial, European journal of obstetrics, gynecology, and reproductive biology, 172, 20-25, 2014	Women in the experimental group were offered induction of labour with different interventions, depending on clinical presentation
Tan, T. L., Ng, G. Y. H., Lim, S. E. L., Tagore, S., Kyaw, E. E. P., Yeo, G. S. H., Cervical ripening balloon as an alternative for induction of labour: A randomized controlled trial, British Journal of Medical Practitioners, 8, 6-11, 2015	Same trial as Lim 2018
Tannirandorn Y, Jumrustanasan T, A comparative study of membrane stripping and nonstripping for induction of labor in uncomplicated term pregnancy, J Med Assoc Thai, 82, 229â□“33, 1999	Included in HTA (already included)
Teimouri, B, Ghasemi, M, Sakhavar, N, Noori, Sk, Comparison of vaginal trinitroglycerin (TNG) and vaginal misoprostol in cervical ripening at term pregnancy, Iranian Journal of Obstetrics, Gynecology and Infertility, 20, 8-14, 2018	Study in Arabic
Ten Eikelder, M. L. G., Rengerink, K. O., Jozwiak, M., De Leeuw, J. W., De Graaf, I. M., Van Pampus, M. G., Holswilder, M., Oudijk, M. A., Van Baaren, G. J., Pernet, P. J. M., Bax, C., Van Unnik, G. A., Martens, G., Porath, M., Van Vliet, H., Rijnders, R. J. P., Feitsma, A. H., Roumen, F. J. M. E., Van Loon, A. J., Versendaal, H., Weinans, M. J. N., Woiski, M., Van Beek, E., Hermsen, B., Mol, B. W., Bloemenkamp, K. W. M., Induction of labour at term with oral misoprostol versus a foley catheter (PROBAAT-II): A multicentre randomised controlled non-inferiority trial, Obstetrical and Gynecological Survey, 71, 447-449, 2016	Abstract/editorial comment - TenEikelder 2017
Ten Eikelder, M. L. G., Rengerink, K. O., Jozwiak, M., De Leeuw, J. W., De Graaf, I., Van Pampus, M. G., Franssen, M., Oudijk, M., Pernet, P. J. M., Bax, C., Van Unnik, G. A., Martens, G., Porath, M., Van Vliet, H., Rijnders, R. J. P., Feitsma, A. H., Roumen, F., Van Loon, A. J., Versendaal, H., Weinans, M. J. N., Woiski, M., Van Beek, E., Hermsen, B., Mol, B. W., Bloemenkamp, K. W. M., Induction of labor at term with oral misoprostol or Foley catheter, the PROBAAT-II trial (NTR3466), American Journal of Obstetrics and Gynecology, 212, S14-S15, 2015	Abstract of Ten Eikelder 2016

Study	Reason for Exclusion
Ten Eikelder, Mieke L. G., Mast, Kelly, van der Velden, Annemarie, Bloemenkamp, Kitty W. M., Mol, Ben W., Induction of Labor Using a Foley Catheter or Misoprostol: A Systematic Review and Meta-analysis, Obstetrical & gynecological survey, 71, 620-630, 2016	Systematic review, references checked for inclusion
Thavarasah AS, Arulkumaran S, Almohdzar SA, A prospective randomized study comparing the effect of intracervical to intravaginal administration of prostaglandin E2, in patients with poor cervical scores at term, Int J Feto-Maternal Med, 3, 177â□“81, 1990	Included in HTA (already included)
Thomas,Jane, Fairclough,Anna, Kavanagh,Josephine, Kelly,Anthony J., Vaginal prostaglandin (PGE2 and PGF2a) for induction of labour at term, Cochrane Database of Systematic Reviews, -, 2014	Systematic review, references checked for inclusion
Titulaer, L. M. L., de Wolf, G. S., Bakkum, E. A., Moll, E., Delayed versus immediate oxytocin infusion after amniotomy for induction of labour: a randomised controlled pilot trial, European journal of obstetrics, gynecology, and reproductive biology, 240, 357â□□363, 2019	Study compared 2 variants of the same intervention from this review's protocol
Torkzahrani, S., Ghobadi, K., Heshmat, R., Shakeri, N., Aria, K. J., Effect of acupressure on cervical ripening, Iranian Red Crescent Medical Journal, 17, e28691, 2015	No relevant outcomes were reported
Trofatter KF, Effect of preinduction cervical softening with dinoprostone gel on outcome of oxytocin-induced labor, Clin Ther, 15, 838â□“44, 1993	Included in HTA (already included)
Trofatter KF, Bowers D, Gall SA, Killam AP, Preinduction cervical ripening with prostaglandin E2 (Prepidil) gel, Am J Obstet Gynecol, 153, 268â□“71, 1985	Included in HTA (already included)
Turnbull, Deborah, Adelson, Pamela, Oster, Candice, Bryce, Robert, Fereday, Jennifer, Wilkinson, Chris, Psychosocial outcomes of a randomized controlled trial of outpatient cervical priming for induction of labor, Birth (Berkeley, Calif.), 40, 75-80, 2013	All women received the same intervention (prostaglandins E2 vaginal gel)
Ugwu, Eo, Obi, Sn, Iferikigwe, Es, Dim, Cc, Ezugwu, Fo, Membrane stripping to prevent post-term pregnancy in Enugu, Nigeria: a randomized controlled trial, Archives of Gynecology and Obstetrics, 289, 29-34, 2014	Included in HTA (already included)
Urban, G., Signorini, S., Romolo, D. I., Tortoli, P., Comparison of prostaglandin E2 (PGE2) and prostaglandin E1 (PGE1) and characterization of uterine response based on vasoactive peptide and flow volume in low risk pregancy at term, Reproductive sciences (Thousand Oaks, Calif.), 26, 219Aâ□□, 2019	No relevant comparison (Prostaglandin E1 [PGE1])
Vakhariya VR, Sherman AI, Prostaglandin F2? for induction of labor, Am J Obstet Gynecol, 113, 212â□“22, 1972	Included in HTA (already included)
Vogel, Joshua P., Osoti, Alfred O., Kelly, Anthony J., Livio, Stefania, Norman, Jane E., Alfirevic, Zarko, Pharmacological and mechanical interventions for labour induction in outpatient settings, The Cochrane database of systematic reviews, 9, CD007701, 2017	Systematic review, references checked for inclusion
Vorontsova, Y., Haas, D., Flannery, K., David, G., Heathman, M., Quinney, S., Masters, A., Pharmacokinetics of buccal versus vaginal misoprostol for labor induction at term, Clinical Pharmacology and Therapeutics, 107, S28, 2020	No relevant outcomes were reported

Study	Reason for Exclusion
Walker, K. F., Bugg, G. J., Macpherson, M., McCormick, C., Grace, N., Wildsmith, C., Bradshaw, L., Smith, G. C. S., Thornton, J. G., Randomized trial of labor induction in women 35 years of age or older, New England Journal of Medicine, 374, 813-822, 2016	Women in the experimental group were offered induction of labour with different interventions, depending on clinical presentation
Walker, K., Bugg, G., Macpherson, M., McCormick, C., Wildsmith, C., Smith, G., Thornton, J., The 35/39 trial: A multi-centre prospective randomised controlled trial of induction of labour versus expectant management for nulliparous women over 35 years of age, International Journal of Gynecology and Obstetrics, 131, E221, 2015	Study protocol
Walker, Kate F., Malin, Gemma, Wilson, Philippa, Thornton, Jim G., Induction of labour versus expectant management at term by subgroups of maternal age: an individual patient data meta-analysis, European journal of obstetrics, gynecology, and reproductive biology, 197, 1-5, 2016	Systematic review, references checked for inclusion
Wang, Hongye, Hong, Shukun, Liu, Yuanyuan, Duan, Yan, Yin, Hongmei, Controlled-release dinoprostone insert versus Foley catheter for labor induction: a meta-analysis, The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians, 29, 2382-8, 2016	Systematic review, references checked for inclusion
Wang, Lina, Zheng, Jianlan, Wang, Wenyan, Fu, Jingli, Hou, Li, Efficacy and safety of misoprostol compared with the dinoprostone for labor induction at term: a meta-analysis, The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians, 29, 1297-307, 2016	Systematic review, references checked for inclusion
Wasalthilaka, C. D., Gunawardana, G. H. K. K., Comparison of peripartum maternal and fetal outcomes in cervical ripening using foley catheter and prostaglandin E2 gel, Journal of Obstetrics and Gynaecology Research, 41, 4-5, 2015	No relevant outcomes were reported
Weinberg, D., Blue, N., Holbrook, B., Rayburn, W., Outpatient preinduction cervical ripening using a balloon catheter: A meta-analysis, Journal of Reproductive Medicine, 62, 486-492, 2017	Systematic review, references checked for inclusion
Wennerholm, U. B., Saltvedt, S., Wessberg, A., Alkmark, M., Bergh, C., Wendel, S. B., Fadl, H., Jonsson, M., Ladfors, L., Sengpiel, V., Wesstrom, J., Wennergren, G., Wikstrom, A. K., Elden, H., Stephansson, O., Hagberg, H., Induction of labour at 41 weeks versus expectant management and induction of labour at 42 weeks (SWEdish Post-term Induction Study, SWEPIS): Multicentre, open label, randomised, superiority trial, The BMJ, 367, l6131, 2019	Women in the experimental group were offered induction of labour with different interventions, depending on clinical presentation
Wise, Michelle R., Marriott, Joy, Battin, Malcolm, Thompson, John M. D., Stitely, Michael, Sadler, Lynn, Outpatient balloon catheter vs inpatient prostaglandin for induction of labour (OBLIGE): a randomised controlled trial, Trials, 21, 190, 2020	Study protocol
Wood,S., Cooper,S., Ross,S., Does induction of labour increase the risk of caesarean section? A systematic review and meta-analysis of trials in women with intact membranes, BJOG: An International Journal of Obstetrics and Gynaecology, 121, 674-685, 2014	Systematic review, references checked for inclusion

Study	Reason for Exclusion
Xing, Y., Li, N., Ji, Q., Hong, L., Wang, X., Xing, B., Double-balloon catheter compared with single-balloon catheter for induction of labor with a scarred uterus, European Journal of Obstetrics and Gynecology and Reproductive Biology, 243, 139â□□143, 2019	All women had a previous caesarean birth
Yang, Fang, Huang, Shijin, Long, Yu, Huang, Lingling, Double-balloon versus single-balloon catheter for cervical ripening and labor induction: A systematic review and meta-analysis, The journal of obstetrics and gynaecology research, 44, 27-34, 2018	Systematic review, references checked for inclusion
Yasmeen, A., Malik, A. M., Outcome of sweeping membrane within 48 hours in the induction of labour in multigravidae, Pakistan Journal of Medical and Health Sciences, 8, 876-881, 2014	No relevant outcomes
Yenuberi, H., Abraham, A., Sebastian, A., Benjamin, S., Londhe, V., Mathews, J., Randomised double-blind placebo controlled trial comparing oral with vaginal misoprostol for induction of labour, BJOG: An International Journal of Obstetrics and Gynaecology, 2), 94-95, 2014	Abstract of Yenuberi 2016
Yetkin, Yildirim G, Koroglu, N, Tayyar, A, Demirezen, G, Tola, En, Preliminary results of a controlled randomized study on double-balloon catheter vs. dinoprostone vaginal insert for induction of labor with an unfavorable cervix, Turkiye klinikleri journal of medical sciences, 38, 40-45, 2018	Unavailable
Zahoor, S., Prostaglandin E2, intravaginal misoprostol and intracervical balloon catheter for induction of labour at term, a randomised controlled trial, BJOG: An International Journal of Obstetrics and Gynaecology, 121, 147, 2014	No relevant outcomes were reported
Zamawe, C., King, C., Jennings, H. M., Mandiwa, C., Fottrell, E., Effectiveness and safety of herbal medicines for induction of labour: A systematic review and meta-analysis, BMJ Open, 8, e022499, 2018	Systematic review, references checked for inclusion
Zamawe, Collins, King, Carina, Jennings, Hannah Maria, Mandiwa, Chrispin, Fottrell, Edward, Effectiveness and safety of herbal medicines for induction of labour: a systematic review and meta-analysis, BMJ Open, 8, e022499, 2018	Systematic review, references checked for inclusion
Zandvakili, F., Shahgheibi, S., Farhadifar, F., Seyedoshohadaei, F., Khalili, A., Effect of early amniotomy on labor outcome in nulliparous women: a randomized clinical trial, Current Issues in Pharmacy and Medical Sciences, 32, 189-192, 2019	No relevant outcomes were reported
Zeng, Xianling, Zhang, Yafei, Tian, Quan, Xue, Yan, Sun, Rong, Zheng, Wei, An, Ruifang, Efficiency of dinoprostone insert for cervical ripening and induction of labor in women of full-term pregnancy compared with dinoprostone gel: A meta-analysis, Drug discoveries & therapeutics, 9, 165-72, 2015	Systematic review, references checked for inclusion
Zhu, L., Zhang, C., Cao, F., Liu, Q., Gu, X., Xu, J., Li, J., Intracervical Foley catheter balloon versus dinoprostone insert for induction cervical ripening: A systematic review and meta-analysis of randomized controlled trials, Medicine, 97, e13251, 2018	Systematic review, references checked for inclusion

Table 48: Excluded studies and reasons for their exclusion. From the original HTA

Study	Reason for Exclusion
Akyol D, Mungan T, Unsal A, Yuksel K. Prelabour rupture of the membranes at term: no advantage of delaying induction for 24 hours. Aus N Z J Obstet Gynaecol 1999;39:291–5.	All participants had ruptured membranes
Al-Hussaini TK, Abdel-Aal SA, Youssef MA. Oral misoprostol vs intravenous oxytocin for labor induction in women with prelabor rupture of membranes at term. Int J Gynecol Obstet 2003;82:73–5.	All participants had ruptured membranes
Alcalay M, Hourvitz A, Reichman B, Luski A, Quint J, Barkai G, et al. Prelabour rupture of membranes at term: early induction of labour versus expectant management. Eur J Obstet Gynecol Reprod Biol 1996;70:129–33.	All participants had ruptured membranes
Allouche C, Dommesent D, Barjot P, Levy G. Cervical ripening: comparison of three methods. Preliminary results of a randomized prospective study. Rev Fr Gynecol Obstet 1993;88:492–7.	Non-English language
Amador LAV, Carmona JCF, Gallego FG, Texido CS, Esteve JLC. Randomized clinical trial of the safety and efficacy of 50 microg sublingual misoprostol versus 25 microg vaginal misoprostol for labor induction at term in pregnant women with diabetes. Prog Obstet Ginecol 2007;50:473–83.	Non-English language
Andersen K, Moller M, Rix P, Larsen KW, Ladehoff P, Zdravkovic M. Induction of labor. Prostaglandin E2 vaginal tablets compared with intravenous oxytocin for induction of labor in premature rupture of the membranes and immature cervix. Ugeskr Laeger 1990;152:3705–7.	All participants had ruptured membranes
Arias F, Rouben D. Extraamniotic saline infusion with foley catheter is better than 2.9 mg prostaglandin E2 gel in ripening the cervix but does not result in vaginal delivery. Am J Obstet Gynecol 1993;168:429.	Intervention not relevant. Secondary publication
Ayad IA. Vaginal misoprostol in managing premature rupture of membranes. East Mediterr Health J 2002;8:515–20.	All participants had ruptured membranes
Ayaz A, Saeed S, Farooq MU, Ahmad F, Bahoo LA, Ahmad I. Pre-labor rupture of membranes at term in patients with an unfavorable cervix: active versus conservative management. Taiwan J Obstet Gynecol 2008;47:192–6.	All participants had ruptured membranes
Barrilleaux P, Bofill J, Rodts-Palenik S, Moore L, May W, Martin J Jr. A randomized clinical trial comparing three methods of cervical ripening to efficiently effect delivery. Am J Obstet Gynecol 2002;187:S174.	Complex intervention (full text not actually included in HTA)
Beer AM, Heiliger F. Randomized, double-blind trial of caulophyllum d4 for induction of labor after premature rupture of the membranes at term. Geburtsh Frauenheilk 1999;59:431–5.	All participants had ruptured membranes
Benedetto C, Pastore G, Zonca M, Ardizzoja M, Mascherpa F, Bocci A. Induction of labour with PGE2 intravaginal gel or oxytocin: a technical comparison. Giornale Italiano di Obstetricia e Ginecologia 1987;5:447–52.	Non-English language

Study	Reason for Exclusion
Benzineb N, Bouhaouala S, Sfar R. Prostaglandin E2 versus Foley catheter for cervical maturation at term. Rev Fr Gynecol Obstet 1996;91:173–6.	Non-English language
Bergsjo P, Jenssen H. Comparison between intranasal and transbuccal oxytocin for the induction of labour. Preliminary report. Acta Obstet Gynecol Scand 1969;48(Suppl. 3):134.	Complex intervention (full text not actually included in HTA)
Bezircioglu I, Akin MK, Baloglu A, Bicer M. The efficacy of dinoprostone vaginal insert for active management of premature rupture of membranes at term: a randomized controlled trial. Clin Exp Obstet Gynecol 2012;39:356–8.	All participants had ruptured membranes
Bilgin T, Kadioglu M, Yildirim V, Cengiz C. A randomised trial of intracervical prostaglandin gel and intravenous oxytocin in prelabor rupture of membranes with unripe cervix at term. Prenatal Neonatal Med 1996;1(Suppl. 1):89.	All participants had ruptured membranes
Bilgin T, Kadiog˘ lu M, Yildirim V, Cengiz C. A randomized trial of intracervical prostaglandin gel and intravenous oxytocin in prelabor rupture of membranes with unripe cervix at term. Clin Exp Obstet Gynecol 1998;25:46–8.	All participants had ruptured membranes
Bolnick J, Velazquez M, Gonzalez J, Leslie K, Rappaport V, McIlwane G, et al. Randomized trial of sustained-release vaginal dinoprostone (PGE2) with concurrent oxytocin versus vaginal misoprostol (PGE1) for induction of labor at term. Am J Obstet Gynecol 2002;187:S175.	Complex intervention (full text not actually included in HTA)
Brandel E, Bascou V, Meeus JB, Magnin G. Results of a randomized trial of cervical maturation in premature rupture of membranes at term: prostine E, intravenous versus prostine E2 vaginal gel. J Gynecol Obstet Biol Reprod 1998;27:111.	All participants had ruptured membranes
Brennan MC, Pevzner L, Wing DA, Powers BL, Rayburn WF. Retention of dinoprostone vaginal insert beyond 12 hours for induction of labor. Am J Perinatol 2011;28:479–84.	Complex intervention (full text not actually included in HTA)
Bricker L, Peden H, Tomlinson AJ, Al-Hussaini TK, Idama T, Candelier C, et al. Titrated low-dose vaginal and/or oral misoprostol to induce labour for prelabour membrane rupture: a randomised trial. BJOG 2008;115:1503–11.	All participants had ruptured membranes
Bung P, Baer S, Djahanschahi D, Huch R, Huch A, Huber JF, et al. [Multicenter experiences with the intracervical administration of a new PGE2 gel in labor induction.] Geburtshilfe Frauenheilk 1986;46:93–7.	Non-English language
Butt KD, Bennett KA, Crane JM, Hutchens D, Young DC. Randomized comparison of oral misoprostol and oxytocin for labor induction in term prelabor membrane rupture. Obstet Gynecol 1999;94:994–9.	All participants had ruptured membranes
Cabrol D, Bernard N, Chouraqui A, Domenichini Y, Lemaire P, Lopes P, et al. [Ripening of the cervix uteri at term by a single intracervical application of prostaglandin E2 gel.] J Gynecol Obstet Biol Reprod 1988;17:527–34.	Non-English language
Campos GA, Guzmn S, Rodrìguez JG, Voto LS, Margulies M. [Misoprostol: a PGE1 analog for induction of labor at term: comparative and randomized study with oxytocin.] Rev Chil Obstet Ginecol 1994;59:190–5.	Non-English language

Study	Reason for Exclusion
Cararach V, Sentis J, Botet F, Costa J, Manau D, Arimany MC. Cervical Prostaglandin E2 Compared with Expectant Management or Systematic Induction in PROM with Bad Cervical condItions: I-Maternal Results. Proceedings of 14th European Congress of Perinatal Medicine, 5–8 June 1994, Helsinki, Finland, abstract no. 405.	All participants had ruptured membranes
Cararach V, Sentis J, Botet F, Foradada C, Manau D, Figueras F, et al. Cervical Prostaglandin E1 Compared with Expectant Management and with Systematic Induction in PROM Near Term, with Bad Cervical Conditions. I-Maternal Results. 3rd World Congress of Perinatal Medicine, 20–24 October 1996, San Francisco, CA, USA, abstract no. 44.	All participants had ruptured membranes
Chang P, Langer O. Premature rupture of membranes at term; a randomized controlled trial. Am J Obstet Gynecol 1997;176:S148.	All participants had ruptured membranes
Chaudhuri S, Mitra SN, Banerjee PK, Biswas PK, Bhattacharyya S. Comparison of vaginal misoprostol tablets and prostaglandin E2 gel for the induction of labor in premature rupture of membranes at term: a randomized comparative trial. J Obstet Gynaecol Res 2011;37:1564–71.	All participants had ruptured membranes
Chen TM. Clinical analysis of misoprostol on induction of labor in term pregnancy. J Zhenjiang Med Coll 2000;4:652–3.	Non-English language
Cheung PC, Yeo EL, Wong KS, Tang LC. Oral misoprostol for induction of labor in prelabor rupture of membranes (PROM) at term: a randomized control trial. Acta Obstet Gynecol Scand 2006;85:1128–33.	All participants had ruptured membranes
Christensen F, Tehranifar M, Gonzalez J, Rappaport V, Gilson G, Rayburn W. Randomized trial of concurrent oxytocin and sustained-release dinoprostone for labor induction. Am J Obstet Gynecol 2001;184:S118.	Full text excluded from HTA as complex intervention
Chua S, Arulkumaran S, Kurup A, Anandakumar C, Tay D, Ratnam SS. Does prostaglandin confer significant advantage over oxytocin infusion for nulliparas with pre-labor rupture of membranes at term? Obstet Gynecol 1991;77:664–7.	All participants had ruptured membranes
Chua S, Arulkumaran S, Yap C, Selamat N, Ratnam SS. Premature rupture of membranes in nulliparas at term with unfavorable cervices: a double-blind randomized trial of prostaglandin and placebo. Obstet Gynecol 1995;86:550–4.	All participants had ruptured membranes
Chung T, Rogers MS, Gordon H, Chang A. Prelabour rupture of the membranes at term and unfavourable cervix; a randomized placebo-controlled trial on early intervention with intravaginal prostaglandin E2 gel. Aust N Z J Obstet Gynaecol 1992;32:25–7.	All participants had ruptured membranes
Cohen SB, Schiff E, Kees S, Lusky A, Mashiach S. Induction of labor using a foley catheter and extra-amniotic corticosteroids. Am J Obstet Gynecol 1997;176:S191.	Full text excluded from HTA report as complex intervention
Collingham J, Fuh K, Caughey A, Pullen K, Lyell D, Druzin M, et al. Randomized clinical trial of cervical ripening and labor induction using oral misoprostol with or without intravaginal isosorbide mononitrate. Am J Obstet Gynecol 2008;199(Suppl. 1):57.	Full text excluded from HTA report as complex intervention

Study	Reason for Exclusion
Crane J, Delaney T, Hutchens D. Oral misoprostol labor induction in term prelabor membrane rupture. Am J Obstet Gynecol 2002;187:S168.	All participants had ruptured membranes
Crane JM, Delaney T, Hutchens D. Oral misoprostol for premature rupture of membranes at term. Am J Obstet Gynecol 2003;189:720–4.	All participants had ruptured membranes
Culver J, Strauss R, Brody S, Dorman K, Timlin S, McMahon M. A randomized trial of intracervical foley catheter with concurrent oxytocin compared to vaginal misoprostol for labor induction in nulliparous women. Am J Obstet Gynecol 2001;185(Suppl. 6):203.	Complex intervention
Da Graça Krupa F, Cecatti JG, de Castro Surita FG, Milanez HM, Parpinelli MA. Misoprostol versus expectant management in premature rupture of membranes at term. BJOG 2005;112:1284–90.	All participants had ruptured membranes
Davies NJ, Martindale E, Haddad NG. Cervical Ripening with Oral PGE2 Tablets and the Effect of the Latent Period in Patients with Premature Rupture of the Membranes at Term. Proceedings of 2nd European Congress on Prostaglandins in Reproduction, 30 April to 3 May 1991, The Hague, The Netherlands, 1991, abstract no. 156.	All participants had ruptured membranes
Day A, MacLennan A, Green R. A comparison of intravaginal PGF2 alpha and intravenous oxytocin to stimulate labour after membrane rupture. Aust N Z J Obstet Gynaecol 1985;25:252–5.	All participants had ruptured membranes
Day AR, MacLennan A, Green R. A Comparison of Intravaginal PGF2 alpha and Intravenous Oxytocin to Stimulate Labour after Membrane Rupture. Proceedings of the 24th British Congress of Obstetrics and Gynaecology, 15–18 April 1986, Cardiff, UK, abstract no. 251.	All participants had ruptured membranes
De A, Bagga R, Gopalan S. The routine use of oxytocin after oral misoprostol for labour induction in women with an unfavourable cervix is not of benefit. Aust N Z J Obstet Gynaecol 2006;46:323–9.	≥1/3 of participants had ruptured membranes
De Koning Gans GHJ, Keirse M. A Comparison Between Intra-Cervical and Intra-Vaginal Application of Prepidil Gel for the Induction of Labour. Personal communication. 1988.	Personal communication only, full text included
De Moraes Filho OB, de Albuquerque RM, Pacheco AJC, Ribeiro RH, Cecatti JG, Welkovic S. Sublingual versus vaginal misoprostol for labor induction of term pregnancies. Rev Bras Ginecol Obstet 2005;27:24–31.	Non-English language
Delaney S, Shaffer B, Cheng Y, Vargas J, Sparks T, Paul K, et al. Labor induction with a foley balloon trial (LIFT) – a randomized controlled trial of 30 ml versus 60 ml foley balloon inflation. Am J Obstet Gynecol 2009;201(Suppl. 1):23–4.	Full text is excluded from HTA
Deng LL, Huang ZJ. Observation on the efficacy of intravaginal misoprostol for cervical ripening in the third trimester of pregnancy. J Nurs Sci 1999;14:67–8.	Non-English language
Di Cecco R, Hannah M, Hodnett E, Foster G, Farine D, Helewa M. Prelabor rupture of the membranes (PROM) at term:	All participants had ruptured membranes

Study	Reason for Exclusion
expectant management at home vs in hospital. Am J Obstet Gynecol 1998;178:S30.	
Dodd JM, Crowther CA, Robinson JS. Oral Misoprostol versus Intravenous Oxytocin for Induction of Labour Following Artificial or Spontaneous Rupture of Membranes: a Randomised Controlled Trial. Perinatal Society of Australia and New Zealand 10th Annual Congress, 3–6 April 2006, Perth, WA, Australia, abstract no. 258.	All participants had ruptured membranes
Domínguez Salgado CR, Gorostieta García A, Vázquez Bretón S. [Induction of labor in patients with premature rupture of membranes in term pregnancy using dinoprostone vs oxytocin. An aleatory study.] Ginecol Obstet Mex 1999;67:461–6.	All participants had ruptured membranes
Duff P, Huff RW, Gibbs RS. Management of premature rupture of membranes and unfavorable cervix in term pregnancy. Obstet Gynecol 1984;63:697–702.	All participants had ruptured membranes
Egarter C, Husslein P. [Sensitivity test in labor induction with prostaglandin E2 vaginal tablets.] Zentralbl Gynakol 1988;110:345–53.	Non-English language
Egarter C, Schurz B, Wagner G, Grünnberger W, Husslein P. [Comparison between prostaglandin E2 gel and oxytocin in medically indicated labor induction.] Geburtshilfe Frauenheilk 1987;47:337–40.	Non-English language
Ekman-Ordeberg G, Uldbjerg N, Ulmsten U. Comparison of intravenous oxytocin and vaginal prostaglandin E2 gel in women with unripe cervixes and premature rupture of the membranes. Obstet Gynecol 1985;66:307–10.	All participants had ruptured membranes
Elliot CL, BrennandJe, Calder A. The Effect of Mifepristone (RU486) on Cervical Ripening and Induction of Labour in Human Pregnancy. 27th British Congress of Obstetrics and Gynaecology, 4–7 July 1995, Dublin, Ireland, abstract no. 207.	Full text is excluded from HTA (no data)
Esteve JLC, Garcia TJP, Iturralde AS, Ferrer YA, Teixido CS. Randomized, controlled clinical trial to evaluate the safety and efficacy of 25 microg of vaginal misoprostol versus 50 microg of sublingual misoprostol for labor induction. Prog Obstet Ginecol 2006;49:369–79.	Non-English language
Ezechi OC, Loto OM, Ezeobi PM, Okogbo FO, Gbajabiamila T, Nwokoro CA. Safety and efficacy of misoprostol in induction of labour in prelabour rupture of fetal membrane in Nigerian women: a multicenter study. Iran J Reprod Med 2008;6:83–7.	All participants had ruptured membranes
Foong LC, Vanaja K, Tan G, Chua S. Effect of Cervical Membrane Sweeping on Induction of Labour. Women's Health – Into the New Millennium. Proceedings of the 4th International Scientific Meeting of the Royal College of Obstetricians and Gynaecologists, 3–6 October 1999, Cape Town, South Africa, abstract no. 63.	Full text is excluded from HTA (not a relevant comparison)
Foradada C, Cararach V, Sentis J, Botet F, Manau D, Figueras F, et al. Cervical Prostaglandin E1 Compared with Expectant Management and with Systematic Induction in PROM Near Term, with Bad Cervical Conditions. II-Fetal and Neonatal Results. 3rd World Congress of Perinatal Medicine, San Francisco, CA, USA, 20–24 October, 1996, pp. 51–2.	All participants had ruptured membranes

Study	Reason for Exclusion
Frohn WE, Simmons S, Carlan SJ. Prostaglandin E2 gel versus misoprostol for cervical ripening in patients with premature rupture of membranes after 34 weeks. Obstet Gynecol 2002;99:206–10.	All participants had ruptured membranes
Frydman R, Taylor S, Paoli C, Pourade A. [RU 486 (mifepristone): a new tool for labor induction women at term with live fetus.] Contracept Fertil Sex 1992;20:1133–6.	Non-English language
Gafni A, Goeree R, Myhr TL, Hannah ME, Blackhouse G, Willan AR, et al. Induction of labour versus expectant management for prelabour rupture of the membranes at term: an economic evaluation. TERMPROM Study Group. Term Prelabour Rupture of the Membranes. CMAJ 1997;157:1519–25.	All participants had ruptured membranes
Gaudernack LC, Forbord S, Hole E. Acupuncture administered after spontaneous rupture of membranes at term significantly reduces the length of birth and use of oxytocin. A randomized controlled trial. Acta Obstet Gynecol Scand 2006;85:1348–53.	All participants had ruptured membranes
Gibson K, Mercer B, Louis J. A randomized control trial of inner thigh taping versus traction for cervical ripening with a Foley catheter. Am J Obstet Gynecol 2013;208(Suppl. 1):145–6.	Full text is excluded from HTA (not a relevant comparison)
Gittens L, Schenkel C, Strassberg S, Apuzzio J. Vaginal birth after cesarean section: comparison of outpatient use of prostaglandin gel to expectant management. Am J Obstet Gynecol 1996;174:354.	Participants had previous caesarean section
Goeschen K. Premature rupture of membranes near term: induction of labor with endocervical prostaglandin E2 gel or intravenous oxytocin. Am J Perinatol 1989;6:181–4.	All participants had ruptured membranes
Gonen R, Samberg I, Degani S. Intracervical prostaglandin E2 for induction of labor in patients with premature rupture of membranes and an unripe cervix. Am J Perinatol 1994;11:436–8.	All participants had ruptured membranes
Grant JM, Serle E, Mahmood T, Sarmandal P, Conway DI. Management of prelabour rupture of the membranes in term primigravidae: report of a randomized prospective trial. Br J Obstet Gynaecol 1992;99:557–62.	All participants had ruptured membranes
Grant JM. Comparison of Hydrostatic Sweeping of the Membranes (Extra-Amniotic Foley Catheter plus Extra-Amniotic Water Injection) and Vaginal Prostaglandin Gel in Women with an Unfavourable Cervix who Require Induction of Labour. Personal communication. 1993.	Comparison not relevant
Griffith-Jones MD, Tyrrell SN, Tuffnell DJ. A prospective trial comparing intravenous oxytocin with vaginal prostaglandin E2 tablets for labour induction in cases of spontaneous rupture of the membranes. Obstet Gynaecol Today 1990;1:104–5.	All participants had ruptured membranes
Guinn D, Davies J, Jones RO, Wolf D. Foley catheter with extraamniotic saline infusion (easi) versus foley catheter alone for induction of labor in gravidas with an unfavorable cervix. Am J Obstet Gynecol 2002;187:S169.	Complex intervention
Guinn DA, Goepfert AR, Owen J, Christine M, Hauth J. Laminaria, extraamniotic saline induction (EASI) or prepidil for	Complex intervention

Study	Reason for Exclusion
cervical ripening prior to labor induction. Am J Obstet Gynecol 1997;176:S143.	
Güngördük K, Asicioglu O, Besimoglu B, Güngördük OC, Yildirm G, Ark C, et al. Labor induction in term premature rupture of membranes: comparison between oxytocin and dinoprostone followed 6 hours later by oxytocin. Am J Obstet Gynecol 2012;206:60.e1–8.	All participants had ruptured membranes
Haghighi L. Intravaginal misoprostol in preterm premature rupture of membranes with low Bishop scores. Int J Gynaecol Obstet 2006;94:121–2.	All participants had ruptured membranes
Hamdan M, Sidhu K, Sabir N, Omar SZ, Tan PC. Serial membrane sweeping at term in planned vaginal birth after cesarean: a randomized controlled trial. Obstet Gynecol 2009;114:745–51.	Participants had previous caesarean section
Hannah M, Ohlsson A, Farine D, Hewson S, Hodnett E, Myhr T, et al. Vaginal Prostaglandin E2 Gel vs Intravenous Oxytocin vs Expectant Management for Prelabour Rupture of Membranes at Term. A Randomised Clinical Trial. Proceedings of the 15th Conference of Priorities in Perinatal Care, 1996, South Africa, abstract no. 14.	All participants had ruptured membranes
Hannah M, Ohlsson A, Wang E, Myhr T, Farine D, Hewson S, et al. Inducing labor with iv oxytocin may reduce the risk of neonatal infection in GBS positive women with PROM at term. Am J Obstet Gynecol 1997;176:S32.	All participants had ruptured membranes
Hannah ME, Ohlsson A, Farine D, Hewson SA, Hodnett ED, Myhr RL, et al. Induction of labor compared with expectant management for prelabor rupture of the membranes at term. N Engl J Med 1996;334:1005–10.	All participants had ruptured membranes
Hannah ME, Ohlsson A, Wang EE, Matlow A, Foster GA, Willan AR, et al. Maternal colonization with group B Streptococcus and prelabor rupture of membranes at term: the role of induction of labor. TermPROM Study Group. Am J Obstet Gynecol 1997;177:780–5.	All participants had ruptured membranes
Hauth JC, Cunningham FG, Whalley PJ. Early labor initiation with oral PGE2 after premature rupture of the membranes at term. Obstet Gynecol 1977;49:523–6.	All participants had ruptured membranes
Hayashi R, Keirse M. PGE2 Gel (Prepidil Gel) for Preinduction Cervical Softening. Personal communication. 1983.	Personal communication only, no full text available
Heinzl S, Ramzin MS, Schneider M, Luescher KP. [Priming of cervix with prostaglandin gel during immature birth situation at term.] Z Geburtshilfe Perinatol 1980;184:395–400.	Non-English language
Henrich W, Dudenhausen JW, Hanel C, Chen FC. [Oral misoprostol against vaginal dinoprostone for labor induction at term: a randomized comparison.] Z Geburtshilfe Neonatol 2008;212:183–8.	Non-English language
Henry A, Reid R, Madan A, Tracy S, Sharpe V, Welsh A, et al. Satisfaction survey: outpatient Foley catheter versus inpatient prostin gel for cervical ripening. Aust N Z J Obstet Gynaecol 2011;51:474.	Full text is excluded from HTA

Study	Reason for Exclusion
Herabutya Y, Suchatwatnachai C, O-Prasertsawat P. Comparison of intravenous oxytocin with and without vaginal prostaglandin E2 gel in term pregnancy with premature rupture of membranes and unfavourable cervix. J Med Assoc Thai 1991;74:92–6.	All participants had ruptured membranes
Hidar S, Bibi M, Jerbi M, Bouguizene S, Nouira M, Mellouli R, et al. [Contribution of intracervical PGE2 administration in premature rupture of the membranes at term. Prospective randomised clinical trial.] J Gynecol Obstet Biol Reprod 2000;29:607–13.	All participants had ruptured membranes
Hjertberg R, Berg A, Ekman G, Granstrom L, Hammarstrom M, Moberger B, et al. Twelve or 24-hours Expectancy in Premature Rupture of the Membranes (PROM) at Term. Proceedings of 14th European Congress of Perinatal Medicine, 5–8 June 1994, Helsinki, Finland, abstract no. 408.	All participants had ruptured membranes
Hjertberg R, Hammarström M, Moberger B, Nordlander E, Granström L. Premature rupture of the membranes (PROM) at term in nulliparous women with a ripe cervix. A randomized trial of 12 or 24 hours of expectant management. Acta Obstet Gynecol Scand 1996;75:48–53.	All participants had ruptured membranes
Hodnett ED, Hannah ME, Weston JA, Ohlsson A, Myhr TL, Wang EEI, et al. Women's evaluations of induction of labor versus expectant management for prelabor rupture of the membranes at term. Birth 1997;24:214–20.	All participants had ruptured membranes
Hoffmann RA, Anthony J, Fawcus S. Oral misoprostol vs. placebo in the management of prelabor rupture of membranes at term. Int J Gynaecol Obstet 2001;72:215–21.	All participants had ruptured membranes
Hoffmann RAM, Fawcus S, Anthony J. Oral Misoprostol versus Placebo in the Management of Prelabour Rupture of Membranes at Term. Women's Health – Into the New Millennium. Proceedings of the 4th International Scientific Meeting of the Royal College of Obstetricians and Gynaecologists, 3–6 October 1999, Cape Town, South Africa, abstract no. 65.	All participants had ruptured membranes
How H, Leaseburge L, Khoury J, Siddiqi T, Sibai B. Is there an ideal route of misoprostol administration for cervical ripening and labor induction. Am J Obstet Gynecol 2001;184:S118.	All participants had ruptured membranes
How HY, Leaseburge L, Khoury JC, Siddiqi TA, Spinnato JA, Sibai BM. A comparison of various routes and dosages of misoprostol for cervical ripening and the induction of labor. Am J Obstet Gynecol 2001;185:911–15.	All participants had ruptured membranes
Husslein P, Egarter C, Sevelda P, Genger H, Salzer H, Kofler E. [Labor induction with 3 mg of prostaglandin E2 vaginal tablets. A renaissance of programmed labor? Results of a prospective randomized study.] Geburtshilfe Frauenheilk 1986;46:83–7.	Non-English language
Jackson N, Paterson-Brown S. Labour characteristics and uterine activity: misoprostol compared with oxytocin in women at term with prelabour rupture of the membranes. BJOG 2000;107:1181–2.	All participants had ruptured membranes

Study	Reason for Exclusion
Jindal P, Avasthi K, Kaur M. A Comparison of Vaginal vs. Oral Misoprostol for Induction of Labor-Double Blind Randomized Trial. J Obstet Gynaecol India 2011;61:538–42.	All participants had ruptured membranes
Kanhai HHH, Keirse M. Intravenous administration of sulfprostone for the induction of labour after fetal death: a randomized comparison of two dose schedules. 12th FIGO World Congress of Gynecology and Obstetrics, 23–8 October 1988, Brazil, pp. 201–2.	Included women undergoing induction for fetal death
Kanhai HHH, Keirse M. Intravenous Administration of Sulprostone for the Induction of Labour After Fetal Death: a Randomized Comparison of Two Dose Schedules. Proceedings of 1st European Congress on Prostaglandins in Reproduction, 6–9 July 1988, Vienna, Austria, abstract no. 45.	Included women undergoing induction for fetal death
Kashanian M, Afshar A, Zarrin Z. A comparison between the effect of oxytocine only and oxytocine plus propanolol on the labor (a double blind randomized trial). J Maternal-Fetal Neonatal Med 2008;21(Suppl. 1):73.	Full text is excluded from HTA
Kashanian M, Naghghash S. A Comparison Between the Effect of Oxitocin only and Oxitocin plus Propranolol on the Labor (a Double Blind Randomized Trial). 31st British International Congress of Obstetrics and Gynaecology, 2007, London, UK, abstract no. 158.	Full text is excluded from HTA
Melchior J, Bernard N, Andre-David F [Artificial induction of labor at term for medical reasons. Comparison of 2 technics for labor induction, oxytocin + early artificial rupture of the membranes versus prostaglandin E2 vaginal gel. Open randomized controlled study]. Rev Fr Gynecol Obstet. 1989 Nov;84(11):747-52.	Non-English language
Kashanian M, Zarrin DR. Evaluation of the effect of extra-amniotic normal saline infusion (EASI) alone or in combination with dexamethazone for the induction of labor. 31st British International Congress of Obstetrics and Gynaecology, July 4–6 2007, London, UK, abstract no. 210.	Full text is excluded from HTA
Kashanian M, Zarrin Z. A comparison between the effect of oxytocin only and oxytocin plus propanolol on the labor: a double blind randomized trial. J Kashan Uni Med Sci 2006;10:7–11.	Full text is excluded from HTA
Kashanian M, Zarrin Z. A comparison between the effect of oxytocin only and oxytocin plus propranolol on the labor (a double blind randomized trial). J Maternal-Fetal Neonatal Med 2010;23(Suppl. 1):616–17.	Full text is excluded from HTA
Kehl S, Welzel G, Ehard A, Berlit S, Spaich S, Siemer J, et al. Women's acceptance of a double-balloon device as an additional method for inducing labour. Eur J Obstet Gynecol Reprod Biol 2013;168:30–5.	Full text is excluded from HTA (complex intervention)
Kehl S, Ziegler J, Schleussner, Tuschy B, Berlit S, Mayer J, et al. Induction of labour with a balloon catheter and misoprostol - a randomised controlled multi centre study. Arch Gynecol Obstet 2012;286(Suppl. 1):145–6.	Full text is excluded from HTA (complex intervention)

Study	Reason for Exclusion
Kemp B, Winkler M, Rath W. Induction of labor by prostaglandin E(2) in relation to the Bishop score. Int J Gynaecol Obstet 2000;71:13–17.	≥1/3 of participants had ruptured membranes
Kunt C, Kanat-Pektas M, Gungor AN, Kurt RK, Ozat M, Gulerman C, et al. Randomized trial of vaginal prostaglandin E2 versus oxytocin for labor induction in term premature rupture of membranes. Taiwan J Obstet Gynecol 2010;49:57–61.	All participants had ruptured membranes
Ladfors L, Mattsson LA, Eriksson M, Fall O. A randomised trial of two expectant managements of prelabour rupture of the membranes at 34 to 42 weeks. Br J Obstet Gynaecol 1996;103:755–62.	All participants had ruptured membranes
Ladfors L, Tessin I, Fall O, Erikson M, Matsson LA. A comparison of neonatal infectious outcome comparing two expectant managements of women with prelabor rupture of the membranes at 34–42 weeks. Am J Obstet Gynecol 1998;178:S197.	All participants had ruptured membranes
Lamki H, Roberts A, Dunlop JM, Pinkerton JH. Induction of labour by prostaglandin E2 compared with Syntocinon. Ir Med J 1974;67:515–19.	All participants had ruptured membranes
Lange AP, Secher NJ, Nielsen FH, Pedersen GT. Stimulation of labor in cases of premature rupture of the membranes at or near term. Acta Obstet Gynecol Scand 1981;60:207–10.	All participants had ruptured membranes
Lelaidier C, Baton C, Benifla JL, Fernandez H, Bourget P, Frydman R. Mifepristone for labour induction after previous caesarean section. Br J Obstet Gynaecol 1994;101:501–3.	Participants had previous caesarean section
Lemke M, Turnquest M. Laminaria tents plus vaginal prostaglandin versus vaginal prostaglandin alone for cervical ripening. Am J Obstet Gynecol 1996;174:482.	Full text is excluded from HTA (not a relevant comparison)
Levy R, Vaisbuch E, Furman B, Brown D, Volach V, Hagay ZJ. Induction of labor with oral misoprostol for premature rupture of membranes at term in women with unfavorable cervix: a randomized, double-blind, placebo-controlled trial. J Perinat Med 2007;35:126–9.	All participants had ruptured membranes
Levy R, Vaisbuch E, Furman B, Doitch H, Oron S, Hagay Z. Prospective randomized clinical trial of immediate induction of labor with oral misoprostol for prelabor rupture of the membranes in women with unfavorable cervix at term. Am J Obstet Gynecol 2005;193(Suppl. 6):44.	All participants had ruptured membranes
Li XH, Ma WZ, Xu SY. The clinical observation on the effect of electroacupuncture to Sanyinjiao(SP6) and Hegu(L14) in influencing parturients' uterine contraction in the first stage. J Beijing Uni Trad Chinese Med 1996;19:38.	Full text is excluded from HTA (no relevant data)
Lin M, Ramsey P, Reid K, Treaster M, Nuthalapaty F, Lu G. The impact of maternal BMI, parity and GA on the comparative efficacy of transcervical foley catheter with or without an extraamniotic saline infusion for cervical ripening and labor induction in women with an unfavorable cervix. Am J Obstet Gynecol 2006;195(Suppl. 1):109.	All participants had ruptured membranes
Lin M, Treaster M, Reid K, Nuthalapaty F, Ramsey P, Lu G. A randomized controlled trial of transcervical foley catheter with	All participants had ruptured membranes

Study	Reason for Exclusion
and without extra-amniotic saline infusion (EASI) for labor induction. Am J Obstet Gynecol 2006;195(Suppl. 1):30.	
Lin MG, Ramsey PS. Foley Catheter for Labor Induction in Women with Term or Near Term Membrane Rupture. 2006. URL: http://clinicaltrials.gov/ (accessed 21 March 2006).	All participants had ruptured membranes
Lo JY, Alexander JM, McIntire DD, Leveno KJ. Efficacy of oral misoprostol in nulliparous women with premature rupture of membranes. Am J Obstet Gynecol 2001;185(Suppl. 6):204.	All participants had ruptured membranes
Lo JY, Alexander JM, McIntire DD, Leveno KJ. Randomized trial of oral misoprostol in nulliparous women with premature rupture of membranes at term. Am J Obstet Gynecol 2001;185(Suppl. 6):204.	All participants had ruptured membranes
Lo JY, Alexander JM, McIntire DD, Leveno KJ. Ruptured membranes at term: randomized, double-blind trial of oral misoprostol for labor induction. Obstet Gynecol 2003;101:685–9.	All participants had ruptured membranes
Lopes P, Besse O, Sagot P, Dantal F, de Morel P, Panel N, et al. [The value of the administration of prostaglandin E2 on the biodegradable support of the maturation of the cervix uteri and the induction of labor.] J Gynecol Obstet Biol Reprod (Paris) 1991;20:827–32.	Non-English language
Lopez-Farfan JA, Gamez-Guevara C. Comparison of dinoprostone (ovules and gel) to achieve cervical ripening in patients with term pregnancy that occurs with premature membranes rupture. Ginecol Obstet Mex 2010;78:110–15.	All participants had ruptured membranes
Lyndrup J, Legarth J, Dahl C, Philipsen T, Eriksen PS, Weber T. Induction of labour: the effect of vaginal prostaglandin or i.v. oxytocin: a matter of time only? Eur J Obstet Gynecol Reprod Biol 1990;37:111–19.	Complex intervention (lamicel plus oxytocin or prostaglandin)
Lyndrup J. Induction of labor by PGE2 and other local methods. Physiology, methods and guidelines for patient selection. Acta Obstet Gynecol Scand 1996;75:86–7.	No relevant data
MacKenzie IZ. Acupuncture for Pain Relief during Induced Labour for Nulliparae. 2011. URL: http://clinicaltrials.gov/ct2/show/record/NCT01165099 (accessed 6 January 2011).	Trial registration. Study considers acupuncture for pain relief, not induction
Macones G, Stamilio D, Rampersad R, Cahill AG, Odibo AO. The efficacy of early amniotomy in nulliparous labor induction: a randomized controlled trial. Am J Obstet Gynecol 2011;204(Suppl. 1):4.	Full text is excluded from HTA (complex intervention)
Magnani M, Cabrol D. Induction of labour with PGE2 after cervical ripening with oestradiol. Control and management of parturition 23rd Baudelocque symposium. 1986;151:109–18.	Non-English language
Magos AL, Noble MCB, Yuen AWT, Rodeck CH. Controlled study comparing vaginal prostaglandin E2 pessaries with intravenous oxytocin for the stimulation of labour after spontaneous rupture of the membranes. Br J Obstet Gynaecol 1983;90:726–31.	All participants had ruptured membranes

Study	Reason for Exclusion
Mahmood TA, Dick MJ, Smith NC, Templeton AA. Role of prostaglandin in the management of prelabour rupture of the membranes at term. Br J Obstet Gynaecol 1992;99:112–17.	All participants had ruptured membranes
Mahmood TA, Dick MJ. A randomized trial of management of pre-labor rupture of membranes at term in multiparous women using vaginal prostaglandin gel. Obstet Gynecol 1995;85:71–4.	All participants had ruptured membranes
Mahmood TA, Dick MJW, Smith NC, Templeton A. Management of Spontaneous Rupture of Membranes at Term without Uterine Activity in Healthy Primigravidae: A Prospective Study (PGE2 Gel vs Conservative Treatment). Proceedings of 2nd European Congress on Prostaglandins in Reproduction, 30 April–3 May 1991, The Hague, The Netherlands, abstract no. 95.	All participants had ruptured membranes
Mahmood TA, Dick MJW, Smith NC. Management of spontaneous rupture of the membranes and no uterine activity in healthy primigravidae after 34 weeks' gestation. Lancet 1989;1:721.	All participants had ruptured membranes
Malik HZ, Khawaja NP, Zahid B, Rehman R. Sublingual versus oral misoprostol for induction of labour in prelabour rupture of membranes at term. J Coll Physicians Surg Pak 2010;20:242–5.	All participants had ruptured membranes
Malik N, Gittens L, Gonzalez D, Bardeguez A, Ganesh V, Apuzzio J. Clinical amnionitis and endometritis in patients with premature rupture of membranes: endocervical prostaglandin E2 gel versus oxytocin for induction of labor. Obstet Gynecol 1996;88:540–3.	All participants had ruptured membranes
Massil HY, Baker AC, O'Brien PM. A comparison of oral prostaglandin E2 tablets with intravenous oxytocin for stimulation of labor after premature rupture of membranes at term. Acta Obstet Gynecol Scand 1988;67:703–9.	All participants had ruptured membranes
McCaul JF, Williams LM, Martin RW, Magann EF, Gallagher L, Morrison JC. Comparison of induction methods for premature rupture of membranes at term. Am J Obstet Gynecol 1992;166:275.	All participants had ruptured membranes
McCaul JFt, Rogers LW, Perry KG, Jr, Martin RW, Allbert JR, Morrison JC. Premature rupture of membranes at term with an unfavorable cervix: comparison of expectant management, vaginal prostaglandin, and oxytocin induction. Southern Med J 1997;90:1229–33.	All participants had ruptured membranes
McQueen D, Neilson JP, Whittle MJ. Pre-labour rupture of membranes with an unripe cervix: a random trial of management. J Obstet Gynaecol 1990;10:495–8.	All participants had ruptured membranes
McQueen D. A Randomized Controlled Trial Comparing Expectant with Active Management in Early Rupture of the Membranes at Term. Personal communication. 1992.	All participants had ruptured membranes
Mercer B, Pilgram P, Sibai B. Low Dose Oxytocin vs a Routine Induction Protocol for the Induction of Labor. Proceedings of 10th Annual Meeting of Society of Perinatal Obstetricians, 23–27 January 1990, Houston, TX, USA, abstract no. 21.	Full text is excluded from HTA report (dose comparison)
Mercer BM, Crocker LG, Boe NM, Sibai BM. Induction versus expectant management in premature rupture of the membranes	All participants had ruptured membranes

Study	Reason for Exclusion
with mature amniotic fluid at 32 to 36 weeks: a randomized trial. Am J Obstet Gynecol 1993;169:775–82.	
Milchev N, Kuzmanov B, Terzhumanov R. [Cytotec: an effective drug for the induction of labor.] Akush Ginekol 2003;42:9–11.	Non-English language
Moberger B, Hammarstrom M, Hjertberg R, Berg A. Neonatal Outcome After 12 vs 24 Hours of Conservative Management in Primigravidae with PROM at Term. Proceedings of 14th European Congress of Perinatal Medicine, 5–8 June 1994, Helsinki, Finland, abstract no. 415.	All participants had ruptured membranes
Møller M, Thomsen AC, Sørensen J, Forman A. Oxytocin- or low-dose prostaglandin F2 alpha-infusion for stimulation of labor after primary rupture of membranes. A prospective, randomized trial. Acta Obstet Gynecol Scand 1987;66:103–6.	All participants had ruptured membranes
Montealegre JA, Botero LF, Sabogal G. Labor induction with unfavorable cervix: randomized controlled trial double blind method. Oxitocyn vs. misoprostol. Rev Colomb Obstet Ginecol 1999;50:133–7.	Non-English language
Morales WJ, Lazar AJ. Expectant management of rupture of membranes at term. South Med J 1986;79:955–8.	All participants had ruptured membranes
Morgan Ortiz F, Báez Barraza J, Quevedo Castro E, Cuetos Martínez CB, Osuna Ramírez I. [Misoprostol and oxytocin for induction of cervical ripening and labor in patients with term pregnancy and premature membrane rupture.] Ginecol Obstet Mex 2002;70:469–76.	All participants had ruptured membranes
Mosquera J, Mesa JC, Navarro H, Cobo E, Neira C, Zuniga J. Study of the efficacy of misoprostol compared with oxytocin for labor induction in women with prolonged amenorrhea. Rev Colomb Obstet Ginecol 1999;50:7–12.	Non-English language
Mozurkewich E, Horrocks J, Daley S, Von Oeyen P, Halvorson M, Johnson M, et al. The MisoPROM study: a multicenter randomized comparison of oral misoprostol and oxytocin for premature rupture of membranes at term. Am J Obstet Gynecol 2003;189:1026–30.	All participants had ruptured membranes
Mozurkewich E, Horrocks J, Daley S, Von Oeyen P, Sarvis A, Halvorson M, et al. The misoprom study: a randomized controlled trial of misoprostol for premature rupture of membranes at term. Am J Obstet Gynecol 2002;187:S168.	All participants had ruptured membranes
Mullin P, House M, Paul R, Wing D. A comparison of vaginally administered misoprostol with extraamniotic saline infusion for cervical ripening and labor induction. Am J Obstet Gynecol 2001;185(Suppl. 6):203.	Complex intervention
Naef RW, Allbert JR, Ross EL, Weber M, Martin RW, Morrison JC. Premature rupture of membranes at 34 to 37 weeks' gestation: aggressive versus conservative management. Am J Obstet Gynecol 1998;178:126–30.	All participants had ruptured membranes
Naef RW, Allbert JR, Weber BM, Roach H, Martin RW, Morrison JC. Premature rupture of membranes at 34-37 weeks' gestation: aggressive vs conservative management. Am J Obstet Gynecol 1994;170:340.	All participants had ruptured membranes

Study	Reason for Exclusion
Nagpal MB, Raghunandan C, Saili A. Oral misoprostol versus intracervical prostaglandin E2 gel for active management of premature rupture of membranes at term. Int J Gynaecol Obstet 2009;106:23–6.	All participants had ruptured membranes
Nasir S, Chaudhry R. Comparison of intracervical foley catheter plus oral misoprostol with oral misoprostol alone for cervical ripening in primigravidas at term. BJOG 2012;119(Suppl. 1):11–12.	Complex intervention
Natale R, Milne JK, Campbell MK, Potts PG, Webster K, Halinda E. Management of premature rupture of membranes at term: randomized trial. Am J Obstet Gynecol 1994;171:936–9.	All participants had ruptured membranes
Natale R, Milne K, Campbell K, Wester K, Halinda E. Management of premature rupture of membranes at term: randomized trial. Am J Obstet Gynecol 1994;170:285.	All participants had ruptured membranes
Ngai CSW, To WWK, Lao T, Ho PC. Cervical Priming with Oral Misoprostol in Prelabour Rupture of Membranes at Term. 27th British Congress of Obstetrics and Gynaecology, 4–7 July 1995, Dublin, Ireland, abstract no. 479.	All participants had ruptured membranes
Ngai SW, Chan YM, Lam SW, Lao T. Prospective randomised study to compare misoprostol and oxytocin for labour induction in prelabour rupture of membranes in term pregnancy. Br J Obstet Gynaecol 1998;105(Suppl. 17):82.	All participants had ruptured membranes
Ngai SW, Chan YM, Lam SW, Lao TT. Labour characteristics and uterine activity: misoprostol compared with oxytocin in women at term with prelabour rupture of the membranes. BJOG 2000;107:222–7.	All participants had ruptured membranes
Ngai SW, To WK, Lao T, Ho PC. Cervical priming with oral misoprostol in pre-labor rupture of membranes at term. Obstet Gynecol 1996;87:923–6.	All participants had ruptured membranes
Nguyen VT, Do DV, Tran TS, Nguyen PT. Labor induction using sub-lingual misoprostol for prelabor rupture of membranes at term: a randomized controlled trial. Int J Gynecol Obstet 2012;119(Suppl. 3):802.	All participants had ruptured membranes
Oliveira MV, Oberst PV, Leite GK, Aguemi A, Kenj G, Leme VD, et al. [Cervical Foley catheter versus vaginal misoprostol for cervical ripening and induction of labor: a randomized clinical trial.] Rev Bras Ginecol Obstet 2010;32:346–51.	Non-English language
Ottervanger HP, Holm JP, Keirse M. A randomized trial of expectant vs active management for prelabour rupture of the membranes at term. J Perinatal Med 1992;20(Suppl. 1):223.	All participants had ruptured membranes
Ottervanger HP, Holm JP, Keirse M. Premature rupture of the membranes at term: induction of labour or expectant care? Int J Gynecol Obstet 1991;36(Suppl.):432.	All participants had ruptured membranes
Ottervanger HP, Keirse MJ, Smit W, Holm JP. Controlled comparison of induction versus expectant care for prelabor rupture of the membranes at term. J Perinat Med 1996;24:237–42.	All participants had ruptured membranes
Parisaei M, Erskine KJ. Is expensive always better? Comparison of two induction agents for term rupture of membranes. J Obstet Gynaecol 2008;28:290–3.	All participants had ruptured membranes

Study	Reason for Exclusion
Parisaei MP, Erskine KJE. Comparison of sub-lingual misoprostol with standard regime vaginal prostaglandin E2 gel for the induction of labour after term rupture of membranes. J Obstet Gynaecol 2005;25(Suppl. 1):69.	All participants had ruptured membranes
Paul S, Bhowmick R. A Randomised Controlled Trial of Oral Prostaglandin E2 (Dinoprostone) and Oxytocin Infusion in Induction of Labour. Personal communication. 1992. pp. 1–4.	Unpublished data only
Perche S, Guerra M, Reyna E, Hidalgo M, Santos J, Mejia J, et al. Vaginal isosorbide mononitrate or misoprostol for cervical ripening in term pregnancies. Clin Invest Ginecol Obstet 2009;36:203–8.	Non-English language
Perez Picanol E, Gamissans O, Lecumberri J, Jimenez M, Vernet M. Ripening the Cervix with Intracervical PGE2 Gel in Term Pregnancies with Premature Rupture of Membranes. Proceedings of 12th European Congress of Perinatal Medicine, 11–14 September 1990, Lyon, France, abstract no. 197.	All participants had ruptured membranes
Perez Picanol E, Vernet M, Armengol R, Perez Ares C, Lecumberri J, Gamissans O. Comparison of two different therapeutic attitudes in premature rupture of membranes. J Perinatal Med 1992;20(Suppl. 1):353.	All participants had ruptured membranes
Pi P, Zhu F. [Clinical observation of misoprostol on induction in late pregnancy.] Hunan Yi Ke Da Xue Xue Bao 1999;24:195–7.	Non-English language
Poornima B, Dharma Reddy DB. Premature rupture of membranes at term: immediate induction with PGE (2) gel compared with delayed induction with oxytocin. J Obstet Gynaecol India 2011;61:516–18.	All participants had ruptured membranes
Prager M, Eneroth-Grimfors E, Edlund M, Marions L. A randomised controlled trial of intravaginal dinoprostone, intravaginal misoprostol and transcervical balloon catheter for labour induction. BJOG 2008;115:1443–50.	Duplicate reference (trial already included)
Puertas A, Mino M, Manzanares S, Ceballos C, Alamo F, Miranda JA. Labor induction with intracervical prostaglandin E2 versus oxytocin in premature rupture of membranes. Prenatal Neonatal Med 1996;1(Suppl. 1):89.	All participants had ruptured membranes
Puertas A, Mino M, Moreno I, Carrillo MP, Mozas J, Miranda JA. Induced labour in the premature rupture of membranes at term. Comparison of E2 intracervical prostaglandine with oxytocine. Prog Obstet Ginecol 1997;40:13–18.	All participants had ruptured membranes
Puga O, Nien JK, Gomez R, Medina L, Carstens M, Gonzalez R, et al. Premature rupture of membranes after 35 weeks: a randomized clinical trial of induction of labor with oral versus vaginal administration of misoprostol. Am J Obstet Gynecol 2001;184:S85.	All participants had ruptured membranes
Rath DM, Manas K. Induction of labor with oral misoprostol in women with prelabor rupture of membranes at term. J Obstet Gynecol India 2007;57:505–8.	All participants had ruptured membranes
Rath W, Heyl W, Kemp B. Intracervical versus intravaginal PGE2 gel for induction of labor. Perinatal Medizin 1998;10:81–3.	Non-English language

Study	Reason for Exclusion
Rath W, Kemp B, Heyl W. Prostaglandin E2 as a vaginal gel, intracervical gel or vaginal tablet for induction of labor: a prospective, randomized, multicenter trial. Geburtsh Frauenheilk 1999;59:323–9.	Non-English language
Ray DA, Garite TJ. Prostaglandin E2 for induction of labor in patients with premature rupture of membranes at term. Am J Obstet Gynecol 1992;166:836–43.	All participants had ruptured membranes
Rayburn W, Lucas M, Gittens L, Goodwin TM, Baxi L, Gall S, et al. Attempted vaginal birth after caesarean section: a multicenter comparison of outpatient prostaglandin E2 gel with expectant management. Prim Care Update Ob/Gyns 1998;5:182–3.	Participants had previous caesarean section
Rayburn WF, Gittens LN, Lucas MJ, Gall SA, Martin ME. Weekly administration of prostaglandin e2 gel compared with expectant management in women with previous cesareans Prepidil gel study group. Obstet Gynecol 1999;94:250–4.	Participants had previous caesarean section
Rizvi S, Umber F, Yusuf AW. Labour induction at term; oral versus intravaginal misoprostol. Ann King Edward Med Coll 2007;13:119–21.	All participants had ruptured membranes
Rolland Souza A. [Titrated oral suspension compared with vaginal misoprostol for labor induction: a randomized controlled trial.] Rev Bras Ginecol Obstet 2011;33:270.	Non-English language abstract
Romer A, Weigel M, Zieger W, Melchert F. Changes in cervix maturity and length of birth after birth-preparation accupuncture therapy: Mannheim Rome Scheme. DZA 1998;41:93–100.	Excluded from HTA report - no relevant outcome data
Romero-Gutiérrez G, Bernal González OE, Ponce-Ponce de León AL. [Comparison of isosorbide dinitrate and dinoprostone for induction of labor in term pregnancy.] Ginecol Obstet Mex 2011;79:285–91.	Non-English language
Roudsari FV, Ghasemi M, Ayati S, Shakeri MT, Farshidi F, Shahabian M. [Comparison of vaginal misoprostol with foley catheter for cervical ripening and induction of labor.] J Isfahan Med School 2010;28:177–85.	Non-English language
Rydhström H, Ingemarsson I. No benefit from conservative management in nulliparous women with premature rupture of the membranes (PROM) at term. A randomized study. Acta Obstet Gynecol Scand 1991;70:543–7.	All participants had ruptured membranes
Rymer J, Parker A. A comparison of syntocinon infusion with prostaglandin vaginal pessaries when spontaneous rupture of the membranes occurs without labour after 34 weeks gestation. Aus N Z J Obstet Gynaecol 1992;32:22–4.	All participants had ruptured membranes
Sahraoui W, Hajji S, Bibi M, Nouira M, Essaidi H, Khairi H. [Management of pregnancies beyond forty-one week's gestation with an unfavorable cervix.] J Gynecol Obstet Biol Reprod 2005;34:454–62.	Non-English language
Sanchez-Ramos L, Chen A, Briones D, Del Valle GO, Gaudier FL, Delke I. Premature rupture of membranes at term: induction of labor with intravaginal misoprostol tablets (PGE1) or intravenous oxytocin. Am J Obstet Gynecol 1994;170:377.	All participants had ruptured membranes

Study	Reason for Exclusion
Sanchez-Ramos L, Chen AH, Kaunitz AM, Gaudier FL, Delke I. Labor induction with intravaginal misoprostol in term premature rupture of membranes: a randomized study. Obstet Gynecol 1997;89:909–12.	All participants had ruptured membranes
Sande HA, Tuveng J, Fønstelien T. A prospective randomized study of induction of labor. Int J Gynaecol Obstet 1983;21:333–6.	Data not reported according to randomised groups
Satin AJ, Hankins GDV, Yeomans ER. A randomized study of two dosing regimens of oxytocin for the induction of patients with an unfavorable cervix. Am J Obstet Gynecol 1991;164:307.	Full text excluded from HTA report as dose comparison
Seaward PG, Hannah ME, Myhr TL, Farine D, Ohlsson A, Wang EE, et al. International multicenter term PROM study: evaluation of predictors of neonatal infection in infants born to patients with premature rupture of membranes at term. Premature Rupture of the Membranes. Am J Obstet Gynecol 1998;179:635–9.	All participants had ruptured membranes
Sellers SM, Ah-Moye M, MacKenzie IZ. Comparison of Vaginal Prostaglandin E2 and Intravenous Oxytocin for Induction of Labour in Women Previously Delivered by Caesarean Section. Proceedings of 1st European Congress on Prostaglandins in Reproduction, 6–9 July 1988, Vienna, Austria, abstract no. 128.	Participants had previous caesarean section
Selmer-Olsen T, Lydersen S, M¯rkved S. Does acupuncture used in nulliparous women reduce time from prelabour rupture of membranes at term to active phase of labour? A randomised controlled trial. Acta Obstet Gynecol Scand 2007;86:1447–52.	All participants had ruptured membranes
Shetty A, Martin R, Danielian P, Templeton A. A comparison of two dose regimens of oral misoprostol in the induction of labour at term: a random allocation controlled trial. J Obstet Gynaecol 2001;21:91.	Same arm for both doses (women in both treatment arms received ≥50µg misoprostol)
Shoaib F. Management of premature rupture of membranes with unfavourable cervix at term, by prostaglandins. Specialist 1994;10:227–32.	All participants had ruptured membranes
Skupski D, Normand N, Eglinton G, Witkin SS. Cyclooxygenase-2 (COX-2) and interleukin-1 receptor antagonist (IL-1RA) gene polymorphisms influence the time interval between labor induction and delivery. Am J Obstet Gynecol 2007;197(Suppl. 1):99.	Full text excluded from HTA report as complex intervention
Sparks T, Caughey AB, Shaffer B, Cheng YW, Vargas J, Delaney S, et al. Predictors of cesarean delivery in women undergoing labor induction with a Foley balloon. Am J Obstet Gynecol 2011;204(Suppl. 1):78.	Full text excluded from HTA report (not a relevant comparison)
Sperling LS, Schantz AL, Wåhlin A, Duun S, Jaszczak P, Scherling B, et al. Management of prelabor rupture of membranes at term. A randomized study. Acta Obstet Gynecol Scand 1993;72:627–32.	All participants had ruptured membranes
Stewart JD, Rayburn WF, Farmer K, Liles E, Schipul A, Stanley J. Effectiveness of prostaglandin E2 as an intracervical gel with immediate oxytocin, or as a sustained-release vaginal insert for induction of labour. Am J Obstet Gynecol 1998;178:S92.	Full text is excluded from HTA report (complex intervention)

Study	Reason for Exclusion
Su H, Li E, Weng L. [Mifepristone for induction of labor.] Zhonghua Fu Chan Ke Za Zhi 1996;31:676–80.	Non-English language
Surbek DV, Boesiger H, Hoesli I, Pavic N, Holzgreve W. A double-blind comparison of the safety and efficacy of intravaginal misoprostol and prostaglandin E2 to induce labor. Am J Obstet Gynecol 1997;177:1018–23.	≥1/3 participants had ruptured membranes
Surbek DV, Bosiger H, Hosli I, Pavic N, Holzgreve W. Cervical priming and labor induction with intravaginal misoprostol versus PGE2: a double-blind randomized trial. Am J Obstet Gynecol 1997;176:S112.	≥1/3 participants had ruptured membranes
Surbek DV, Bosiger H, Pavic N, Hosli I, Stoz F, Holzgreve W. The safety of misoprostol for labor induction. Acta Obstet Gynecol Scand 1997;76:36.	≥1/3 participants had ruptured membranes
Surbek DV, Bosiger H, Pavic N, Stoz F, Holzgreve W. Misoprostol (Cytotec) for Labor Induction in term Pregnancies. 20th Congress of the Swiss Society of Gynecology and Obstetrics, June 1997, Lugano, Switzerland, abstract no. 11.	≥1/3 participants had ruptured membranes
Tamsen L, Lyrenas S, Cnattingius S. Premature rupture of the membranes: intervention or not. Gynecol Obstet Invest 1990;29:128–31.	All participants had ruptured membranes
Taylor AVG, Sellers S, Ah-Moye M, MacKenzie IZ. A prospective random allocation trial to compare vaginal prostaglandin e2 with intravenous oxytocin for labour induction in women previously delivered by caesarean section. J Obstet Gynaecol 1993;13:333–6.	Participants had previous caesarean section
Tessier F, Danserau J. Oral Misoprostol versus Vaginal Dinoprostone for Labor Induction: A Double-Blind Randomized Controlled Trial. Personal communication. 1997.	Personal communication only
Thiery M, De Gezelle H, Van Kets H, Voorhoof L, Verheugen C, Smis B, et al. Extra-amniotic oestrogens for the unfavourable cervix. Lancet 1978;2:835–6.	Not in HTA. Irrelevant comparison
Thigpen B, Bofill J, Bufkin L, Woodring T, Moore L, Morrison J. A randomized controlled trial comparing vaginal misoprostol to cervical foley plus oral misoprostol for cervical ripening and labor induction. Am J Obstet Gynecol 2004;191(Suppl. 1):18.	Full text excluded from HTA report (complex intervention)
Thomas N, Longo SA, Rumney PJ, Nageotte MP, Asrat T. Intravaginal misoprostol in prelabor rupture of membranes at term. Am J Obstet Gynecol 2000;182:S136.	All participants had ruptured membranes
Trabelsi H, Mathlouthi N, Zayen S, Dhouib M, Chaabene K, Trabelsi K, et al. [Cervical ripening at term. A randomized and prospective study: Misoprotol versus dinoprostone.] Tunis Med 2012;90:362–9.	Non-English language
Tremeau ML, Fontanie-Ravier P, Teurnier F, Demouzon J. [Protocol of cervical maturation by acupuncture.] J Gynecol Obstet Biol Reprod 1992;21:375–80.	Non-English language
van der Walt D, Venter PF. Management of term pregnancy with premature rupture of the membranes and unfavourable cervix. S Afr Med J 1989;75:54–6.	All participants had ruptured membranes
Vernant M, Perez Picanol E, Armengol R, Carreras N, Gamissans O. Intracervical Prostaglandins vs Oxytocin in	All participants had ruptured membranes

Study	Reason for Exclusion
Premature Rupture of Membranes. Proceedings of 2nd World Congress of Perinatal Medicine, 1993, Rome, Italy, abstract no. 449.	
Wagner MV, Chin VP, Peters CJ, Drexler B, Newman LA. A comparison of early and delayed induction of labor with spontaneous rupture of membranes at term. Obstet Gynecol 1989;74:93–7.	All participants had ruptured membranes
Wang H, Li L, Pu L. [The effect of 25 micrograms misoprostol on induction of labor in late pregnancy.] Zhonghua Fu Chan Ke Za Zhi 1998;33:469–71.	Non-English language
Weston J, Hannah M, Ohlsson A. Changing the study design during the recruitment phase of an international perinatal multicentre clinical trial. Controlled Clin Trials 1993;14:401.	Secondary publication of excluded study (all women had ruptured membranes)
Wing D, Guberman C, Fassett M. A comparison of oral mifepristone to intravenous oxytocin for pre-induction cervical ripening and labor induction in women with prelabor rupture of membranes beyond 36 weeks gestation. Am J Obstet Gynecol 2003;189(Suppl. 1):204.	All participants had ruptured membranes
Wing DA, Guberman C, Fassett M. A randomized comparison of oral mifepristone to intravenous oxytocin for labor induction in women with prelabor rupture of membranes beyond 36 weeks' gestation. Am J Obstet Gynecol 2005;192:445–51.	All participants had ruptured membranes
Wing DA, Paul RH. Induction of labor with misoprostol for premature rupture of membranes beyond 36 weeks gestation. Am J Obstet Gynecol 1998;178:S93.	All participants had ruptured membranes
Wing DA, Paul RH. Induction of labor with misoprostol for premature rupture of membranes beyond thirty-six weeks' gestation. Am J Obstet Gynecol 1998;179:94–9.	All participants had ruptured membranes
Yang ZY, Li E, Yu SS. [15-Methyl-PGF2 alpha vaginal suppository for induction of term labor.] Zhonghua Fu Chan Ke Za Zhi 1994;29:273–5.	Non-English language
Yazdani SH, Bouzari Z, Farahi S, Tabary AM. Oral misoprostol with oxytocin versus oxytocin alone for labor induction in pre-labor rupture of membranes (PROM) at term pregnancy. J Babol Uni Med Sci 2012;14:7–12.	All participants had ruptured membranes
Yin CY, Zhou JZ, Wang BP, Lü XY. [Effect and risk analysis of misoprostol in stimulating cervical maturity for post-term pregnancy.] Nan Fang Yi Ke Da Xue Xue Bao 2006;26:182–4.	Non-English language
Zahradnik HP, Quaas L, Kröner-Fehmel EE, Kieback DG, Lippert TH. [Cervix ripening using drugs before oxytocin labor induction. Clinical study of a new prostaglandin E2 triacetin gel.] Geburtshilfe Frauenheilk 1987;47:190–2.	Non-English language
Zanini A, Norchi S, Beretta E, Cortinovis I, Fenaroli G, Scian A. [Cervical ripening and induction of labor in term pregnancy using prostaglandin E2. Controlled clinical study comparing the intracervical and intravaginal routes.] Ann Ostet Ginecol Med Perinat 1989;110:209–16.	Non-English language
Zeterog˘ lu S, Engin-Ustün Y, Ustün Y, Güvercinçi M, Sahin G, Kamaci M. A prospective randomized study comparing	All participants had ruptured membranes

Study	Reason for Exclusion
misoprostol and oxytocin for premature rupture of membranes at term. J Matern Fetal Neonatal Med 2006;19:283–7.	
Shetty A, Stewart K, Stewart G, Rice P, Danielian P, Templeton A. Active management of term prelabour rupture of membranes with oral misoprostol. BJOG 2002;109:1354-8	All participants had ruptured membranes

Table 49: Excluded studies and reasons for their exclusion. From check for epidural outcomes

Study	Reason for exclusion
Adewole IF, Franklin O, Matiluko AA. Cervical ripening and induction of labour by breast stimulation. Afr J Med Med Sci 1993;22:81–5.	No relevant data
Afolabi BB, Oyeneyin OL, Ogedengbe OK. Intravaginal misoprostol versus Foley catheter for cervical ripening and induction of labor. Int J Gynaecol Obstet 2005;89:263–7.	No relevant data
Averill KA, Scardo JA, Chauhan SP. Weekly membrane stripping to decrease the incidence of postterm pregnancy: a randomized clinical trial. Obstet Gynecol 1999;93(Suppl. 4):47	No relevant data
Azhari S, Pirdadeh S, Lotfalizadeh M, Shakeri MT. Evaluation of the effect of castor oil on initiating labor in term pregnancy. Saudi Med J 2006;27:1011–14.	No relevant data
Babcock RJ, Peterson JH. Relaxin; its effect on electively induced labor. Am J Obstet Gynecol 1959;78:33–7.	No relevant data
Baev O, Rumyantseva V. Mifepristone versus intracervical prostaglandin E2 gel for cervical ripening and labor induction. Geburtsh Frauenheilk 2011;71:904–5.	No relevant data
Balintona J, Meyer L, Ramin K, Vasdev G, Ramsey P. Cardiotocographic abnormalities associated with labor induction. Anesthesiology 2001;94: abstract no. 67.	No relevant data
Bamford PN. Trial to Compare Prostaglandin Gel vs Prostaglandin Pessary in Nulliparous Inductions. Personal communication. 1992.	Personal communication.
Bates CD, Nicoll AE, Mullen AB, Mackenzie F, Thomson AJ, Norman JE. Serum profile of isosorbide mononitrate after vaginal administration in the third trimester. BJOG 2003;110:64–7.	No relevant data
Baxi LV, Petrie RH, Caritis SN. Induction of labor with low-dose prostaglandin F2 alpha and oxytocin. Am J Obstet Gynecol 1980;136:28–31.	No relevant data
Beazley JM, Gillespie A. Double-blind trial of prostaglandin E2 and oxytocin in induction of labour. Lancet 1971;1:152–5.	No relevant data

Study	Reason for exclusion
Bendvold, E. (1990). "Coitus and induction of labour." Tidsskrift for Jordmodre 96: 6–8.	Unavailable
Beigi A, Kazemipour SM, Tabarestani H. Induction of labor in term pregnancy: sublingual versus vaginal misoprostol. Tehran Uni Med J 2010;68:175–81.	No relevant data
Bernstein, E., N. Leyland, G. P and G. D (1986). Effect of Administration of PGE2 Gel and Placebo Gel into the Cervical Canal on Cervical Softening and Induction of Labour. Proceedings of Annual Meeting of Society of Obstetricians and Gynaecologists of Canada, 1986, Vancouver, BC, Canada: Abstract no 108.	Unavailable
Bex P, Gunasekera PC, Phipps JH. Difficulties with controlled release prostaglandin E2 pessaries (letter). Lancet 1990;336:119.	No relevant data
Blackburn MG, Mancusi-Ungaro HR, Orzalesi MM, Hobbins JC, Anderson GG. Effects on the neonate of the induction of labor with prostaglandin F2alpha and oxytocin. Am J Obstet Gynecol 1973;116:847–53.	No relevant data
Bonebrake R, Haag T, Fleming A, Temp M, Haynatzki G. Vaginal misoprostol is more effective with fewer side effects than oral misoprostol for cervical ripening and induction of labor. Am J Obstet Gynecol 2001;185(Suppl. 6):204.	No relevant data
Cai LL, Hu LQ, Hua YR. [Effect of cuichan zhunsheng decoction for promoting cervical ripening in late pregnancy.] Chin J Integrat Trad West Med 2010;30:682–5.	No relevant data
Calder AA, Moar VA, Ounsted MK, Turnbull AC. Increased bilirubin levels in neonates after induction of labour by intravenous prostaglandin E2 or oxytocin. Lancet 1974;2:1339–42.	No relevant data
Caliskan E, Bodur H, Ozeren S, Corakci A, Ozkan S, Yucesoy I. Misoprostol 50 µg sublingually versus vaginally for labor induction at term: a randomized study. Gynecol Obstet Invest 2005;59:155–61.	INCLUDED
Cameron AD, Calder AA, Walker JJ. Randomised Comparison of PGE2 Vaginal Gel vs Amniotomy and Intravenous Oxytocin in Favourable Induction. Proceedings of 11th European Congress of Perinatal Medicine, 1988, Rome, Italy, abstract no. 157.	No relevant data
Cetin, A., M. Cetin, A. Taskurt and E. Izgic (1997). "Misoprostol versus dinoprostone for labor induction in term pregnancies." Jinekoloji Ve Obstetrik Dergisi 11: 51–54.	Not in English
Chou, M. (1991). "Double-Blind Randomized Trial of Human Relaxin Gel for Cervical Ripening and Induction of Labour."	Personal communication.
Craft IL, Cullum AR, May DT, Noble AD, Thomas DJ. Prostaglandin E2 compared with oxytocin for the induction of labour. Br Med J 1971;3:276–9.	INCLUDED

Study	Reason for exclusion
Cross WG, Pitkin RM. Laminaria as an adjunct in induction of labor. Obstet Gynecol 1978;51:606–8.	No relevant data
D'Souza SW, Lieberman B, Cadman J, Richards B. Oxytocin induction of labour: hyponatraemia and neonatal jaundice. Eur J Obstet Gynecol Reprod Biol 1986;22:309–17.	No relevant data
Day L, Fleener D, Andrews J. Membrane sweeping with labor induction: a randomized controlled trial. Am J Obstet Gynecol 2009;201(Suppl. 1):47.	No relevant data
De Laat W, Egberink J. A Highly Viscous Prostaglandin E2 gel (Cerviprost) for Cervical Ripening. Proceedings of 2nd European Congress on Prostaglandins in Reproduction, 30 April–3 May 1991, The Hague, The Netherlands, abstract no. 98.	No relevant data
De Oliveira MGM. A prospective randomized study of the foley catheter for ripening of the unfavourable cervix before induction of labour. Rev Bras Ginecol Obstet 2003;25:375.	No relevant data
Deo S, Iqbal B, Das V, Agarwal A, Singh R. Preinduction cervical ripening: a prospective randomised comparison of intracervical foley catheter versus PGE2 gel. BJOG 2013;120(Suppl. 1):85.	No relevant data
Di Lieto A, Miranda L, Ardito P, Favale P, Albano G. Changes in the bishop score induced by manual nipple stimulation. A cross-over randomized study. Clin Exp Obstet Gynecol 1989;16:26–9.	No relevant data
De Laat W, Egberink J. A Highly Viscous Prostaglandin E2 gel (Cerviprost) for Cervical Ripening. Proceedings of 2nd European Congress on Prostaglandins in Reproduction, 30 April–3 May 1991, The Hague, The Netherlands, abstract no. 98.	No relevant data
Dommisse J, Davey DA, Martin B, Cohen M. An evaluation of prostaglandin E2 administered intrarectally to induce labour. S Afr Med J 1981;59:817–18.	No relevant data
Duhl A, Tolosa J, Leiva M, Nemiroff R. Randomized trial of intravaginal gel, intravaginal time release insert, and intracervical gel with prostaglandin E2 for induction of labor. Am J Obstet Gynecol 1997;176:S113.	No relevant data
Dunn PA, Rogers D, Halford K. Transcutaneous electrical nerve stimulation at acupuncture points in the induction of uterine contractions. Obstet Gynecol 1989;73:286–90.	No relevant data
Ehrenberg-Buchner S, Wing D, Brown R, Plante L, Rugarn O, Powers B. Comparison of misoprostol vaginal insert and dinoprostone vaginal insert: incidence of treatment-emergent adverse events. Am J Obstet Gynecol 2013;208(Suppl. 1):150.	No relevant data

Study	Reason for exclusion
Elliott CL, Brennand JE, Calder AA. The effects of mifepristone on cervical ripening and labor induction in primigravidae. Obstet Gynecol 1998;92:804–9.	No relevant data
Elliott JP, Flaherty JF. The use of breast stimulation to prevent postdate pregnancy. Am J Obstet Gynecol 1984;149:628–32.	No relevant data
Elliott JP, Flaherty JF. The use of breast stimulation to ripen the cervix in term pregnancies. Am J Obstet Gynecol 1983;145:553–6.	No relevant data
ElSedeek MSh, Awad EE, ElSebaey SM. Evaluation of postpartum blood loss after misoprostol-induced labour. BJOG 2009;116:431–5.	No relevant data
Emery, S., E. Neal, S. Ward, R. Morrison and M. Filshie (1988). Prospective Controlled Trial of Three Methods for Ripening the Unfavourable Cervix Prior to Induction of Term Labour. Proceedings of 1st European Congress on Prostaglandins in Reproduction, 6–9 July 1988, Vienna, Austria: Abstract no. 140.	Unavailable – arrived 30 April – No relevant data
Friedman EA, Sachtleben MR. Oral prostaglandin E2 for induction of labor at term. Obstet Gynecol 1974;43:178–85.	No relevant data
Fuchs K, Brard L, Hodgman D, Silver H. Prostaglandin E1 gel vs. oxytocin for induction of labor at term. Am J Obstet Gynecol 2006;195(Suppl. 1):101.	No relevant data
Gemer O, Kapustian V, Harari D, Sassoon E, Segal S. Sweeping of membranes vs. intracervical prostaglandin e2 gel for cervical ripening. Randomized trial. J Reprod Med 2001;46:706–8.	No relevant data
Ghanaie, M., F. Mirblouk, R. Godarzi and M. Shakiba (2013). "Effect of outpatient isosorbide mononitrate on success of labor induction." J Babol Uni Med Sci 15: 12–17	Unavailable
Gilad R, Hochner H, Vinograd O, Saam R, Hochner-Celnikier D, Porat S. The CIC Trial - castor oil for induction of contractions in post-term pregnancies. Am J Obstet Gynecol 2012;206(Suppl. 1):77–8.	No relevant data
Gonsoulin W, Moise KJ, Cano L. Efficacy of Dilapan (TM) Laminaria to Intracervical Prostaglandin E2 Gel in Cervical Ripening. Proceedings of 9th Annual Meeting of the Society of Perinatal Obstetricians, 1–4 February 1989, New Orleans, LA, USA, abstract no. 94.	No relevant data
Gordon AJ, Calder AA. Oestradiol applied locally to ripen the unfavourable cervix. Lancet 19772431;2:1319–21.	No relevant data
Gordon-Wright AP, Elder MG. Prostaglandin E2 tablets used intravaginally for the induction of labour. Br J Obstet Gynaecol 1979;86:32–6.	No relevant data
Gowenlock AH, Taylor DS, Sanderson JH. Biochemical and haematological changes during the induction of	No relevant data

Study	Reason for exclusion
labour at term with oxytocin, prostaglandin E-2 and prostaglandin F-2alpha. Br J Obstet Gynaecol 1975;82:215–20.	
Green PS. Intracervical injection of hyaluronidase. Effect on dilatation and length of labor. Am J Obstet Gynecol 1967;99:337–40.	No relevant data
Greer, I., M. McLaren and A. Calder (1988). Endogenous PGE2 and PGE2 alpha Production is Stimulated by Vaginal PGE2 Administration for the Induction of Labour. Proceedings of 11th European Congress of Perinatal Medicine, 10–13 April 1988, Rome, Italy: Abstract no. 57.	Unavailable
Greer, I., M. McLaren, V. Godfree, B. Michie and A. Calder (1988). The Effects of Vaginal Prostaglandin E2 Administration on Plasma Concentrations of Prostaglandin E3 and Prostaglandin F2 Metabolites. Proceedings of 1st European Congress on Prostaglandins in Reproduction, 6–9 July 1988, Vienna, Austria: Abstract no. 108.	No relevant data
Griffin C. Outpatient cervical ripening using sequential oestrogen: a randomised controlled pilot study. Aust N Z J Obstet Gynaecol 2003;43:183.	No relevant data
Hage P, Shaw J, Zarou D, Fleisher J, Wehbeh H. Double blind randomized trial to evaluate the role of outpatient use of PGE 2 in cervical ripening. Am J Obstet Gynecol 1993;168:430.	No relevant data
Harms K, Nguyen C, Toy EC, Baker B. Intravaginal misoprostol versus cervidil for cervical ripening in term pregnancies. Obstet Gynecol 2001;97(Suppl. 4):36.	No relevant data
Henson, B. (1987). "Cervical Ripening with Prostaglandin E2.".	Personal communication
Iftikhar M, Price J, Beattie RB, Heasley RN, Armstrong MJ. Pre-induction cervical ripening in primigravida with unfavourable cervix. A randomised controlled trial using PGE2 intracervical gel or vaginal pessary. J Perinatal Med 1992;20(Suppl. 1):96.	No relevant data
Imsuwan Y, Tanapat Y. Reduction of pregnancy with gestational age more than 41 weeks by membrane stripping to induce labor: a randomized controlled clinical trial. Thai J Obstet Gynaecol 1999;11:267.	No relevant data
Ingemarsson, I., et al. (1991). " Effect of Intracervical Prostaglandin Gel in Postterm Women."	Personal communication.
Jasper MP, Blossom S, Peedicayil A. A Randomised Controlled Trial of Extra Amniotic Saline Infusion and Intracervical Foley Catheter for Cervical Ripening. XVI FIGO World Congress of Obstetrics & Gynecology, Washington DC, USA, 3–8 September 2000, Book 4, pp. 69–70.	No relevant data
Jenssen H, Wright PB. The effect of dexamethasone therapy in prolonged pregnancy. Acta Obstet Gynecol Scand 1977;56:467–73.	No relevant data

Study	Reason for exclusion
Joo, S., et al. (2000). "A comparison of the safety and efficacy of intravaginal prostaglandin e1 (misoprostol) and prostaglandin e2 (dinoprostone) to induce labor." Korean J Obstet Gynecol 43: 444–450.	Unavailable
Kadar N, Tapp A, Wong A. The influence of nipple stimulation at term on the duration of pregnancy. J Perinatol 1990;10:164–6.	No relevant data
Knogler, W., C. Egarter, R. Fitz and H. P (1988). Comparison of Prostaglandin (PG) E2 Vaginal Gel and Tablet for Elective Induction of Labor. Proceedings of 1st European Congress on Prostaglandins in Reproduction, 6–9 July,1988, Vienna, Austria: abstract no. 111	No relevant data
Knox GE, Huddleston JF, Flowers CE. Management of prolonged pregnancy: results of a prospective randomized trial. Am J Obstet Gynecol 1979;134:376–84.	No relevant data
Krammer J, O'Brien W, Williams M. Outpatient cervical ripening does not affect gestational age at delivery. Am J Obstet Gynecol 1995;172:425.	No relevant data
Lamont RF, Neave S, Baker AC, Steer PJ. Intrauterine pressures in labours induced by amniotomy and oxytocin or vaginal prostaglandin gel compared with spontaneous labour. Br J Obstet Gynaecol 1991;98:441–7.	No relevant data
Lange AP, Secher NJ, Westergaard JG, Skovgard I. Neonatal jaundice after labour induced or stimulated by prostaglandin E2 or oxytocin. Lancet 1982;1:991–4.	No relevant data
Lass, A., D. Rosen, R. Nahum, S. Markov, H. Kaneti, M. Fejgin and e. al (1994). Variable Decelerations during Pre-induction Oxytocin Challenge Test Predict Fetal Distress During Labor In Pregnancies With Uncomplicated Oligohydramnios. Proceedings of 14th European Congress of Perinatal Medicine, 5–8 June 1994, Helsinki, Finland: Abstract no. 475.	Unavailable
LeMaire, W., W. Spellacy, A. Shevach and S. Gall (1972). "Changes in plasma estriol and progesterone during labor induced with prostaglandin F2alpha or oxytocin." Prostaglandins 2(2): 93–101	No relevant data
Leijon I, Finnstrom O, Hedenskog S, Ryden G, Tylleskar J. Spontaneous labor and elective induction – a prospective randomized study. II Bilirubin levels in the neonatal period. Acta Obstet Gynecol Scand 1980;59:103–6.	No relevant data
Leijon I, Finnstrom O, Hedenskog S, Ryden G, Tylleskar J. Spontaneous labour and elective induction – a prospective randomised study. Behavioural assessment and neurological examination in the newborn period. Acta Paediatrica Scand 1979;68:553–60.	No relevant data
Li GQ. [Effect of electrode-stimulation point for oxytocic.] Shanghai J Acupunct Moxibustion 1996;15:16.	Not in English

Study	Reason for exclusion
Li WJ, Li ZL, Ha KW. Effect of hyaluronidase on cervical ripening. Chin Med J 1994;107:552–3.	No relevant data
Lindblad A, Ekman G, Marsal K, Ulmsten U. Fetal circulation 60 to 80 minutes after vaginal prostaglandin E2 in pregnant women at term. Arch Gynecol 1985;237:31–6.	No relevant data
Lindmark G, Nilsson BA. A comparative study of uterine activity in labour induced with prostaglandin F2alpha or oxytocin and in spontaneous labour I. Pattern of uterine contractions. Acta Obstet Gynecol Scand 1976;55:453–60.	No relevant data
Loto OM, Ikuomola AA, Ayuba I, Onwudiegwu U. Comparative study of outcome of induction of labor using 25 µg and 50 µg of vaginal misoprostol. Int J Gynecol Obstet 2012;119(Suppl. 3):805. Loto OM, Ikuomola AA, Ayuba II, Onwudiegwu U. Comparative study of the outcome of induction of labor using 25 µg and 50 µg of vaginal misoprostol. J Matern Fetal Neonatal Med 2012;25:2359–62.	No relevant data (abstract and full text)
Lyons C, Rumney P, Huang W, Morrison E, Thomas S, Nageotte M, et al. Outpatient cervical ripening with oral misoprostol post-term: induction rates decreased. Am J Obstet Gynecol 2001;184:S116.	No relevant data
Leszczyn ´ska-Gorzelak, B., A. Jakimiuk and J. Oleszczuk (1993). " Cortisol in amniotic fluid during induced deliveries by prostaglandin E2." Zentralblatt fur Gynakologie 115: 550–552.	Not in English
Lindholm, P. (1981). "Induced labor: A comparative study of prostaglandin gel placed in the cervix and parenteral oxytocin." Ugeskr Laeger 143: 878–881	Not in English
MacKenzie IZ, Annan B, Jackson C, Hurley P, Hey F, Newman M. A Randomised Trial Comparing a Non-biodegradable Polymer PGE2 Pessary with a Glyceride PGE2 Pessary for Labour Induction. 12th World Congress of Gynecology and Obstetrics, 23–28 October 1988, Rio de Janeiro, Brazil, pp. 199–200. Mackenzie IZ, Annan B, Jackson C, Hurley P, Hey F, Newman M. A Randomized Trial Comparing a Non-biodegradable Polymer PGE2 Pessary with a Glyceride PGE2 Pessary for Labour Induction. 12th FIGO World Congress of Gynecology and Obstetrics, 23–28 October 1988, Brazil, abstract no. 199.	No relevant data
MacKenzie IZ, Embrey MP. Cervical ripening with intravaginal prostaglandin E2 gel. Br Med J 1977;2:1381–4.	No relevant data
MacLennan, A., A. Day and R. Green (1988). Intravaginal PGF2alpha vs Intravenous Oxytocin to Stimulate Labour After Membrane Rupture. A Randomised Controlled Trial. Proceedings of 1st European Congress on Prostaglandins in Reproduction 6–9 July 1988 Vienna Austria Abstract no. 118	No relevant data
Macpherson M, Welch C, Powell M, Filshie M. A Trial to Compare Lamicel, a New Induction Agent with	No relevant data

Study	Reason for exclusion
Prostaglandin E2 Gel to Ripen the Cervix Prior to Induction of Labour. Proceedings of 23rd British Congress of Obstetrics and Gynaecology, 12–15 July 1983, Birmingham, UK, abstract no. 79.	
Mamo J. Intravaginal oestriol pessary for preinduction cervical ripening. Int J Gynecol Obstet 1994;46:137.	No relevant data
Manabe, Y., S. Yoshimura, T. Mori and T. Aso (1985). "Plasma levels of 13, 14-dihydro-15-keto prostaglandin F2 alpha, estrogens, and progesterone during stretch-induced labor at term." Prostaglandins 30(1): 141–152	No relevant data
Manidakis G, Sifakis S, Orfanoudaki E, Mikelakis G, Prokopakis P, Magou M, et al. Prostaglandin versus stripping of membranes in management of pregnancy beyond 40–1 weeks. Eur J Obstet Gynecol Reprod Biol 1999;86:S79–80.	No relevant data
Martin DH, Thompson W, Pinkerton JH, Watson JD. A randomized controlled trial of selective planned delivery. Br J Obstet Gynaecol 1978;85:109–13.	No relevant data
Martin, J., J. Sessums, P. Howard, R. Martin and J. Morrison (1989). "Alternative approaches to the management of gravidas with prolonged-postterm-postdate pregnancies." J Miss State Med Assoc 30: 105–111.	INCLUDED
Martinez, A., L. Rivera and C. Arangel (2004). Acupuncture as an Alternative Technique for Uterine Contraction in Term Pregnant Patients. 5th World Congress on Controversies in Obstetrics and Gynecology Las Vegas NV USA 3–6 June 2004.	Unavailable
McColgin SW, Bennett WA, Roach H, Cowan BD, Martin JN, Morrison JC. Parturitional factors associated with membrane stripping. Am J Obstet Gynecol 1993;169:71–7.	No relevant data
Megalo, A. and P. Hohlfeld (1999). "Cervical ripening with vaginal misoprostol or PGE2 gel." Gynakol Geburtshilfliche Rundsch 39: 165.	Not in English
Moise, K., L. Cano and D. Hesketh (1991). A Prospective Randomized Comparison of a New Synthetic Laminaria, Intracervical Prostaglandin E2 gel, and Oxytocin for Preinduction Ripening of the Term Cervix. Proceedings of 39th Annual Clinical Meeting of the American College of Obstetricians and Gynecologists, 1991, USA, : Abstract no. 24.	Unavailable
Mokgokong, E. (1974). "Use of prostaglandins in minor cephalopelvic disproportion and abnormal uterine action." S Afr Med J 48(Suppl)(Oct): 15–19	No relevant data
Mukhopadhyay M, Lim KJ, Fairlie FM. Is Propess a better method of induction of labour in nulliparous women? J Obstet Gynaecol 2002;22:294–5.	Included
Mollo, M. (1991). "Trial to Assess the Effects of PGE2 Vaginal Tablets vs iv Oxytocin for Induction in Pregnancies with Favourable Cervical Scores."	Personal communication.

Study	Reason for exclusion
Nesbitt, R. and G. Cirigliano (1961). "Use of relaxin during parturition: Clinical observations." N Y State J Med 61(Jan 1): 90–97	No relevant data
Mariani Neto, C., A. Delbin and R. do Val Júnior (1988). "Tocographic pattern induced by misoprostol." Rev Paul Med 106: 205–208.	Not in English
Nikolov, A., A. Dimitrov, K. Krusteva and S. Nashar (2003). "Study of the effect of Propess for ripening of the unfavorable cervix for the induction of labor due to medical indications." Akush Ginekol 42: 5–8.	Not in English
Nilsson B, Bremme K. Prediction of start of contractions in labor induced with oral prostaglandin E2 or oxytocin: a life table analysis approach. Int J Gynecol Obstet 1984;22:145–50.	No relevant data
Norchi S, Zanini A, Ragusa A, Maccario L, Valle A. Induction of labor with intravaginal prostaglandin E2 gel. Int J Gynecol Obstet 1993;42:103–7.	No relevant data
Nuutila M, Cacciatore B, Ylikorkala O. Effect of local prostaglandin E2 on uterine and fetal Doppler flow in pregnancy-induced hypertension. Hypertens Pregn 1997;16:357–66.	No relevant data
Rees, A. (1992). "Randomised Trial Comparing Oxytocin with Vaginal Prostaglandin E2 Gel in the Induction of Labour in the Presence of Ruptured Membranes."	Personal communication.
Paul, R. and R. Romero (1988). "Clinical Trial of Induction vs Expectant Management in Post-Term Pregnancy."	Personal communication.
Parker, M. (1990). "Comparison of Prostaglandin E2 Gel vs Vaginal Tablet for Cervical Ripening."	Personal communication.
Palermo MSF, Damiano MS, Lijdens E, Cassale E, Monaco A, Gamarino S, et al. Dinoprostone vs oestradiol for induction to delivery Clinical controlled trial. Acta Obstet Gynecol Scand 1997;76:97.	No relevant data
Patterson WM. Amniotomy, with or without simultaneous oxytocin infusion. J Obstet Gynaecol Br Commonwealth 1971;78:310–16.	No relevant data
Perales, A., D. VJ, J. Monleon-Sancho, R. Grifol, D. R, M. JA and e. al. (1994). Pulsatile Oxytocin Challenge Test. Proceedings of 14th European Congress of Perinatal Medicine, 5–8 June 1994,Helsinki, Finland: Abstract no. 520.	Unavailable
Polvi HJ, Pirhonen JP, Erkkola RU. Vaginal and intracervical prostaglandin E2 for cervical ripening: a Doppler study of hemodynamic effects. Am J Perinatol 1994;11:337–9.	No relevant data
Porat S. The Use of Castor Oil as a Labor Initiator in Post-Date Pregnancies. 2006. URL: http://clinicaltrials.gov/ (accessed 21 March 2006).	Non-RCT
Pranuth, i. R., A. Padmaja and a. P. Padmaj (2011). Comparison of Oral Misoprostol with Vaginal Misoprostol For Induction of Labour. . 54th All India Congress of Obstetrics and	Unavailable

Study	Reason for exclusion
Gynaecology, 5–9 January 2011, Hyderabad, Andhra Pradesh, India: Abstract no. 118.	
Romer, A., M. Weigel, W. Zieger and F. Melchert (2000). "Prenatal acupuncture: effects on cervical maturation and duration of labor." Geburtsh Frauenheilk 60: 513–518	Not in English
Reichel, R., P. Husslein, K. Göschen, M. Rasche and H. Sinzinger (1985). "Resorption of prostaglandin E2 following various methods of local administration for ripening of the cervix and end the induction of labor." Wien Klin Wochenschr 97: 500–503.	Not in English
Rangarajan NS, LaCroix GE, Moghissi KS. Induction of labor with prostaglandin. Obstet Gynecol 1971;38:546–50.	No relevant data
Rosa P. A comparison of the efficiency of oxytocin and prostaglandin F2alpha in the treatment of dystocia in the primiparous woman at term. J Gynecol Obstet Biol Reprod 1974;6:571–80.	Not in English
Rudra T. Is Foley's catheter a safe and cost effective way of IOL in low resource countries? Int J Gynecol Obstet 2012;119(Suppl. 3):468.	No relevant data
Saberi F, Abedzadeh M, Sadat Z, Eslami A. Effect of castor oil on induction of labour. J Kashan Uni Med Sci 2008;11:19–23.	Not in English
Sabir N. Randomised Control Trial of the Effect of Advice on Sexual Intercourse after 36 Weeks on Pregnancy Duration and the Rate of Induction of Labour Thereafter. 2007. URL: www.controlled-trials.com/ (accessed 30 October 2007).	INCLUDED – results published in Omar 2013
Sadaty A, Pagano M, Greer C, Sison C, Schaffir J. A randomized trial of vaginal prostaglandin E(2) gel and dinoprostone vaginal insert for induction of labor at term. Prim Care Update Ob Gyns 1998;5:183.	No relevant data
Sahin HG, Sahin HA, Kocer M. Induction of labor in toxemia with misoprostol. Acta Obstet Gynecol Scand 2002;81:252–7	Original reason for exclusion (checked and agreed): Methodological – women not in labour after 12 hours - excluded for all outcomes
Saldivar D, Triana H, Soria A, Guzman A, Cabero L, Farran I, et al. Oral misoprostol versus intracervical dinoprostone for induction of labour in women with an unfavourable cervix. J Perinatal Med 2001;29(Suppl. 1):293.	Not in English
Salmanian R, Khayamzadeh M. Prostaglandin & stripping in ripening of cervix and shortening of labor in post date pregnancies. Int J Gynecol Obstet 2012;119(Suppl. 3):811.	No relevant data

Study	Reason for exclusion
Schreyer P, Sherman DJ, Ariely S, Herman A, Caspi E. Ripening the highly unfavorable cervix with extra-amniotic saline instillation or vaginal prostaglandin E2 application. Obstet Gynecol 1989;73:938–42 –	Original reason for exclusion (checked and agreed): Incomplete reporting of data
Seidl A, Stopfer H, Gruber W, Fröhlich H, Baumgarten K. [Prostaglandins compared with oxytocin for induction of labour at term.] Wien Klin Wochenschr 1976;88:315–18	Not in English
Sellers S, MacKenzie IZ. Prostaglandin Release following Vaginal Prostaglandin Treatment for Labour Induction. In Wood C, editor. The Role of Prostaglandins in Labour. London: RSM Services; 1985. pp. 80–3.	No relevant data
Sharami SH. Comparison of Sublingual and Vaginal Misoprostol in Primiparous Women. 2010. URL: www.irct.ir (accessed 6 December 2010).	Included in the most up to date dataset (Sharami 2014)
So LK, Sung ML, Yeung KK. Induction of Labour by Acupuncture. 9th World Congress of Gynecology and Obstetrics, 26–31 October 1979, Tokyo, Japan, abstract no. 281	No relevant data
Sorensen MB, Evans C, Ekpe A, Cotzias C. Comparison of Three Modes of Administration of Prostaglandin for Induction of Labour. 36th Nordic Congress of Obstetrics and Gynecology, 14–17 June 2008, Reykjavik, Iceland, pp. 123–4.	No relevant data
Sorokin Y, Hallak M, Klein O, Kalderon I, Abramovici H. Effects of induction of labor with prostaglandin E2 on fetal breathing and body movements: controlled, randomized, double-blind study. Obstet Gynecol 1992;80:788–91.	No relevant data
Spellacy WN, Buhi WC, Holsinger KK. The effect of prostaglandin F 2 and E 2 on blood glucose and plasma insulin levels during pregnancy. Am J Obstet Gynecol 1971;111:239–43	No relevant data
Spitzberg E, Yonekura ML. Preinduction cervical ripening with controlled-release PGE2 pessary. Am J Obstet Gynecol 1991;164:313.	No relevant data
Suri V, Dalui R, Guptal, Ray P. Preinduction Cervical Ripening: A Comparison of Extraamniotic Foley Catheter Balloon and Intracervical Prostaglandin E2 gel. XVI FIGO World Congress of Obstetrics & Gynecology, 3–8 September 2000, Washington DC, USA, Book 4, abstract no. 69	No relevant data
Swann O. Induction of labor by stripping membranes. Obstet Gynecol 1958;11:74–8.	No relevant data
Tan ASA, Abu J, Cheng HH, Liauw P. Comparing the efficacy of prepidil gel vs prostin E2 vaginal pessaries	No relevant data

Study	Reason for exclusion
in cervical priming and induction of labour. Int J Gynecol Obstet 1994;46:7.	
Thornton S, Davison JM, Baylis PH. Amniotomy-induced labour is not mediated by endogenous oxytocin. Br J Obstet Gynaecol 1989;96:945–8	No relevant data
Tiwari N, Maru L. Comparative Study of Sublingual versus Pervaginal Misoprostol in Induction of Term Labor. 54th All India Congress of Obstetrics and Gynaecology, 5–9 January 2011, Hyderabad, Andhra Pradesh, India, abstract no. 122.	Unavailable
Toppozada M, El-Ghazzawi E, Meleis M, Abd-Rabbo S. Effect of 9-deoxo-16,16-dimethy-l9-methyleneprostaglandin E2 vaginal gel on the tissues of the pregnant unripe cervix at term. J Obstet Gynaecol 1992;12:228–31	No relevant data
Tuipae S, Khooarmornpattana S. Effectiveness of oral misoprostol for cervical priming in term pre-labor rupture of membranes (PROM). Thai J Obstet Gynaecol 1999;11:276.	No relevant data
Vaisanen-Tommiska M, Mikkola T, Ylikorkala O. Vaginal Nitro Induces Cervical Nitric Oxide Release in Women Postterm. 36th Nordic Congress of Obstetrics and Gynecology, 14–17 June, Reykjavik, Iceland. abstract no. 123.	No relevant data
Varaklis K, Cuming R, Stubblefield P. Misoprostol: a prostaglandin E1 analogue. Int J Gynecol Obstet 1994;46:105.	No relevant data
Vijitrawiwat A, Pongsatha S. A comparison between oral misoprostol 100 micrograms every 3 hours and vaginal misoprostol 50 micrograms every 4 hours for labor induction. Thai J Obstet Gynaecol 2003;15:285.	No relevant data
Vidanagamage RS, Goonewardene IM. The efficacy of two different doses of vaginal isosorbide mononitrate in pre induction cervical ripening: a double blind randomised controlled trial. Ceylon Med J 2011;56:91–100.	No relevant data
Vroman S, Thiery M, Yo Le Sian A, Depiere M, Vanderheyden C, Derom R, et al. A double blind comparative study of prostaglandin F2alpha and oxytocin for the elective induction of labor. Eur J Obstet Gynecol Reprod Biol 1972;4S:115–23.	No relevant data
Ward SJ. Induction of Labour Using Prostaglandin Gel in Patients with a Favourable Cervix. Proceedings of 2nd European Congress on Prostaglandins in Reproduction, 30 April–3 May, The Hague, The Netherlands, abstract no. 143.	Unavailable
Weiss G, Teichman S, Stewart D, Nader D, Wood S, Unemori E. A randomized, double-blind, placebocontrolled	No relevant data

Study	Reason for exclusion
trial of relaxin for cervical ripening in post-delivery date pregnancies. Ann N York Acad Sci 2009;1160:385–6.	
Wei ZT, Wang XY. Analysis of 98 cases about labour induction in women at term with mifepristone and oxytocin. J Weifang Med Coll 2000;22:184–5.	Unavailable
Weissberg SM, Spellacy WN. Membrane stripping to induce labor. J Reprod Med 1977;19:125–7.	No relevant data
Wildemeersch DA, Schellen AM. Double-blind trial of prostaglandin F2alpha and oxytocin in the induction of labour. Curr Med Res Opin 1976;4:263–6.	No relevant data
Yeung KK, Pang JC. Oral prostaglandins E2 and F2alpha in the induction of labour. Aust N Z J Obstet Gynaecol 1977;17:32–5	No relevant data
Zimmer EZ, Jakobi P, Weissman A. The effect of ripening the cervix with prostaglandin E2 or transcervical catheter on fetal breathing and body movements. J Maternal-Fetal Invest 1996;6:104–6.	No relevant data

Economic studies

Table 50: Studies excluded from the ecomomic review for the pharmacological and mechanical methods for the induction of labour

Study	Reason for Exclusion
Alfirevic, Z., Keeney, E., Dowswell, T., Welton, N. J., Medley, N., Dias, S., Jones, L. V., Gyte, G., Caldwell, D. M., Which method is best for the induction of labour? A systematic review, network meta-analysis and cost-effectiveness analysis, Health Technology Assessment (Winchester, England)Health Technol Assess, 20, 1-584, 2016	The health economic model in this report was updated for this guideline
Bierut, A., Dowgiallo-Smolarczyk, J., Pieniazek, I., Stelmachowski, J., Pacocha, K., Sobkowski, M., Baev, O. R., Walczak, J., Misoprostol Vaginal Insert in Labor Induction: A Cost-Consequences Model for 5 European Countries-An Economic Evaluation Supported with Literature Review and Retrospective Data Collection, Advances in Therapy, 33, 1755-1770, 2016	Cost-consequence analysis - indirect comparisons calculated using Bucher method

Appendix L – Research recommendations

Research recommendations for review question: What are the benefits and harms of pharmacological and mechanical methods in induction of labour?

No research recommendations were made for this review question.

Appendix M – Post-hoc analysis

Post-hoc extra-amniotic saline infusion analysis for review question: What are the benefits and harms of pharmacological and mechanical methods in induction of labour?

Overview of evidence

Following the committee's original discussion, post-hoc analysis was requested to examine the impact of the use of EASI in some studies that had been coded as Foley or Cook's catheter (balloon catheters). Of the 77 papers examining balloon catheters, 9 were re-coded as either Foley+EASI, or Cook's+EASI. Recoding can be seen in Table 51

Table 51: Balloon catheter study breakdown, including re-coding to examine the effects of extra-amniotic saline infusion (EASI). (Studies in red font included the use of EASI)

Trial Name	Arm 1 code	Arm 2 code	Arm 3 code	Arm 4 code	Arm 5 code	No VD <24	Hyper-stimulation with FHR	Caesarean section	Perinatal mortality	Maternal mortality	Maternal satisfaction	Instrumental delivery	NICU admission	Epidural
Adeniji 2005	Vaginal misoprostol >50mcg	Foley catheter				yes	yes	yes	yes	yes	yes	yes		
Aduloju 2016	Vaginal misoprostol <50mcg	Foley catheter					yes	yes		yes			yes	
Al-Taani 2004	Vaginal PGE2 (tablet)	Foley catheter						yes	yes	yes		yes	yes	
Atad 1996	Vaginal PGE2 (tablet)	IV oxytocin	Double balloon/Cook's catheter					yes						

Trial Name	Arm 1 code	Arm 2 code	Arm 3 code	Arm 4 code	Arm 5 code	No VD <24	Hyper-stimulation with FHR	Caesarean section	Perinatal mortality	Maternal mortality	Maternal satisfaction	Instrumental delivery	NICU admission	Epidural
Barda 2018	Vaginal PGE2 (tablet)	Foley catheter						yes				yes	yes	
Biron-Shental 2004	Vaginal PGE2 (gel)	Double balloon/Cook's catheter												
Chai 2018	Vaginal PGE2 pessary (normal release)	Foley catheter						yes						
Chavakula 2015	Vaginal misoprostol <50mcg	Foley catheter				yes	yes	yes			yes		yes	
Chung 2003	Vaginal misoprostol <50mcg	Foley catheter					yes	yes				yes	yes	yes
Cromi 2011	Vaginal PGE2 (pessary – slow release)	Foley catheter					yes	yes	yes			yes	yes	yes
Cromi 2012	Vaginal PGE2 (pessary – slow release)	Double balloon/Cook's catheter				yes	yes	yes				yes	yes	yes

Trial Name	Arm 1 code	Arm 2 code	Arm 3 code	Arm 4 code	Arm 5 code	No VD <24	Hyper-stimulation with FHR	Caesarean section	Perinatal mortality	Maternal mortality	Maternal satisfaction	Instrumental delivery	NICU admission	Epidural
Dalui 2005	Intracervical PGE2	Foley catheter					yes	yes				yes		
Deo 2012	Vaginal PGE2 (gel)	Vaginal misoprostol <50mcg	Foley catheter					yes				yes		
Deshmukh 2011	Intracervical PGE2	Foley catheter						yes	yes			yes	yes	
Edwards 2014	Vaginal PGE2 (pessary – slow release)	Foley catheter				yes		yes					yes	
Gelisen 2005	No treatment	Vaginal misoprostol >50mcg	IV oxytocin	Foley catheter			yes	yes	yes				yes	
Ghanaie 2013	Intracervical PGE2	Foley catheter					yes	yes					yes	
Greybush 2001	Vaginal misoprostol <50mcg	Foley catheter					yes	yes		yes			yes	yes
Haugland 2012	Foley catheter	Double balloon/Cook's catheter						yes				yes		

Trial Name	Arm 1 code	Arm 2 code	Arm 3 code	Arm 4 code	Arm 5 code	No VD <24	Hyper-stimulation with FHR	Caesarean section	Perinatal mortality	Maternal mortality	Maternal satisfaction	Instrumental delivery	NICU admission	Epidural
Hemlin 1998	Intracervical PGE2	Foley catheter + EASI						yes				yes		
Henry 2013	Vaginal PGE2 (gel)	Foley catheter				yes	yes	yes			yes	yes	yes	
Hofmeyr 2001	Vaginal PGE2 (gel)	Titrated (low dose) oral misoprostol solution	Foley catheter			yes	yes	yes	yes	yes		yes	yes	
Hoppe 2016	Foley catheter	Double balloon/Cook's catheter				yes		yes					yes	yes
Hudon 1999	Intracervical PGE2	Foley catheter					yes	yes						
Jagani 1982	No treatment	IV oxytocin	Amniotomy	Foley catheter	Laminaria			yes						
Jozwiak 2011	Vaginal PGE2 (gel)	Foley catheter					yes	yes		yes		yes	yes	yes
Jozwiak 2013	Vaginal PGE2 (pessary – slow release)	Foley catheter						yes		yes		yes	yes	yes

Trial Name	Arm 1 code	Arm 2 code	Arm 3 code	Arm 4 code	Arm 5 code	No VD <24	Hyper-stimulation with FHR	Caesarean section	Perinatal mortality	Maternal mortality	Maternal satisfaction	Instrumental delivery	NICU admission	Epidural
Jozwiak 2014	Vaginal misoprostol <50mcg	Foley catheter						yes		yes		yes	yes	yes
Kandil 2012	Vaginal misoprostol <50mcg	Foley catheter					yes	yes				yes	yes	
Karatas 2016	Vaginal PGE2 (pessary – slow release)	Foley catheter						yes						
Kashanian 2006a	Vaginal misoprostol <50mcg	Foley catheter						yes						
Khatib 2019	Vaginal PGE2 (pessary – slow release)	Double balloon/Cook's catheter						yes				yes		
Lemyre 2006	Vaginal misoprostol <50mcg	Foley catheter												
Levine 2016	Vaginal misoprostol <50mcg	Foley catheter						yes					yes	yes
Lewis 1983	No treatment	Vaginal PGE2	Foley catheter				yes	yes						

Trial Name	Arm 1 code	Arm 2 code	Arm 3 code	Arm 4 code	Arm 5 code	No VD <24	Hyper-stimulation with FHR	Caesarean section	Perinatal mortality	Maternal mortality	Maternal satisfaction	Instrumental delivery	NICU admission	Epidural
		pessary (normal release)												
Lim 2018	Vaginal PGE2 (tablet)	Double balloon/Cook's catheter				yes		yes			yes		yes	yes
Lokkegaard 2015	Vaginal PGE2 (tablet)	Double balloon/Cook's catheter						yes				yes	yes	
Lyndrup 1994	Vaginal PGE2 pessary (normal release)	Foley catheter + EASI				yes	yes	yes			yes	yes		
Mawire 1999 *	Foley catheter + EASI	Extra-amniotic PGE2 or PGF2						yes	yes	yes		yes	yes	
Mei-Dan 2012	Foley catheter + EASI	Double balloon/Cook's catheter						yes			yes	yes		
Mei-Dan 2014	Foley catheter + EASI	Double balloon/Cook's catheter + EASI						yes			yes	yes		yes

Trial Name	Arm 1 code	Arm 2 code	Arm 3 code	Arm 4 code	Arm 5 code	No VD <24	Hyper-stimulation with FHR	Caesarean section	Perinatal mortality	Maternal mortality	Maternal satisfaction	Instrumental delivery	NICU admission	Epidural
Moini 2003	Intracervical PGE2	Foley catheter + EASI						yes						
Moraes Filho 2010	Vaginal misoprostol <50mcg	Foley catheter				yes	yes	yes		yes				
Movahed 2016	Nitric oxide	Foley catheter	Laminaria					yes						
Mundle 2018	Oral misoprostol tablet <50mcg	Foley catheter				yes	yes	yes	yes	yes	yes	yes	yes	yes
Niromanesh 2003	Vaginal PGE2 (tablet)	Foley catheter						yes						
Noor 2015	Vaginal misoprostol <50mcg	Foley catheter					yes	yes		yes			yes	
Ntsaluba 1997	Intracervical PGE2	Foley catheter					yes							
Ophir 1992	Vaginal PGE2 (tablet)	Foley catheter						yes	yes			yes		
Orhue 1995	Vaginal PGE2 pessary	IV oxytocin plus	Foley catheter				yes	yes		yes		yes		

Trial Name	Arm 1 code	Arm 2 code	Arm 3 code	Arm 4 code	Arm 5 code	No VD <24	Hyper-stimulation with FHR	Caesarean section	Perinatal mortality	Maternal mortality	Maternal satisfaction	Instrumental delivery	NICU admission	Epidural
	(normal release)	amniotomy												
Owolabi 2005	Vaginal misoprostol >50mcg	Foley catheter					yes	yes				yes	yes	
Peedicayil 1998	Intracervical PGE2	Foley catheter												
Pennell 2009	Vaginal PGE2 (gel)	Foley catheter	Double balloon/Cook's catheter			yes	yes	yes				yes	yes	yes
Prager 2008	Vaginal PGE2 (gel)	Vaginal misoprostol <50mcg	Foley catheter					yes		yes		yes	yes	yes
Quinn 1981 *	Foley catheter + EASI	Extra-amniotic PGE2 or PGF2						yes	yes			yes		
Rouben 1993	Vaginal PGE2 (gel)	Foley catheter + EASI						yes						
Saad 2019	Foley catheter	Laminaria						yes				yes		yes
Saleem 2006	Vaginal PGE2 pessary	Vaginal misoprostol >50mcg	Foley catheter					yes						

Trial Name	Arm 1 code	Arm 2 code	Arm 3 code	Arm 4 code	Arm 5 code	No VD <24	Hyper-stimulation with FHR	Caesarean section	Perinatal mortality	Maternal mortality	Maternal satisfaction	Instrumental delivery	NICU admission	Epidural
	(normal release)													
Salim 2011	Foley catheter	Double balloon/Cook's catheter				yes		yes				yes		yes
Sayed 2016	Foley catheter	Double balloon/Cook's catheter						yes			yes			
Sciscione 1999	Intracervical PGE2	Foley catheter					yes	yes						yes
Sciscione 2001	Vaginal misoprostol >50mcg	Foley catheter				yes	yes	yes						yes
Shechter-Maor 2015	Vaginal PGE2 (pessary – slow release)	Double balloon/Cook's catheter						yes			yes	yes		yes
Sheikher 2009	Vaginal misoprostol <50mcg	Oral misoprostol tablet >50mcg	Foley catheter			yes		yes					yes	
Sherman 2001 *	Foley catheter + EASI	Extra-amniotic PGE2 or PGF2						yes				yes		

Trial Name	Arm 1 code	Arm 2 code	Arm 3 code	Arm 4 code	Arm 5 code	No VD <24	Hyper-stimulation with FHR	Caesarean section	Perinatal mortality	Maternal mortality	Maternal satisfaction	Instrumental delivery	NICU admission	Epidural
Solt 2019	Foley catheter	Double balloon/Cook's catheter						yes						
Somirathne 2017	Oral misoprostol tablet >50mcg	Foley catheter						yes	yes	yes		yes	yes	
St Onge 1995	Intracervical PGE2	Foley catheter						yes				yes		
Suffecool 2014	Vaginal PGE2 (pessary – slow release)	Double balloon/Cook's catheter						yes				yes		
Surita 2005	Hyaluronidase	Foley catheter						yes			yes			
Tabowei 2003	Vaginal misoprostol <50mcg	Foley catheter				yes	yes	yes	yes			yes	yes	
Ten Eikelder 2016	Oral misoprostol tablet >50mcg	Foley catheter					yes	yes	yes	yes	yes	yes	yes	yes
Thomas 1986	PGF2 gel	Foley catheter						yes				yes		

Trial Name	Arm 1 code	Arm 2 code	Arm 3 code	Arm 4 code	Arm 5 code	No VD <24	Hyper-stimulation with FHR	Caesarean section	Perinatal mortality	Maternal mortality	Maternal satisfaction	Instrumental delivery	NICU admission	Epidural
Tulek 2018	IV oxytocin	Double balloon/Cook's catheter						yes					yes	
Ugwu 2013	Vaginal misoprostol <50mcg	Foley catheter					yes	yes		yes		yes	yes	
Vahid Roudsari 2011	Vaginal misoprostol <50mcg	Foley catheter						yes						
Yuen 1996	Intracervical PGE2	Vaginal PGE2 pessary (normal release)	Double balloon/Cook's catheter			yes	yes	yes				yes		

* (Mawire 1999, Quinn 1981, and Sherman 2001) actually used a cervical catheter or specifically Foley in both groups to deliver either the EASI or other intervention in cases where it was a gel for example (eg .Foley+ EASI and Foley+ EA PGF2), but the second intervention fulfils the criteria for coding as it currently is (eg. EA PGF2 instead of Foley+ EA PGF2).

The nine studies that used EASI (shown in red font in the table above) were: Hemlin 1998, Lyndrup 1994, Mawire 1999, Mei-Dan 2012, Mei-Dan 2014, Moini 2003, Quinn 1981, Rouben 1993, Sherman 2001. Three of these studies (Mawire 1999, Quinn 1981, and Sherman 2001) used a cervical catheter or specifically Foley in both groups to deliver either the EASI or other intervention in cases where it was a gel for example (eg. Foley+ EASI and Foley+ EA PGF2), however, the second intervention fulfils the criteria for coding as it was, and was not re-coded.

Due to limited data (equivalent comparisons, and outcomes), pairwise analysis was possible for one comparison (Foley versus intracervical gel), for two outcomes (caesarean birth and instrumental birth), where it was possible to assess the impact of EASI by subgrouping

Quality of the evidence

Quality of the evidence was downgraded for high risk of bias in blinding of participants and/or personnel, as this is not possible due to the nature of the two interventions being compared (catheter or gel). Additionally, there was unclear risk of bias for all studies for selective reporting, and for most studies for random sequence generation.

Quality of evidence was also downgraded due to imprecision (wide confidence intervals) and inconsistency (largely seen in EASI studies).

Evidence statement

Caesarean birth and Instrumental birth

There were no significant or clinical differences between intracervical gel and Foley; overall or for the subgroups of Foley alone or Foley+EASI.

Evidence table

Table 52: Data used for post-hoc EASI analysis

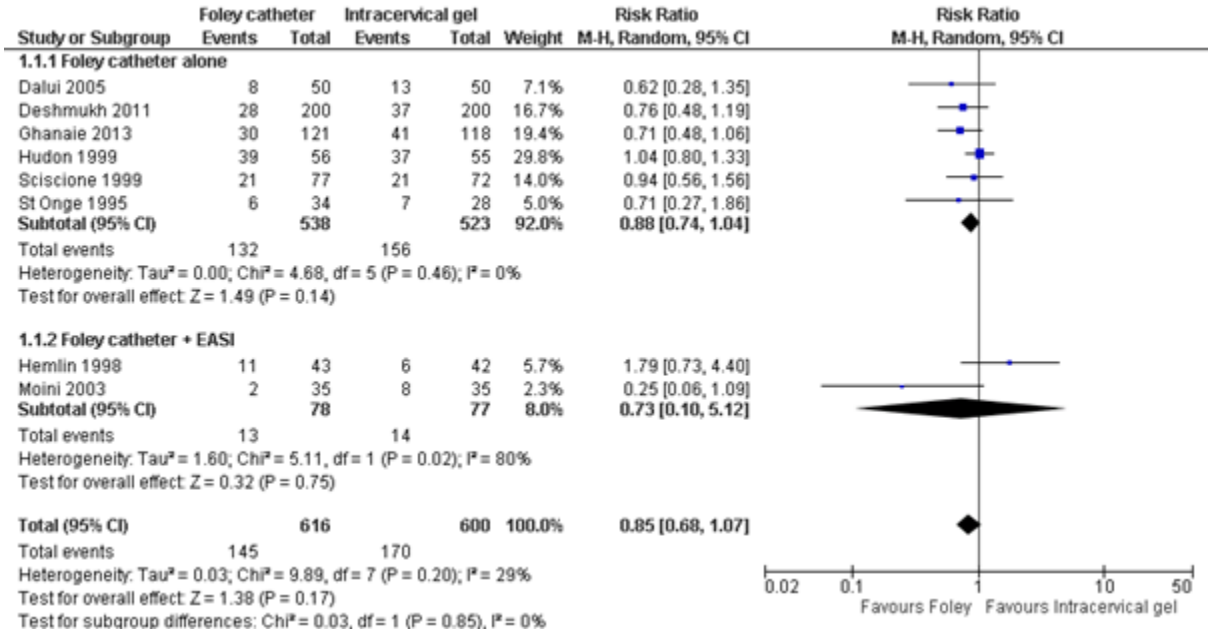
	Caesarean birth				Instrumental birth			
Trial Name	Gel events	Gel total	Foley events	Foley total	Gel events	Gel total	Foley events	Foley total
Foley alone versus intracervical gel								
Dalui 2005	13	50	8	50	10	50	4	50
Deshmukh 2011	37	200	28	200	6	200	8	200
Ghanaie 2013	41	118	30	121	NA	NA	NA	NA
Hudon 1999	37	55	39	56	NA	NA	NA	NA
Sciscione 1999	21	72	21	77	NA	NA	NA	NA
St Onge 1995	7	28	6	34	8	28	13	34
Foley+EASI versus intracervical gel								
Hemlin 1998	6	42	11	43	3	42	1	43
Moini 2003	8	35	2	35	NA	NA	NA	NA

NA: not available; EASI: extra-amniotic saline infusion

Forest plots for the balloon catheter study breakdown: effects of catheter plus extra-amniotic saline infusion (EASI) compared to catheter alone.

Critical outcome

Figure 138: Caesarean birth



Important outcome

Figure 139: Instrumental birth

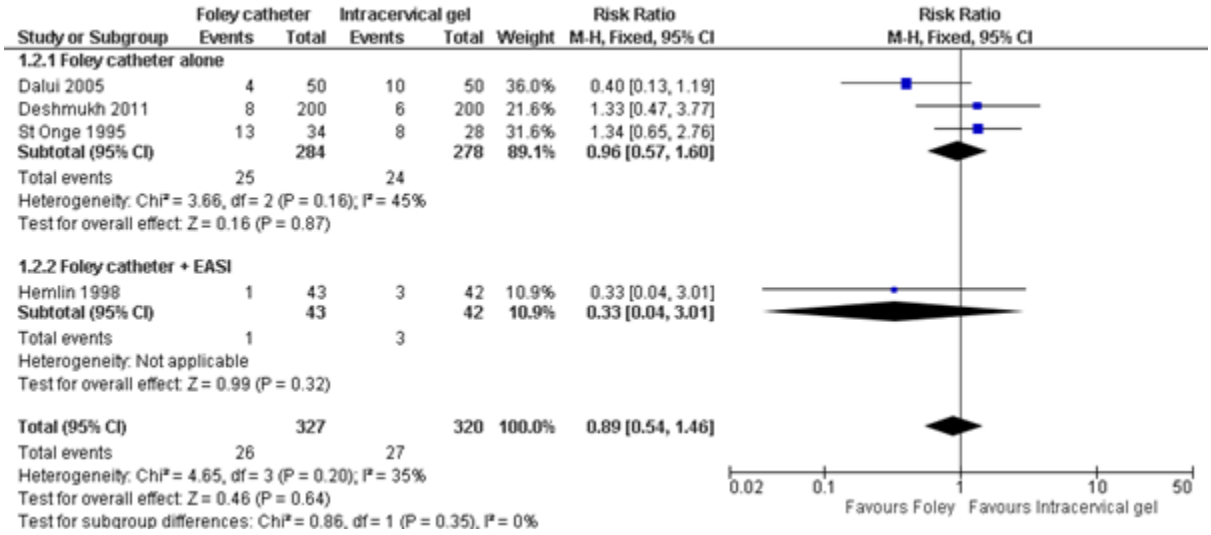


Table 53: GRADE table for the balloon catheter study breakdown: effects of catheter plus extra-amniotic saline infusion (EASI) compared to catheter alone

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Foley catheter	Intracervical gel (Control)	Relative (95% CI)	Absolute	Quality	Importance
Caesarean birth												
8	randomised trials	very serious[1]	no serious inconsistency[2]	no serious indirectness	serious[3]	none	145/616 (23.5%)	170/600 (28.3%)	RR 0.85 (0.68 to 1.07)4	42 fewer per 1000 (from 91 fewer to 20 more)	VERY LOW	CRITICAL
Caesarean birth - Foley catheter alone												
6	randomised trials	very serious[1]	no serious inconsistency[2]	no serious indirectness	serious[3]	none	132/538 (24.5%)	156/523 (29.8%)	RR 0.88 (0.74 to 1.04)4	36 fewer per 1000 (from 78 fewer to 12 more)	VERY LOW	CRITICAL
Caesarean birth - Foley catheter + EASI												
2	randomised trials	very serious[5]	very serious[6]	no serious indirectness	very serious[7]	none	13/78 (16.7%)	14/77 (18.2%)	RR 0.73 (0.1 to 5.12)4	49 fewer per 1000 (from 164 fewer to 749 more)	VERY LOW	CRITICAL
Instrumental birth												
4	randomised trials	very serious[1]	no serious inconsistency[2]	no serious indirectness	very serious[7]	none	26/327 (8%)	27/320 (8.4%)	RR 0.89 (0.54 to 1.46)	9 fewer per 1000 (from 39 fewer to 39 more)	VERY LOW	IMPORTANT
Instrumental birth - Foley catheter alone												
3	randomised trials	very serious[1]	no serious inconsistency[8]	no serious indirectness	very serious[7]	none	25/284 (8.8%)	24/278 (8.6%)	RR 0.96 (0.57 to 1.6)	3 fewer per 1000 (from 37 fewer to 52 more)	VERY LOW	IMPORTANT
Instrumental birth - Foley catheter + EASI												
1	randomised trials	very serious[5]	no serious inconsistency[9]	no serious indirectness	very serious[7]	none	1/43 (2.3%)	3/42 (7.1%)	RR 0.33 (0.04 to 3.01)	48 fewer per 1000 (from 69 fewer to 144 more)	VERY LOW	IMPORTANT

CI: confidence interval; EASI: extra-amniotic saline infusion; RR: risk ratio

[1] High ROB in one domain in all studies, unclear in at least 2 domains in majority of studies; [2] i2=0%; [3] 95%CI crosses one default MID boundary (0.8 to 1.25); [4] random effects model used as large heterogeneity in one subgroup; [5] High ROB in one domain in all studies, unclear in at least 2 domains in all studies; [6] i2=80% (random effects model used); [7] 95%CI crosses two default MID boundaries (0.8 to 1.25); [8] i2=45%; [9] single study for this subgroup

1

Appendix N – Network meta-analysis methods

Network meta-analysis methods for review question: What are the benefits and harms of pharmacological and mechanical methods in induction of labour?

Introduction

The results of conventional pairwise meta-analyses of direct evidence alone do not help to fully inform a number of outcomes for the review on pharmacological and mechanical methods for the induction of labour.

Each pairwise comparison does not fully inform the choice between the different treatments and having a series of discrete pairwise comparisons can be incoherent and difficult to interpret.

In addition, direct comparisons of treatments of clinical interest are not fully available, for all comparisons.

To overcome these issues, a Bayesian NMA was performed. Advantages of performing this type of analysis are as follows.

- It allows the synthesis of evidence on multiple treatments to be compared directly and indirectly without breaking randomisation. If treatment A has never been compared to treatment B in a head to head trial, but these two interventions have been compared to a common comparator, then an indirect treatment comparison can be derived using the relative effects of the two treatments versus the common comparator. Indirect estimates can be calculated whenever there is a path linking two treatments through a set of common comparators, although there does not have to be a common comparator to which all treatments have been compared merely a connected network of treatments. All the randomised evidence is considered simultaneously within the same model.
- For every intervention in a connected network, a relative effect estimate (with its 95% CrIs) between any two interventions can be estimated. These estimates provide a useful clinical summary of the results and facilitate the formation of recommendations based on all relevant evidence, whilst appropriately accounting for uncertainty. Ranks of interventions may also be calculated.
- Estimates from the NMA can be used to directly parameterise treatment effectiveness in cost-effectiveness modelling of multiple treatments.

Conventional fixed effect meta-analysis assumes that the relative effect of one treatment compared to another is the same across an entire set of trials. In a random effects model, it is assumed that the relative effects are different in each trial but that they are from a single common distribution and that this distribution is common across all sets of trials.

NMA assumes that the included studies are similar in terms of factors that might interact with the intervention effects (effect modifiers). So, the relative effect of intervention B vs intervention A would be expected to be similar in all of the studies (if they had included A and B interventions). This assumption is the same as that made in conventional pairwise meta-analysis, but we have to be particularly careful that the studies making different comparisons do not differ in effect modifiers (the data are consistent). We can assess this assumption by

measuring statistical heterogeneity, and also by checking if the direct and indirect estimates are in agreement when there are loops of evidence in the network.

The terms indirect treatment comparisons, mixed treatment comparisons and NMA are used interchangeably. We use the term NMA as the network consists of both indirect treatment comparisons (some trials have a common comparator and some do not) and mixed treatment comparisons (with at least one closed loop, combination of direct and indirect evidence).

Study selection and data collection

For full details see analysis protocol in appendix A.

Outcome measures

The protocol for this review stated that NMA would be considered for all outcomes, if feasible. Based on the availability of data and the formation of a connected network, six outcomes were deemed suitable for synthesis using NMA: vaginal birth not achieved within 24 hours, caesarean birth, hyperstimulation with fetal heart rate changes, NICU admission, instrumental birth and epidural. NMAs were performed on these outcomes for all women requiring induction of labour, and for a subgroup of women with a Bishop score ≤6. The committee agreed it was important to consider results separately according to subgroups based on the Bishop score as their clinical experience suggested that different treatments are likely to be effective depending on the Bishop score.

The remaining outcomes were not suitable for NMA. For the outcomes serious maternal morbidity or mortality and perinatal mortality there were a large number of zero events in the trials (meaning no serious maternal morbidity/mortality or perinatal mortality occurred). This led to difficulties achieving convergence with the NMA models, and it was felt that the results would be unreliable for decision making. Therefore the data for these outcomes are reported with standard pairwise meta-analysis done in RevMan using either Peto odds ratios or risk differences as appropriate based on the event rates.

Results for maternal satisfaction were also reported rarely, using widely varying methods and with no common comparator between the studies that was suitable for NMA. Therefore these results are reported using pairwise meta-analysis, or a narrative summary only, as appropriate.

For the subgroup of women with a Bishop score >6, there were fewer studies, therefore results for this subgroup of women are also reported using standard pairwise meta-analysis, rather than NMA.

Vaginal birth not achieved within 24 hours

Data for vaginal birth not achieved within 24 hours was reported as number of women experiencing an event in the RCTs. The probability of not achieving a vaginal birth within 24 hours in each arm of a trial was estimated as the number of women who did not achieve a vaginal birth within 24 hours, divided by the total number of women in this arm. The results are presented as posterior median ORs.

Hyperstimulation with fetal heart rate changes

Data for hyperstimulation with fetal heart rate changes was reported as number of women experiencing an event in the RCTs. The probability of hyperstimulation with fetal heart rate

changes in each arm of a trial was estimated as the number of women who developed hyperstimulation with fetal heart rate changes, divided by the total number of women in this arm. The results are presented as posterior median ORs.

NICU admission

Data for NICU admission was reported as number of infants experiencing an eventin the RCTs. The probability of NICU admission in each arm of a trial was estimated as the number of infants requiring NICU admission, divided by the total number of infants in this arm. It was noted that the terminology “NICU admission” may be subject to variation between different trials. Some authors clearly distinguished between admission to neonatal intensive care, and admission to a neonatal unit (which offers for high or low dependency care), whilst others used the term “NICU admission” to refer to all infants admitted to a neonatal unit. It was not possible to clearly and consistently distinguish between these definitions, therefore this is recognised as a potential source of heterogeneity in this NMA. The results are presented as posterior median ORs.

Caesarean birth

Data for caesarean birth was reported as number of women experiencing an event in the RCTs. The probability of undergoing a caesarean birth in each arm of a trial was estimated as the number of women who had a caesarean birth, divided by the total number of women in this arm. The results are presented as posterior median ORs.

Instrumental birth

Data for instrumental birth was reported as number of women experiencing an event in the RCTs. The probability of having an instrumental birth in each arm of a trial was estimated as the number of women who had an instrumental birth, divided by the total number of women in this arm. The results are presented as posterior median ORs.

Epidural

Data for epidural use was reported as number of women experiencing an event in the RCTs. The probability of having an epidural in each arm of a trial was estimated as the number of women who had an epidural, divided by the total number of women in this arm. The results are presented as posterior median ORs.

Instability as a result of zero cells

The modelling framework used in this guideline permits the inclusion of zero cells, so typically a continuity correction is not needed. A continuity correction may be helpful when there are many small trials and trials with zero cells, since there is little information within the contrast to inform estimates of treatment effect. In this case, reducing the range of values that could be taken by the prior distributions on the mean and the treatment effect stabilised the model without the need to apply a continuity correction. The more precise uninformative prior specified that the trial baselines and treatment effects variance to be within 10^2 rather than within 100^2. Whilst this restricts the range of the prior distribution, it can still be considered a vague, uninformative prior that covers the full range of potential parameter values.

Methodology

Model description

Both fixed and random effects Binomial models with logit link were run to synthesise data for all six outcomes, for the entire population, and for women with a Bishop score ≤6.

The full description of standard fixed and random effects models using binomial likelihood with logit link can be found in NICE DSU Technical Support Document 2 (Dias 2011). Example of WinBUGS codes used to synthesise data can also be found in Appendix P – Inconsistency checks.

Analysis was undertaken following Bayesian statistics principles and conducted using MCMC simulation techniques implemented in WinBUGS 1.4.3. (Lunn 2000; Spiegelhalter 2001).

For baseline and treatment effects non informative priors were used Normal(mean=0, variance=10000) and a non-informative prior uniform (0,5) was specified for the between study SD for all outcomes except instrumental delivery. For instrumental delivery an empirical prior based on Turner 2015 was used for the between study variance: log-normal(mean=-2.49, variance=2.25).

Each model was run until convergence was satisfactory and then the results were based on further sample of iterations on four chains, the following iterations were used:

	Overall population		Bishop score ≤6	
Outcome	**Burn-ins**	**Post-convergence**	**Burn-ins**	**Post-convergence**
Vaginal delivery	50000	50000	30000	50000
Caesarean birth	30000	30000	30000	30000
NICU admission	70000	70000	70000	70000
Hyperstimulation	90000	90000	90000	90000
Instrumental delivery	60000	60000	60000	60000
Epidural	60000	60000	60000	60000

The posterior mean of the residual deviance, which measures the magnitude of the differences between the observed data and the model predictions of the data, was used to assess and compare the goodness of fit of each model. Smaller values are preferred and in a well-fitting model the posterior mean residual deviance should be close to the number of data points in the network (each study arm contributes 1 data point) (Spiegelhalter 2002).

In addition to comparing how well the models fit the data using the posterior mean of the residual deviance, models were compared using the deviance information criterion (DIC). This is equal to the sum of the posterior mean of the residual deviance and the effective number of parameters and thus penalizes model fit with model complexity. Lower values are preferred and typically differences of 3-5 points are considered meaningful (Spiegelhalter 2002).

For each analysis fixed and random effects models were compared and the best fitting model was chosen based on the criteria described above.

An important assumption made in NMA concerns the consistency, that is, the agreement of the direct and indirect evidence informing the treatment contrasts and there should be no

meaningful differences between these two sources of evidence. The consistency checks were undertaken by TSU and are summarised in Appendix P – Inconsistency checks.

NMA methods references

Dias 2011

Dias S, Welton N, Sutton A, Ades A. NICE DSU Technical Support Document 2: A Generalised Linear Modelling Framework for Pairwise and Network Meta-Analysis of Randomised Controlled Trials, 2011, last updated September 2016, available from http://scharr.dept.shef.ac.uk/nicedsu/technical-support-documents/evidence-synthesis-tsd-series/

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Lunn DJ, Thomas A, Best N, Spiegelhalter D. WinBUGS -- a Bayesian modelling framework: concepts, structure, and extensibility, Statistics and Computing, 10, 325-337, 2000

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Spiegelhalter D, Best N, Carlin B, van der Linde A. Bayesian measures of model complexity and fit. Journal of the Royal Statistical Society: Series B, 64, 583-616, 2002

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Appendix O – Model fit characteristics

Model fit characteristics for review question: What are the benefits and harms of pharmacological and mechanical methods in induction of labour?

Model fit characteristics for no vaginal birth within 24 hours: whole population

Model	Between-study standard deviation (95% CrI)	Residual deviance[a]	DIC
Random effects - consistency (selected – all results reported in this guideline are based on this model)	0.52 (95% CrI: 0.42, 0.63)	302.7	1880.03
Random effects - inconsistency	0.49 (95% CrI: 0.38, 0.61)	298.3	1886.75
Fixed effects – consistency	-	606.6	2097.13

CrI: credible interval; DIC: deviance information criterion

(a) Compare 293 data points

Model fit characteristics for no vaginal birth within 24 hours: subgroup analysis for women with a Bishop score ≤6

Model	Between-study standard deviation (95% CrI)	Residual deviance[a]	DIC
Random effects – consistency (selected – all results reported in this guideline are based on this model)	0.54 (95% CrI: 0.44, 0.67)	246.7	1540.61
Random effects - inconsistency	0.51 (95% CrI: 0.38, 0.66)	244.6	1547.55
Fixed effects - consistency	-	515.2	1737.3

CrI: credible interval; DIC: deviance information criterion

(a) Compare 239 data points

Model fit characteristics for hyperstimulation with fetal heart rate changes: whole population

Model	Between-study standard deviation (95% CrI)	Residual deviance[a]	DIC
Random effects – consistency (selected – all results reported in this guideline are based on this model)	0.64 (95% CrI: 0.45, 0.86)	379.1	1471.7
Random effects - inconsistency	0.59 (95% CrI: 0.38, 0.85)	362.5	1469.2
Fixed effects - consistency	-	495.1	1542.7

CrI: credible interval; DIC: deviance information criterion

(a) Compare 358 data points

Model fit characteristics for hyperstimulation with fetal heart rate changes: subgroup analysis for women with a Bishop score ≤6

Model	Between-study standard deviation (95% CrI)	Residual deviance[a]	DIC
Random effects – consistency (selected – all results reported in this guideline are based on this model)	0.68 (95% CrI: 0.47, 0.93)	306.5	1208.2
Random effects - inconsistency	0.69 (95% CrI: 0.43, 1.00)	294.6	1212.0
Fixed effects - consistency	-	409.9	1274.8

CrI: credible interval; DIC: deviance information criterion
(a) Compare 298 data points

Model fit characteristics for caesarean birth: whole population

Model	Between-study standard deviation (95% CrI)	Residual deviance[a]	DIC
Random effects – consistency (selected – all results reported in this guideline are based on this model)	0.27 (95% CrI: 0.21, 0.33)	1043	5668.63
Random effects - inconsistency	0.26 (95% CrI: 0.19, 0.33)	1038	5742.93
Fixed effects - consistency	-	1243	5741.25

CrI: credible interval; DIC: deviance information criterion
(a) Compare 1011 data points

Model fit characteristics for caesarean birth: subgroup analysis for women with a Bishop score ≤6

Model	Between-study standard deviation (95% CrI)	Residual deviance[a]	DIC
Random effects – consistency (selected – all results reported in this guideline are based on this model)	0.24 (95% CrI: 0.17, 0.31)	783.9	4327.71
Random effects - inconsistency	0.24 (95% CrI: 0.16, 0.33)	783.0	4394.14
Fixed effects - consistency	-	909	4366.38

CrI: credible interval; DIC: deviance information criterion
(a) Compare 758 data points

Model fit characteristics for instrumental birth: whole population

Model	Between-study standard deviation (95% CrI)	Residual deviance[a]	DIC
Random effects model[b] – consistency (selected – all results reported in this guideline are based on this model)	0.12 (95% CrI: 0.04, 0.22)	493.3	2528.99
Random effects - inconsistency	0.17 (95% CrI: 0.05, 0.31)	510.5	2624.28
Fixed effect model	-	504	2526.75

CrI: credible interval; DIC: deviance information criterion

(a) Compare 500 data points

(b) With an informative prior given to the between-study variance

Model fit characteristics for instrumental birth: subgroup analysis for women with a Bishop score ≤6

Model	Between-study standard deviation (95% CrI)	Residual deviance[a]	DIC
Random effects model[b] – consistency(selected – all results reported in this guideline are based on this model)	0.13 (95% CrI: 0.04, 0.25)	346.8	1776.53
Random effects - inconsistency	0.17 (95% CrI: 0.05, 0.34)	359.1	1844.37
Fixed effect model	-	354.7	1774.60

CrI: credible interval; DIC: deviance information criterion

(a) Compare 354 data points

(b) With an informative prior given to the between-study variance

Model fit characteristics for NICU admission: whole population

Model	Between-study standard deviation (95% CrI)	Residual deviance[a]	DIC
Fixed effect – consistency (selected – all results reported in this guideline are based on this model)	-	417.4	1874.98
Random effect – consistency[b]	0.13 (95% CrI: 0.04, 0.25)	410.50	1879.71

CrI: credible interval; DIC: deviance information criterion

(a) Compare 386 data points

(b) Model did not converge

Model fit characteristics for NICU admission: subgroup analysis for women with a Bishop score ≤6

Model	Between-study standard deviation (95% CrI)	Residual deviance[a]	DIC
Fixed effect – consistency (selected – all results reported in this guideline are based on this model)	-	331.1	1480.12
Random effect – consistency[b]	0.14 (95% CrI: 0.05, 0.28)	-	-

CrI: credible interval; DIC: deviance information criterion
(a) Compare 303 data points
(b) Model did not converge

Model fit characteristics for use of epidural: whole population

Model	Between-study standard deviation (95% CrI)	Residual deviance[a]	DIC
Fixed effect	-	190	1062.6
Random effects model – consistency (selected – all results reported in this guideline are based on this model)	0.18 (95% CrI: 0.07, 0.30)	173.8	1059.64
Random effects - inconsistency	0.12 (95% CrI: 0.01, 0.30)	169.8	1076.92

CrI: credible interval; DIC: deviance information criterion
(a) Compare 174 data points

Model fit characteristics for use of epidural: subgroup analysis for women with a Bishop score ≤6

Model	Between-study standard deviation (95% CrI)	Residual deviance[a]	DIC
Fixed effect	-	143.1	773.22
Random effects model[b] – consistency (selected – all results reported in this guideline are based on this model)	0.22 (95% CrI: 0.08, 0.38)	125.9	768.13
Random effects - inconsistency	0.20 (95% CrI: 0.07, 0.39)	122.0	777.86

CrI: credible interval; DIC: deviance information criterion
(a) Compare 123 data points

Appendix P – Inconsistency checks

Inconsistency checks for review question: What are the benefits and harms of pharmacological and mechanical methods in induction of labour?

Introduction

The purpose of this analysis was to assess the consistency assumption in the NMA model used to estimate the comparative effectiveness of pharmacological and mechanical methods for induction of labour. The outcomes included in this analysis were 1) no vaginal birth within 24 hours, 2) hyperstimulation with fetal heart rate changes, 3) caesarean birth, 4) instrumental birth, 5) NICU admission, 6) use of epidural.

Methods

Inconsistency checks

NMA assumes that the included studies are similar in terms of factors that might interact with the intervention effects (effect modifiers). So, the relative effect of intervention B vs intervention A would be expected to be similar in all of the studies (if they had included A and B interventions). This assumption is the same as that made in conventional pairwise meta-analysis, but we have to be particularly careful that the studies making different comparisons do not differ in effect modifiers (the data are consistent). We can assess this assumption by measuring statistical heterogeneity, and also by checking if the direct and indirect estimates are in agreement when there are loops of evidence in the network.

To conduct consistency checks, an appropriate base-case model (fixed or random effects) must be determined beforehand. We assessed and compared the fit of a fixed effect model and a random effects model with either a vague prior distribution (for no vaginal birth within 24 hours, hyperstimulation, caesarean birth, NICU admission, or epidural) or an informative prior distribution (for instrumental birth) on the between-study standard deviation. The vague prior used on the between-study standard deviation was Uniform (0,5), whilst the informative prior was on the variance and was log-normal (-2.49, 1.502). To determine if there is evidence of inconsistency, the selected consistency model (fixed or random effects) was compared to an “inconsistency”, or unrelated mean effects, model (Dias 2013, Dias 2014). The latter is equivalent to having separate, unrelated, meta-analyses for every pairwise contrast, with a common variance parameter assumed in the case of random effects models. Note that the consistency assumption can only be assessed when there are closed loops of direct evidence on 3 treatments that are informed by at least 3 independent sources of evidence (Van Valkenoef 2016)

The posterior mean of the residual deviance, which measures the magnitude of the differences between the observed data and the model predictions of the data, was used to assess and compare the goodness of fit of each model (Spiegelhalter 2002). Smaller values are preferred and in a well-fitting model the posterior mean residual deviance should be close to the number of data points in the network (each study arm contributes 1 data point on average) (Spiegelhalter 2002).

Where the base-case model assumes random effects, if the inconsistency model has smaller heterogeneity (measured by the posterior median between-study standard deviation) compared to the consistency model, then this indicates potential inconsistency in the data.

We performed further checks for evidence of inconsistency through Bucher's method and node-splitting (Dias 2013, Dias 2014, van Valkenhoef 2016, Bucher 1997, Dias 2010). Bucher's method compares the direct and indirect estimates for a contrast in a loop (e.g., A-B-C) where the direct estimate of contrast B versus. C is compared to its corresponding indirect estimate, which is informed from the direct estimates of the other contrasts in the loop (A versus. B and A versus. C) (Dias 2014, Bucher 1997). The node-splitting method permits the direct and indirect evidence contributing to an estimate of a relative effect to be split and compared (Dias 2014, Dias 2010).

There are some small differences between the NMA estimates produced by the NMA models (presented in the main results) and the node-splitting models for exploring inconsistency (presented in forest plot below). Where these occur, these are due to a difference in modelling software, since the node-splitting models were run in the GeMTC package. The NMA estimates presented in the main results were used to compare the safety and effectiveness of the interventions. In a separate exercise, the direct, indirect, and NMA estimates produced by the node-splitting modelling were used to assess how potential inconsistency between the direct and indirect estimates impacted the NMA estimates.

Results

Vaginal birth not achieved within 24 hours

Inconsistency checks were performed using the random effects model, as this had lower DIC than the fixed effects model and there was evidence of heterogeneity. Convergence was satisfactory for the random effects model assuming inconsistency after 20,000 iterations, and the consistency and inconsistency models were compared using results based on samples from a further 20,000 iterations on three chains. WinBUGS code for the inconsistency model is provided below.

Analysis of the full dataset included 141 trials of 20 treatments (293 arms) whilst analysis of the unfavourable cervix dataset included 115 trials of 18 treatments (239 arms).

There was estimated to be high between-study SD, with estimates of 0.52 (95% credible interval [CrI] 0.42-0.63) in the full dataset and 0.55 (95% CrI 0.44-0.67) in the subgroup dataset. This, together with the substantial decrease in model residual deviance and DIC supported selection of the random-effects model as the base-case model.

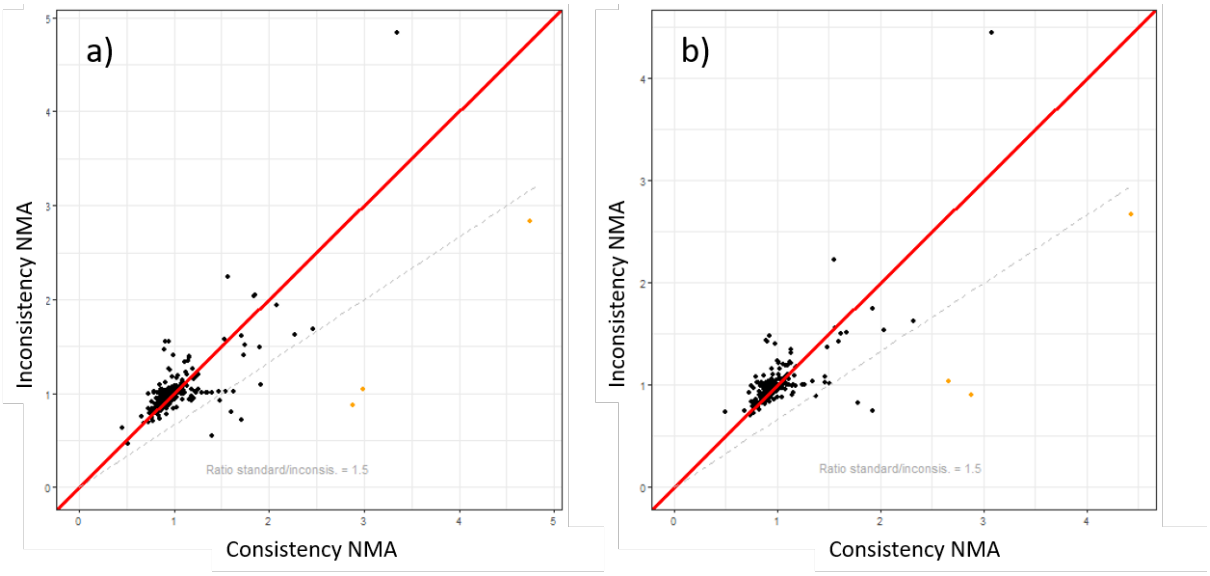
Consistency and inconsistency random-effects NMA models were fitted to the full and subgroup datasets. In both the full and subgroup datasets there was no strong evidence of inconsistency when comparing based on DIC (fewer than 3 units between RE consistency and inconsistency models).

To explore this further, we plotted the contribution of each study arm to the total residual deviance for the inconsistency model vs the consistency model in a dev-dev plot. A simple rule was used to identify study arms with relatively high deviance in the consistency model: points with relatively high deviance were those with mean deviance in the consistency NMA model greater than 2, and where the residual deviance in the consistency NMA was at least 1.5 times that estimated under the inconsistency model. The same two studies, Ulmsten 1985 and Cheng 2008, were flagged by this process in both the full and subgroup analyses. These studies were those flagged in the 2019 analysis.

- Ulmsten 1985 was a three-armed trial comparing two dosing levels of vaginal misoprostol with placebo: dose less than 50 mcg vs dose 50 mcg or more vs placebo.
- Cheng 2008 was a two-armed trial comparing oral misoprostol tablet (dose less than 50 mcg) with IV oxytocin.

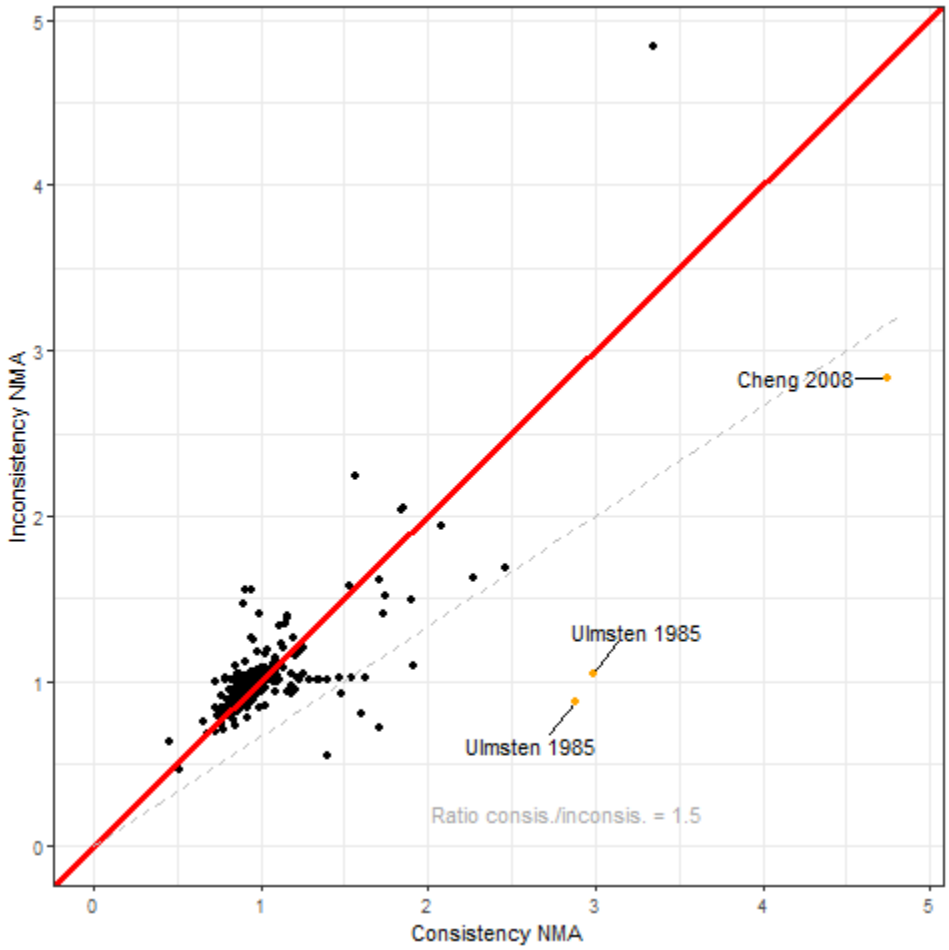
Network meta-analysis (NMA) models of the outcome vaginal delivery in 24 hours, comparison of fixed- (FE) and random-effect (RE) models.

Dataset	Model	Between-study SD (mean)			Mean residual deviance	Data points (arms)	DIC
		Mean	2.5% CrI	97.5% CrI			
Full	Consistency NMA (FE)	-	-	-	606.6	293	2097.13
	Consistency NMA (RE)	0.52	0.42	0.63	302.7	293	1880.03
	Inconsistency NMA (RE)	0.49	0.38	0.61	298.3	293	1886.75
Subgroup (unfav. cervix)	Consistency NMA (FE)	-	-	-	515.2	239	1737.3
	Consistency NMA (RE)	0.55	0.44	0.67	246.70	239	1540.61
	Inconsistency NMA (RE)	0.51	0.38	0.66	244.6	239	1547.55



Dev-dev plots of each study arm's deviance in the RE consistency and inconsistency NMA models of vaginal delivery in 24 hours. Deviance is shown for a) the full dataset and b) the unfavourable cervix subgroup dataset indicating study arms that were relatively poorly predicted by the consistency NMA in orange. Red line indicates line of equivalence.

Dev-dev plot of the outcome vaginal delivery, full dataset, indicating distribution of studies with relatively high deviance in the consistency model.



Random-effects node-splitting models conducted on the full dataset tested direct and indirect evidence on 61 treatment comparisons. Six comparisons showed indication of an inconsistency between direct and indirect evidence when analysing the full dataset: nitric oxide vs placebo; intracervical PGE2 vs placebo; titrated (low dose) oral misoprostol solution vs vaginal misoprostol (dose less than 50 mcg); IV oxytocin vs vaginal PGE2 pessary (normal release); nitric oxide vs vaginal PGE2 (gel); and intracervical PGE2 vs vaginal PGE2 pessary (normal release).

The comparison between vaginal PGE2 (gel) and nitric oxide is highlighted: not only is the direct and indirect evidence judged to be inconsistent, but the two components predict the treatment effect to work in opposite directions (treatments 3 and 15 in the full dataset; treatments 3 and 14 in the unfavourable cervix subgroup). This effect was also noted in the subgroup analysis. Similar inconsistencies were seen between the treatment comparisons between 7 vs 11 and 10 vs 11 in the unfavourable subgroup analysis, where treatment 7 was vaginal misoprostol (dose less than 50 mcg), treatment 10 was oral misoprostol tablet (dose 50mcg or more) and treatment 11 titrated (low dose) oral misoprostol solution.

Direct and indirect estimates of the treatment difference seen in the outcome vaginal delivery in 24 hours, full dataset, between pairs of interventions (LOR). Where the direct and indirect evidence showed inconsistency ($p < 0.05$), comparisons are presented at the top of the table, highlighted in yellow.

Intervention 1	Intervention 2	P - value	Residual deviance	Direct			Indirect		
				Median	2.5% CrI	97.5% CrI	Median	2.5% CrI	97.5% CrI
Consistency model		-	302.6	-	-	-	-	-	-
Placebo	Nitric oxide	0.014	302.9	-0.085	-1.228	1.057	-2.029	-3.107	-1.002
Placebo	Intracervical PGE2	0.001	296.9	-2.785	-3.890	-1.788	-0.475	-1.436	0.461
Titrated (low dose) oral misoprostol solution	Vaginal misoprostol (dose less than 50 mcg)	0.027	301.2	0.614	-0.061	1.299	-0.312	-0.786	0.156
IV oxytocin	Vaginal PGE2 pessary (normal release)	0.040	300.9	-2.899	-5.268	-0.925	-0.701	-1.401	0.011
Nitric oxide	Vaginal PGE2 (gel)	0.006	304.7	0.666	-0.401	1.738	-1.135	-1.826	-0.443
Intracervical PGE2	Vaginal PGE2 pessary (normal release)	0.029	299.4	-0.275	-0.876	0.329	-1.417	-2.270	-0.590
Placebo	Vaginal PGE2 pessary (normal release)	0.266	299.5	-1.005	-3.379	1.136	-2.386	-3.273	-1.518
Placebo	Vaginal misoprostol (dose less than 50 mcg)	0.491	302	-1.532	-3.016	-0.137	-2.117	-2.946	-1.325
Oral misoprostol tablet (dose 50mcg or more)	Titrated (low dose) oral misoprostol solution	0.069	301.9	0.846	-0.610	2.323	-0.564	-1.016	-0.120
Oral misoprostol tablet (dose 50mcg or more)	IV oxytocin	0.110	302.7	-0.528	-1.675	0.589	0.504	-0.090	1.101
Oral misoprostol tablet (dose 50mcg or more)	Mechanical methods – Foley catheter	0.61	300.3	0.438	-1.011	1.910	0.041	-0.402	0.485
Oral misoprostol tablet (dose 50mcg or more)	Vaginal PGE2 (tablet)	0.674	302.2	-0.084	-1.266	1.097	0.190	-0.316	0.699
Oral misoprostol tablet (dose 50mcg or more)	Buccal/sublingual misoprostol	0.552	302.5	-0.582	-1.305	0.135	-0.324	-0.792	0.139
Oral misoprostol tablet (dose 50mcg or more)	Vaginal PGE2 (gel)	0.76	299.5	-0.367	-1.171	0.440	-0.229	-0.627	0.165

Oral misoprostol tablet (dose 50mcg or more)	Intracervical PGE2	0.918	301.5	-0.023	-0.733	0.675	0.019	-0.343	0.374
Oral misoprostol tablet (dose 50mcg or more)	Vaginal misoprostol (dose less than 50 mcg)	0.966	298.4	-0.469	-0.879	-0.068	-0.482	-0.867	-0.098
Oral misoprostol tablet (dose 50mcg or more)	Vaginal misoprostol (dose 50 mcg or more)	0.905	301.2	-0.607	-1.081	-0.137	-0.572	-0.935	-0.210
Titrated (low dose) oral misoprostol solution	Sustained release misoprostol insert	0.835	302.2	-0.213	-1.390	0.967	-0.059	-0.954	0.830
Titrated (low dose) oral misoprostol solution	IV oxytocin	0.741	302.2	0.896	-0.279	2.082	0.671	0.021	1.328
Titrated (low dose) oral misoprostol solution	Mechanical methods – Foley catheter	0.841	301	0.655	-0.447	1.762	0.534	0.015	1.056
Titrated (low dose) oral misoprostol solution	Vaginal PGE2 (gel)	0.267	300.4	-0.098	-0.735	0.538	0.364	-0.160	0.893
Titrated (low dose) oral misoprostol solution	Vaginal PGE2 (pessary – slow release)	0.636	302.5	0.653	-0.565	1.883	0.336	-0.145	0.819
Titrated (low dose) oral misoprostol solution	Vaginal PGE2 pessary (normal release)	0.677	302.2	-0.431	-1.543	0.673	-0.160	-0.813	0.490
Titrated (low dose) oral misoprostol solution	Oral misoprostol tablet (dose less than 50 mcg)	0.512	302.4	-0.084	-0.960	0.786	0.329	-0.568	1.227
Sustained release misoprostol insert	Vaginal PGE2 (pessary – slow release)	0.846	302.1	0.457	-0.294	1.208	0.603	-0.674	1.870
IV oxytocin	Buccal/sublingual misoprostol	0.201	302.3	0.146	-1.250	1.535	-0.847	-1.478	-0.221
IV oxytocin	Vaginal PGE2 (gel)	0.821	302.2	-0.660	-1.876	0.557	-0.506	-1.098	0.085
IV oxytocin	Vaginal misoprostol (dose less than 50 mcg)	0.783	302.4	-0.891	-2.115	0.320	-0.706	-1.272	-0.146
IV oxytocin	Vaginal misoprostol (dose 50 mcg or more)	0.521	302.5	-1.263	-2.573	0.048	-0.798	-1.357	-0.238
IV oxytocin plus amniotomy	Vaginal PGE2 (tablet)	0.379	302.5	0.877	-0.612	2.463	1.933	0.166	3.831
IV oxytocin plus amniotomy	Buccal/sublingual misoprostol	0.373	302.5	1.326	-0.348	3.108	0.265	-1.329	1.925

Nitric oxide	Vaginal misoprostol (dose 50 mcg or more)	0.573	303.1	-1.077	-1.818	-0.344	-0.740	-1.655	0.160
Mechanical methods – Foley catheter	Mechanical methods – Double balloon or Cook's catheter	0.383	301.8	0.025	-0.688	0.730	-0.461	-1.290	0.373
Mechanical methods – Foley catheter	Vaginal PGE2 (gel)	0.597	299.9	-0.515	-1.221	0.189	-0.283	-0.788	0.217
Mechanical methods – Foley catheter	Vaginal PGE2 (pessary – slow release)	0.376	302.2	0.280	-0.827	1.388	-0.261	-0.749	0.219
Mechanical methods – Foley catheter	Vaginal PGE2 pessary (normal release)	0.355	302.6	-1.332	-2.647	-0.028	-0.658	-1.283	-0.037
Mechanical methods – Foley catheter	Vaginal misoprostol (dose less than 50 mcg)	0.52	301.2	-0.763	-1.425	-0.111	-0.500	-0.986	-0.023
Mechanical methods – Foley catheter	Vaginal misoprostol (dose 50 mcg or more)	0.49	302.1	-0.303	-1.512	0.899	-0.749	-1.175	-0.332
Mechanical methods – Foley catheter	Oral misoprostol tablet (dose less than 50 mcg)	0.926	302.3	-0.397	-1.492	0.689	-0.462	-1.280	0.356
Mechanical methods – Double balloon or Cook's catheter	Vaginal PGE2 (tablet)	0.954	302.5	0.280	-1.091	1.656	0.233	-0.471	0.939
Mechanical methods – Double balloon or Cook's catheter	Vaginal PGE2 (gel)	0.803	301.7	-0.255	-1.424	0.910	-0.088	-0.729	0.550
Mechanical methods – Double balloon or Cook's catheter	Vaginal PGE2 (pessary – slow release)	0.133	302.8	0.808	-0.362	1.969	-0.210	-0.850	0.429
Mechanical methods – Double balloon or Cook's catheter	Intracervical PGE2	0.527	301.7	-0.293	-1.679	1.097	0.196	-0.417	0.810
Mechanical methods – Double balloon or Cook's catheter	Vaginal PGE2 pessary (normal release)	0.568	301.5	-0.936	-2.352	0.457	-0.475	-1.239	0.293
Vaginal PGE2 (tablet)	Vaginal PGE2 (gel)	0.831	302.7	-0.545	-1.972	0.854	-0.385	-0.888	0.112

Vaginal PGE2 (tablet)	Vaginal PGE2 (pessary – slow release)	0.491	302.2	0.158	-1.019	1.335	-0.291	-0.834	0.244
Vaginal PGE2 (tablet)	Intracervical PGE2	0.204	302.5	-0.612	-1.478	0.246	0.032	-0.483	0.537
Vaginal PGE2 (tablet)	Vaginal misoprostol (dose 50 mcg or more)	0.871	302.4	-0.694	-1.374	-0.034	-0.766	-1.314	-0.223
Buccal/sublingual misoprostol	Vaginal misoprostol (dose less than 50 mcg)	0.262	303.4	-0.287	-0.825	0.250	0.126	-0.361	0.609
Buccal/sublingual misoprostol	Vaginal misoprostol (dose 50 mcg or more)	0.118	303.1	0.195	-0.412	0.809	-0.410	-0.873	0.052
Vaginal PGE2 (gel)	Vaginal PGE2 (pessary – slow release)	0.943	302.6	0.147	-1.136	1.425	0.195	-0.218	0.606
Vaginal PGE2 (gel)	Intracervical PGE2	0.555	302.6	0.080	-0.634	0.789	0.320	-0.053	0.687
Vaginal PGE2 (gel)	Vaginal misoprostol (dose less than 50 mcg)	0.338	299.9	0.073	-0.578	0.718	-0.286	-0.644	0.071
Vaginal PGE2 (gel)	Vaginal misoprostol (dose 50 mcg or more)	0.451	301.3	-0.501	-1.016	0.017	-0.257	-0.632	0.117
Vaginal PGE2 (gel)	Oral misoprostol tablet (dose less than 50 mcg)	0.52	302.5	0.245	-0.929	1.422	-0.208	-0.964	0.544
Vaginal PGE2 (pessary – slow release)	Intracervical PGE2	0.051	302.9	0.599	-0.034	1.232	-0.160	-0.584	0.263
Vaginal PGE2 (pessary – slow release)	Vaginal misoprostol (dose less than 50 mcg)	0.554	301.7	-0.216	-0.931	0.493	-0.462	-0.870	-0.055
Vaginal PGE2 (pessary – slow release)	Vaginal misoprostol (dose 50 mcg or more)	0.753	301.3	-0.611	-1.243	0.019	-0.490	-0.912	-0.065
Intracervical PGE2	Vaginal misoprostol (dose less than 50 mcg)	0.319	300.3	-0.644	-1.051	-0.238	-0.373	-0.719	-0.027
Intracervical PGE2	Vaginal misoprostol (dose 50 mcg or more)	0.386	301	-0.762	-1.221	-0.306	-0.512	-0.853	-0.170
Vaginal misoprostol (dose less than 50 mcg)	Vaginal misoprostol (dose 50 mcg or more)	0.36	300.7	0.015	-0.378	0.407	-0.218	-0.523	0.095

[a] *Posterior mean residual deviance compared to 174 total data points.*
[b] *p-values < 0.05 are indicative of evidence of inconsistency between the direct and indirect estimates. Comparisons where this is the case are highlighted in yellow.*

Direct and indirect treatment effect estimates (LOR) for node-split models of the outcome vaginal delivery in 24 hours (unfavourable cervix dataset).

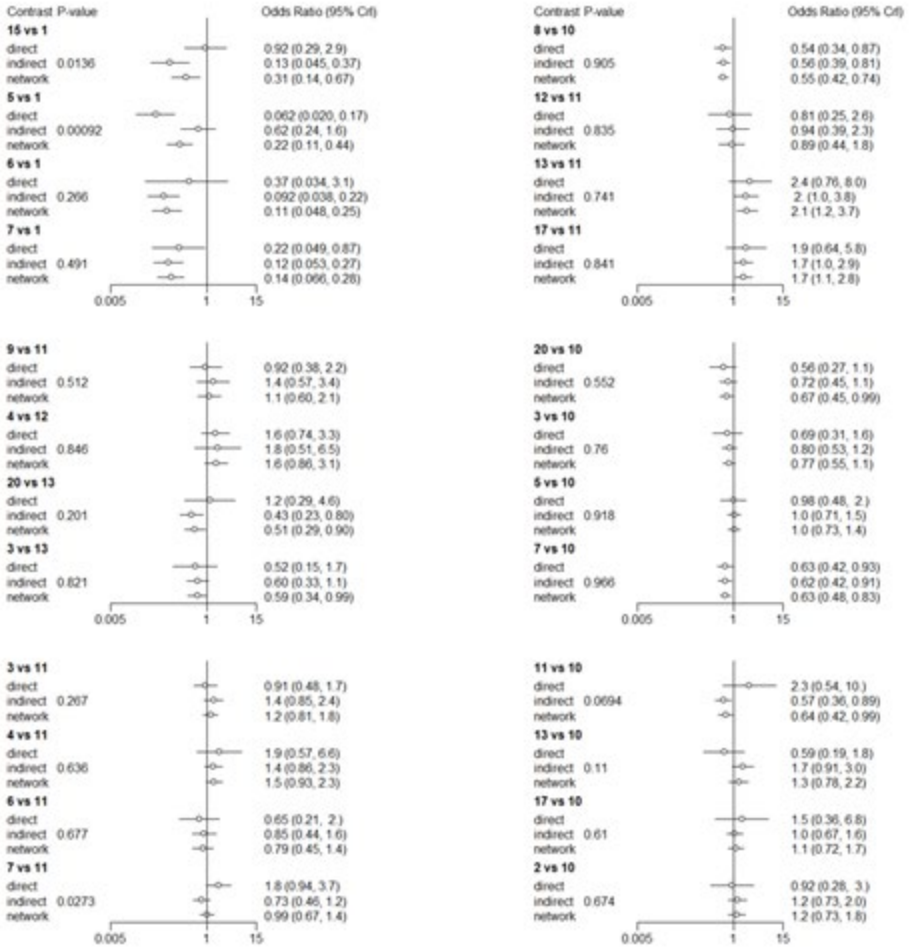
Intervention 1	Intervention 2	p-value	Residual deviance	Direct			Indirect		
				Median	2.5% CrI	97.5% CrI	Median	2.5% CrI	97.5% CrI
consistency		-	246.7	-	-	-	-	-	-
Placebo	Nitric oxide	0.038	247	-0.086	-1.279	1.105	-1.822	-3.009	-0.700
Placebo	Intracervical PGE2	0.003	241.8	-2.879	-4.248	-1.643	-0.475	-1.469	0.492
Titrated (low dose) oral misoprostol solution	Vaginal misoprostol (dose less than 50 mcg)	0.018	245	0.617	-0.083	1.320	-0.438	-0.986	0.100
Nitric oxide	Vaginal PGE2 (gel)	0.011	248.2	0.663	-0.457	1.784	-1.070	-1.803	-0.335
Intracervical PGE2	Vaginal PGE2 pessary (normal release)	0.036	243.9	-0.269	-0.888	0.357	-1.413	-2.313	-0.536
Placebo	Vaginal PGE2 pessary (normal release)	0.367	243.7	-0.998	-3.368	1.161	-2.127	-3.121	-1.178
Placebo	Vaginal misoprostol (dose less than 50 mcg)	0.673	246.5	-1.544	-3.073	-0.102	-1.920	-2.887	-1.009
Oral misoprostol tablet (dose 50mcg or more)	Titrated (low dose) oral misoprostol solution	0.069	246	0.839	-0.654	2.350	-0.630	-1.154	-0.112
Oral misoprostol tablet (dose 50mcg or more)	IV oxytocin	0.363	246.6	-0.449	-2.869	1.792	0.631	-0.050	1.321
Oral misoprostol tablet (dose 50mcg or more)	Mechanical methods – Foley catheter	0.542	244.5	0.441	-1.051	1.942	-0.046	-0.558	0.466
Oral misoprostol tablet (dose 50mcg or more)	Buccal/sublingual misoprostol	0.904	246.7	-0.588	-1.335	0.156	-0.530	-1.121	0.053
Oral misoprostol tablet (dose 50mcg or more)	Vaginal PGE2 (gel)	0.509	245.2	-0.626	-1.816	0.562	-0.203	-0.668	0.263
Oral misoprostol tablet (dose 50mcg or more)	Intracervical PGE2	0.981	245.8	-0.027	-0.765	0.699	-0.017	-0.463	0.424
Oral misoprostol tablet (dose 50mcg or more)	Vaginal misoprostol (dose less than 50 mcg)	0.664	243.7	-0.635	-1.164	-0.119	-0.483	-0.932	-0.034
Oral misoprostol tablet (dose 50mcg or more)	Vaginal misoprostol (dose 50 mcg or more)	0.383	245.7	-0.811	-1.400	-0.230	-0.489	-0.931	-0.053

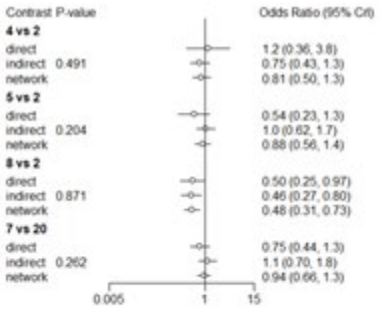
Titrated (low dose) oral misoprostol solution	Sustained release misoprostol insert	0.881	246.3	-0.208	-1.440	1.021	-0.092	-1.050	0.862
Titrated (low dose) oral misoprostol solution	IV oxytocin	0.834	246.4	0.901	-0.330	2.127	1.059	0.281	1.834
Titrated (low dose) oral misoprostol solution	Vaginal PGE2 (gel)	0.394	245.4	-0.079	-0.897	0.743	0.350	-0.223	0.919
Titrated (low dose) oral misoprostol solution	Vaginal PGE2 (pessary – slow release)	0.599	246.5	0.655	-0.616	1.923	0.289	-0.276	0.848
Titrated (low dose) oral misoprostol solution	Vaginal PGE2 pessary (normal release)	0.688	246.5	-0.431	-1.594	0.735	-0.159	-0.856	0.543
Titrated (low dose) oral misoprostol solution	Oral misoprostol tablet (dose less than 50 mcg)	0.541	246.5	-0.083	-0.990	0.819	0.327	-0.633	1.297
Sustained release misoprostol insert	Vaginal PGE2 (pessary – slow release)	0.879	246.5	0.456	-0.334	1.246	0.575	-0.778	1.924
IV oxytocin	Vaginal PGE2 (gel)	0.806	246.6	-0.661	-1.921	0.606	-0.841	-1.577	-0.112
IV oxytocin	Vaginal PGE2 pessary (normal release)	0.08	246	-2.900	-5.300	-0.910	-0.975	-1.774	-0.164
IV oxytocin	Vaginal misoprostol (dose less than 50 mcg)	0.754	246.5	-0.889	-2.155	0.368	-1.118	-1.824	-0.422
IV oxytocin	Vaginal misoprostol (dose 50 mcg or more)	0.865	246.6	-1.256	-2.617	0.087	-1.126	-1.820	-0.432
Nitric oxide	Vaginal misoprostol (dose 50 mcg or more)	0.483	247	-1.074	-1.830	-0.320	-0.635	-1.623	0.324
Mechanical methods – Foley catheter	Mechanical methods – Double balloon or Cook's catheter	0.423	245.6	0.023	-0.725	0.750	-0.481	-1.479	0.510
Mechanical methods – Foley catheter	Vaginal PGE2 (gel)	0.898	245.5	-0.330	-1.287	0.602	-0.261	-0.806	0.288
Mechanical methods – Foley catheter	Vaginal PGE2 (pessary – slow release)	0.403	246.3	0.282	-0.887	1.443	-0.260	-0.825	0.297
Mechanical methods – Foley catheter	Vaginal PGE2 pessary (normal release)	0.33	246.8	-1.337	-2.697	0.018	-0.591	-1.263	0.073

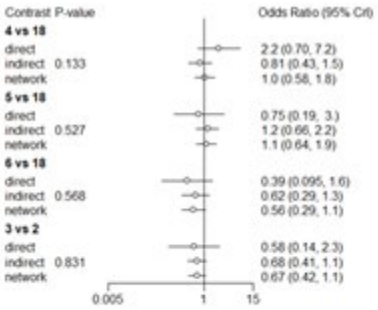
Mechanical methods – Foley catheter	Vaginal misoprostol (dose less than 50 mcg)	0.48	245.4	-0.771	-1.455	-0.102	-0.460	-1.015	0.094
Mechanical methods – Foley catheter	Vaginal misoprostol (dose 50 mcg or more)	0.532	246.4	-0.288	-1.522	0.952	-0.709	-1.193	-0.234
Mechanical methods – Foley catheter	Oral misoprostol tablet (dose less than 50 mcg)	0.999	246.2	-0.401	-1.537	0.737	-0.398	-1.285	0.476
Mechanical methods – Double balloon or Cook's catheter	Vaginal PGE2 (gel)	0.74	245.4	-0.249	-1.468	0.962	-0.015	-0.759	0.738
Mechanical methods – Double balloon or Cook's catheter	Vaginal PGE2 (pessary – slow release)	0.131	246.8	0.806	-0.403	2.014	-0.282	-1.035	0.469
Mechanical methods – Double balloon or Cook's catheter	Intracervical PGE2	0.516	245.8	-0.289	-1.727	1.146	0.238	-0.473	0.951
Mechanical methods – Double balloon or Cook's catheter	Vaginal PGE2 pessary (normal release)	0.535	245.8	-0.947	-2.403	0.504	-0.423	-1.263	0.426
Buccal/sublingual misoprostol	Vaginal misoprostol (dose less than 50 mcg)	0.187	247.5	-0.282	-0.902	0.348	0.290	-0.294	0.869
Buccal/sublingual misoprostol	Vaginal misoprostol (dose 50 mcg or more)	0.198	246.8	0.318	-0.416	1.056	-0.279	-0.821	0.268
Vaginal PGE2 (tablet)	Vaginal PGE2 (gel)	0.993	246.8	-0.540	-1.993	0.903	-0.533	-1.189	0.109
Vaginal PGE2 (tablet)	Intracervical PGE2	0.371	246.9	-0.618	-1.515	0.276	-0.107	-0.815	0.586
Vaginal PGE2 (tablet)	Vaginal misoprostol (dose 50 mcg or more)	0.391	246.9	-0.696	-1.399	-0.011	-1.160	-1.971	-0.352
Vaginal PGE2 (gel)	Intracervical PGE2	0.718	246.8	0.076	-0.855	1.011	0.263	-0.164	0.688
Vaginal PGE2 (gel)	Vaginal misoprostol (dose less than 50 mcg)	0.188	245.6	0.218	-0.605	1.030	-0.388	-0.791	0.011
Vaginal PGE2 (gel)	Vaginal misoprostol (dose 50 mcg or more)	0.516	245.1	-0.500	-1.043	0.038	-0.271	-0.729	0.187
Vaginal PGE2 (gel)	Oral misoprostol tablet (dose less than 50 mcg)	0.485	246.6	0.252	-0.971	1.472	-0.263	-1.082	0.550

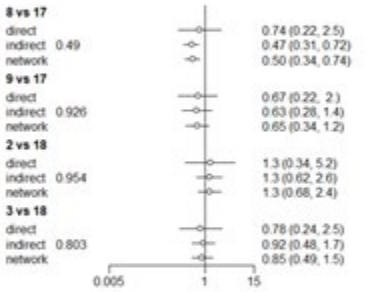
Vaginal PGE2 (pessary – slow release)	Intracervical PGE2	0.054	247.1	0.698	-0.045	1.444	-0.184	-0.687	0.320
Vaginal PGE2 (pessary – slow release)	Vaginal misoprostol (dose less than 50 mcg)	0.533	245.7	-0.215	-0.961	0.521	-0.497	-0.994	0.003
Vaginal PGE2 (pessary – slow release)	Vaginal misoprostol (dose 50 mcg or more)	0.61	245.7	-0.664	-1.438	0.109	-0.426	-0.931	0.085
Intracervical PGE2	Vaginal misoprostol (dose less than 50 mcg)	0.263	244.4	-0.707	-1.160	-0.259	-0.367	-0.765	0.034
Intracervical PGE2	Vaginal misoprostol (dose 50 mcg or more)	0.842	245.5	-0.637	-1.198	-0.083	-0.570	-0.951	-0.185
Vaginal misoprostol (dose less than 50 mcg)	Vaginal misoprostol (dose 50 mcg or more)	0.495	245.2	0.012	-0.397	0.417	-0.177	-0.538	0.194

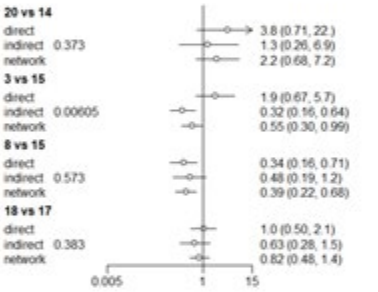
Forest plots displaying direct, indirect and network estimates generated by node-splitting models of the outcome vaginal delivery in 24h, full dataset. Treatment codes: 1 – Placebo, 2 - Vaginal PGE2 (tablet), 3 - Vaginal PGE2 (gel), 4 - Vaginal PGE2 (pessary – slow release), 5 - Intracervical PGE2, 6 - Vaginal PGE2 pessary (normal release), 7 - Vaginal misoprostol (Dose less than 50 mcg), 8 - Vaginal misoprostol (Dose 50 mcg or more), 9 - Oral misoprostol tablet (Dose less than 50 mcg), 10 - Oral misoprostol tablet (dose 50mcg or more), 11 - Titrated (low dose) oral misoprostol solution, 12 - Sustained release misoprostol insert, 13 - IV oxytocin, 14 - IV oxytocin plus amniotomy, 15 - Nitric oxide, 16 – Mifepristone, 17 - Mechanical methods – Foley catheter, 18 - Mechanical methods – Double balloon or Cook's catheter, 19 - Extra-amniotic PGE2 or PGF2, 20 - Buccal/sublingual misoprostol.

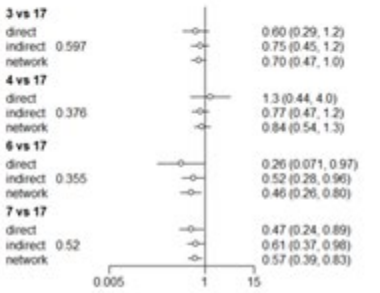


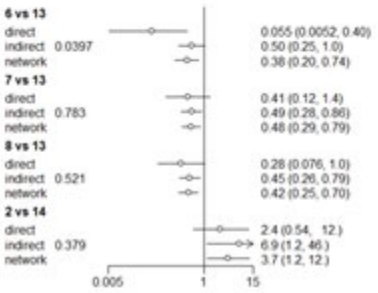

Contrast P-value
Odds Ratio (95% CrI)
4 vs 2
direct
indirect 0.491
network
1.2 (0.36, 3.8)
0.75 (0.43, 1.3)
0.81 (0.50, 1.3)
5 vs 2
direct
indirect 0.204
network
0.54 (0.23, 1.3)
1.0 (0.62, 1.7)
0.88 (0.56, 1.4)
8 vs 2
direct
indirect 0.871
network
0.50 (0.25, 0.97)
0.46 (0.27, 0.80)
0.48 (0.31, 0.73)
7 vs 20
direct
indirect 0.262
network
0.75 (0.44, 1.3)
1.1 (0.70, 1.8)
0.94 (0.66, 1.3)
0.005
1
15

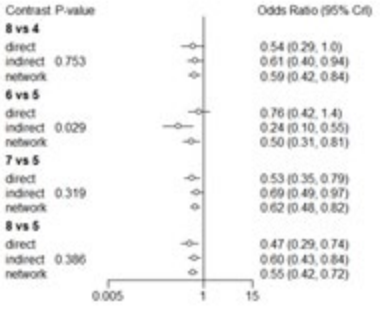

Contrast P-value
Odds Ratio (95% CrI)
4 vs 18
direct
indirect 0.133
network
2.2 (0.70, 7.2)
0.81 (0.43, 1.5)
1.0 (0.58, 1.8)
5 vs 18
direct
indirect 0.527
network
0.75 (0.19, 3.)
1.2 (0.66, 2.2)
1.1 (0.64, 1.9)
6 vs 18
direct
indirect 0.568
network
0.39 (0.095, 1.6)
0.62 (0.29, 1.3)
0.56 (0.29, 1.1)
3 vs 2
direct
indirect 0.831
network
0.58 (0.14, 2.3)
0.68 (0.41, 1.1)
0.67 (0.42, 1.1)
0.005
1
15

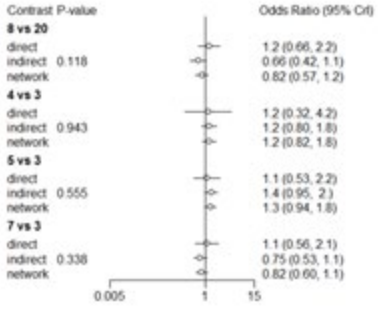

8 vs 17
direct
indirect 0.49
network
0.74 (0.22, 2.5)
0.47 (0.31, 0.72)
0.50 (0.34, 0.74)
9 vs 17
direct
indirect 0.926
network
0.67 (0.22, 2.)
0.63 (0.28, 1.4)
0.65 (0.34, 1.2)
2 vs 18
direct
indirect 0.954
network
1.3 (0.34, 5.2)
1.3 (0.62, 2.6)
1.3 (0.68, 2.4)
3 vs 18
direct
indirect 0.803
network
0.78 (0.24, 2.5)
0.92 (0.48, 1.7)
0.85 (0.49, 1.5)
0.005
1
15

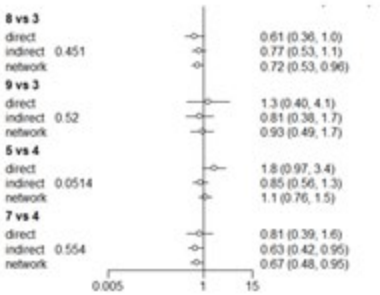

20 vs 14
direct
indirect 0.373
network
3.8 (0.71, 22.)
1.3 (0.26, 6.9)
2.2 (0.68, 7.2)
3 vs 15
direct
indirect 0.00605
network
1.9 (0.67, 5.7)
0.32 (0.16, 0.64)
0.55 (0.30, 0.99)
8 vs 15
direct
indirect 0.573
network
0.34 (0.16, 0.71)
0.48 (0.19, 1.2)
0.39 (0.22, 0.68)
18 vs 17
direct
indirect 0.383
network
1.0 (0.50, 2.1)
0.63 (0.28, 1.5)
0.82 (0.48, 1.4)
0.005
1
15


3 vs 17
direct
indirect 0.597
network
0.60 (0.29, 1.2)
0.75 (0.45, 1.2)
0.70 (0.47, 1.0)
4 vs 17
direct
indirect 0.376
network
1.3 (0.44, 4.0)
0.77 (0.47, 1.2)
0.84 (0.54, 1.3)
6 vs 17
direct
indirect 0.355
network
0.26 (0.071, 0.97)
0.52 (0.28, 0.96)
0.46 (0.26, 0.80)
7 vs 17
direct
indirect 0.52
network
0.47 (0.24, 0.89)
0.61 (0.37, 0.98)
0.57 (0.39, 0.83)
0.005
1
15


6 vs 13
direct
indirect 0.0397
network
0.055 (0.0052, 0.40)
0.50 (0.25, 1.0)
0.38 (0.20, 0.74)
7 vs 13
direct
indirect 0.783
network
0.41 (0.12, 1.4)
0.49 (0.28, 0.86)
0.48 (0.29, 0.79)
8 vs 13
direct
indirect 0.521
network
0.28 (0.076, 1.0)
0.45 (0.26, 0.79)
0.42 (0.25, 0.70)
2 vs 14
direct
indirect 0.379
network
2.4 (0.54, 12.)
6.9 (1.2, 46.)
3.7 (1.2, 12.)
0.005
1
15

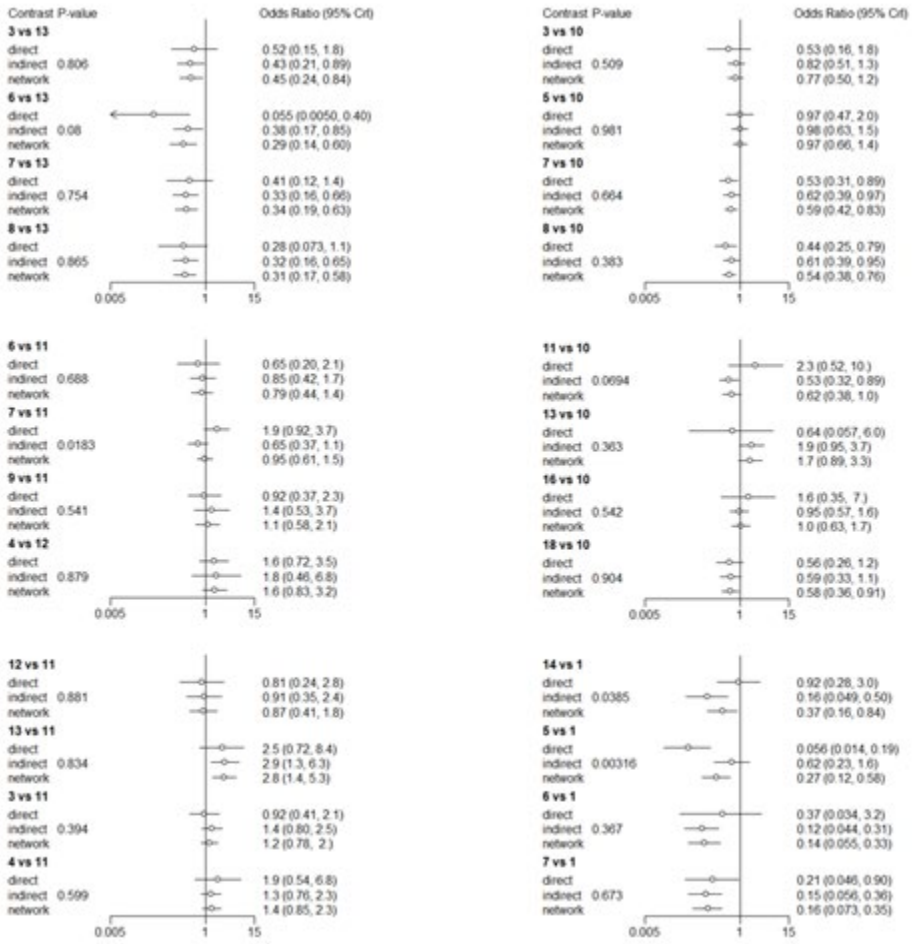

Contrast P-value
Odds Ratio (95% CrI)
8 vs 4
direct
indirect 0.753
network
0.54 (0.29, 1.0)
0.61 (0.40, 0.94)
0.59 (0.42, 0.84)
6 vs 5
direct
indirect 0.029
network
0.76 (0.42, 1.4)
0.24 (0.10, 0.55)
0.50 (0.31, 0.81)
7 vs 5
direct
indirect 0.319
network
0.53 (0.35, 0.79)
0.69 (0.49, 0.97)
0.62 (0.48, 0.82)
8 vs 5
direct
indirect 0.386
network
0.47 (0.29, 0.74)
0.60 (0.43, 0.84)
0.55 (0.42, 0.72)
0.005
1
15

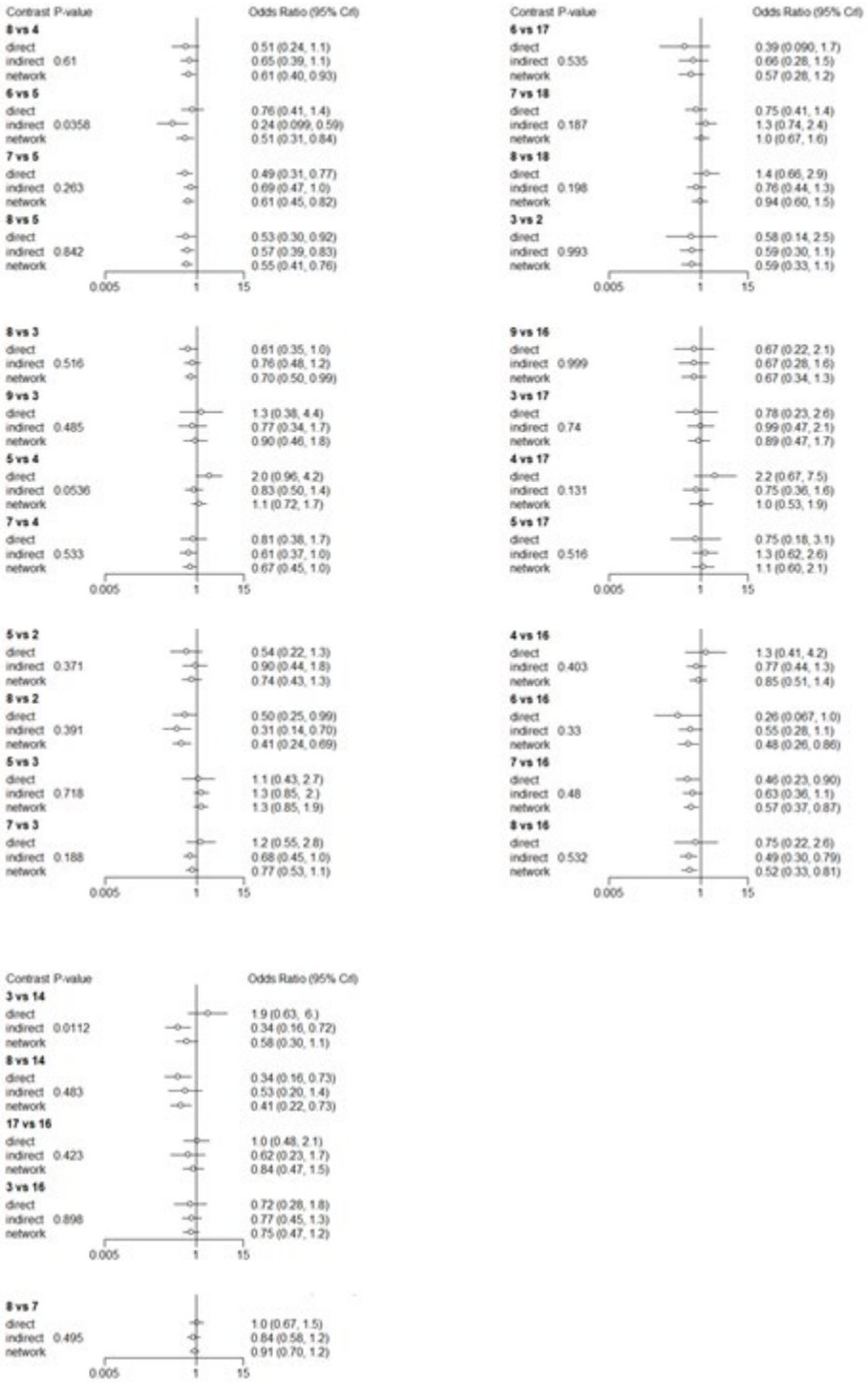

Contrast P-value
Odds Ratio (95% CrI)
8 vs 20
direct
indirect 0.118
network
1.2 (0.66, 2.2)
0.66 (0.42, 1.1)
0.82 (0.57, 1.2)
4 vs 3
direct
indirect 0.943
network
1.2 (0.32, 4.2)
1.2 (0.80, 1.8)
1.2 (0.82, 1.8)
5 vs 3
direct
indirect 0.555
network
1.1 (0.53, 2.2)
1.4 (0.95, 2.)
1.3 (0.94, 1.8)
7 vs 3
direct
indirect 0.338
network
1.1 (0.56, 2.1)
0.75 (0.53, 1.1)
0.82 (0.60, 1.1)
0.005
1
15


8 vs 3
direct
indirect 0.451
network
0.61 (0.36, 1.0)
0.77 (0.53, 1.1)
0.72 (0.53, 0.96)
9 vs 3
direct
indirect 0.52
network
1.3 (0.40, 4.1)
0.81 (0.38, 1.7)
0.93 (0.49, 1.7)
5 vs 4
direct
indirect 0.0514
network
1.8 (0.97, 3.4)
0.85 (0.56, 1.3)
1.1 (0.76, 1.5)
7 vs 4
direct
indirect 0.554
network
0.81 (0.39, 1.6)
0.63 (0.42, 0.95)
0.67 (0.48, 0.95)
0.005
1
15


8 vs 7
direct
indirect 0.36
network
1.0 (0.69, 1.5)
0.80 (0.59, 1.1)
0.88 (0.69, 1.1)
0.005
1
15

Forest plots displaying direct, indirect and network estimates generated by node-splitting models of the outcome vaginal delivery in 24h, unfavourable cervix dataset. 1 – Placebo, 2 - Vaginal PGE2 (tablet), 3 - Vaginal PGE2 (gel), 4 - Vaginal PGE2 (pessary – slow release), 5 - Intracervical PGE2, 6 - Vaginal PGE2 pessary (normal release), 7 - Vaginal misoprostol (Dose less than 50 mcg), 8 - Vaginal misoprostol (Dose 50 mcg or more), 9 - Oral misoprostol tablet (Dose less than 50 mcg), 10 - Oral misoprostol tablet (dose 50mcg or more), 11 - Titrated (low dose) oral misoprostol solution, 12 - Sustained release misoprostol insert, 13 - IV oxytocin, 14 - Nitric oxide, 15 – Mifepristone, 16 - Mechanical methods – Foley catheter, 17 - Mechanical methods – Double balloon or Cook's catheter, 18 - Buccal/sublingual misoprostol.




Contrast P-value
Odds Ratio (95% CrI)
8 vs 4
direct
indirect 0.61
network
0.51 (0.24, 1.1)
0.65 (0.39, 1.1)
0.61 (0.40, 0.93)
6 vs 5
direct
indirect 0.0358
network
0.76 (0.41, 1.4)
0.24 (0.099, 0.59)
0.51 (0.31, 0.84)
7 vs 5
direct
indirect 0.263
network
0.49 (0.31, 0.77)
0.69 (0.47, 1.0)
0.61 (0.45, 0.82)
8 vs 5
direct
indirect 0.842
network
0.53 (0.30, 0.92)
0.57 (0.39, 0.83)
0.55 (0.41, 0.76)
0.005
1
15
6 vs 17
direct
indirect 0.535
network
0.39 (0.090, 1.7)
0.66 (0.28, 1.5)
0.57 (0.28, 1.2)
7 vs 18
direct
indirect 0.187
network
0.75 (0.41, 1.4)
1.3 (0.74, 2.4)
1.0 (0.67, 1.6)
8 vs 18
direct
indirect 0.198
network
1.4 (0.66, 2.9)
0.76 (0.44, 1.3)
0.94 (0.60, 1.5)
3 vs 2
direct
indirect 0.993
network
0.58 (0.14, 2.5)
0.59 (0.30, 1.1)
0.59 (0.33, 1.1)
8 vs 3
direct
indirect 0.516
network
0.61 (0.35, 1.0)
0.76 (0.48, 1.2)
0.70 (0.50, 0.99)
9 vs 3
direct
indirect 0.485
network
1.3 (0.38, 4.4)
0.77 (0.34, 1.7)
0.90 (0.46, 1.8)
5 vs 4
direct
indirect 0.0536
network
2.0 (0.96, 4.2)
0.83 (0.50, 1.4)
1.1 (0.72, 1.7)
7 vs 4
direct
indirect 0.533
network
0.81 (0.38, 1.7)
0.61 (0.37, 1.0)
0.67 (0.45, 1.0)
9 vs 16
direct
indirect 0.999
network
0.67 (0.22, 2.1)
0.67 (0.28, 1.6)
0.67 (0.34, 1.3)
3 vs 17
direct
indirect 0.74
network
0.78 (0.23, 2.6)
0.99 (0.47, 2.1)
0.89 (0.47, 1.7)
4 vs 17
direct
indirect 0.131
network
2.2 (0.67, 7.5)
0.75 (0.36, 1.6)
1.0 (0.53, 1.9)
5 vs 17
direct
indirect 0.516
network
0.75 (0.18, 3.1)
1.3 (0.62, 2.6)
1.1 (0.60, 2.1)
5 vs 2
direct
indirect 0.371
network
0.54 (0.22, 1.3)
0.90 (0.44, 1.8)
0.74 (0.43, 1.3)
8 vs 2
direct
indirect 0.391
network
0.50 (0.25, 0.99)
0.31 (0.14, 0.70)
0.41 (0.24, 0.69)
5 vs 3
direct
indirect 0.718
network
1.1 (0.43, 2.7)
1.3 (0.85, 2.)
1.3 (0.85, 1.9)
7 vs 3
direct
indirect 0.188
network
1.2 (0.55, 2.8)
0.68 (0.45, 1.0)
0.77 (0.53, 1.1)
4 vs 16
direct
indirect 0.403
network
1.3 (0.41, 4.2)
0.77 (0.44, 1.3)
0.85 (0.51, 1.4)
6 vs 16
direct
indirect 0.33
network
0.26 (0.067, 1.0)
0.55 (0.28, 1.1)
0.48 (0.26, 0.86)
7 vs 16
direct
indirect 0.48
network
0.46 (0.23, 0.90)
0.63 (0.36, 1.1)
0.57 (0.37, 0.87)
8 vs 16
direct
indirect 0.532
network
0.75 (0.22, 2.6)
0.49 (0.30, 0.79)
0.52 (0.33, 0.81)
3 vs 14
direct
indirect 0.0112
network
1.9 (0.63, 6.)
0.34 (0.16, 0.72)
0.58 (0.30, 1.1)
8 vs 14
direct
indirect 0.483
network
0.34 (0.16, 0.73)
0.53 (0.20, 1.4)
0.41 (0.22, 0.73)
17 vs 16
direct
indirect 0.423
network
1.0 (0.48, 2.1)
0.62 (0.23, 1.7)
0.84 (0.47, 1.5)
3 vs 16
direct
indirect 0.898
network
0.72 (0.28, 1.8)
0.77 (0.45, 1.3)
0.75 (0.47, 1.2)
8 vs 7
direct
indirect 0.495
network
1.0 (0.67, 1.5)
0.84 (0.58, 1.2)
0.91 (0.70, 1.2)

Hyperstimulation with fetal heart rate changes

Analysis of the full dataset included 172 trials of 21 treatments (358 arms) whilst analysis of the unfavourable cervix dataset included 143 trials of 21 treatments (298 arms). These datasets contained a substantial number of trials containing zero- and single-event arms. Where there are several zero-event arms, or where a treatment contrast is based entirely on zero event arms there will be less information available to the model. Whilst no treatment difference was based entirely on zero-event trials, where a zero-event arm could be contributing to inconsistency, this has been flagged.

Inconsistency checks were performed using the random effects model, as this had lower DIC than the fixed effects model and there was evidence of heterogeneity. Convergence was satisfactory for the random effects model assuming inconsistency after 12,000 iterations, and the consistency and inconsistency models were compared using results based on samples from a further 20,000 iterations on two chains. The precision on the vague priors was updated from 0.0001 to 0.01, equivalent to a variance of 10^2, to constrain the range of parameter values without applying a continuity correction. WinBUGS code for the inconsistency model is provided below.

There was estimated to be high between-study SD, with estimates of 0.64 (95% credible interval [CrI] 0.45-0.86) in the full dataset and 0.68 (95% CrI 0.47-0.93) in the subgroup dataset. Posterior mean residual deviance and penalized deviance (DIC) were both substantially lower in the random-effect network meta-analysis models, supporting use of the random-effect model structure.

Network meta-analysis (NMA) models of the outcome hyperstimulation, comparison of fixed- (FE) and random-effect (RE) models.

Dataset	Model	Between-study SD (mean)			Mean residual deviance	Data points (arms)	DIC
		Mean	2.5% CrI	97.5% CrI			
Full	Consistency NMA (FE)	-	-	-	495.1	358	1542.7
	Consistency NMA (RE)	0.64	0.45	0.86	379.1	358	1471.7
	Inconsistency NMA (RE)	0.59	0.38	0.85	362.5	358	1469.2
Subgroup (unfav. cervix)	Consistency NMA (FE)	-	-	-	409.9	298	1274.8
	Consistency NMA (RE)	0.68	0.47	0.93	306.5	298	1208.2
	Inconsistency NMA (RE)	0.69	0.43	1.00	294.6	298	1212.0

Consistency and inconsistency random-effects NMA models were fitted to the full and subgroup datasets. In both the full and subgroup datasets there was no strong evidence of inconsistency when comparing based on DIC. However, in the full dataset there was a reduction in mean between-study SD and residual deviance in the inconsistency model, suggesting that the consistency model is attributing variation that is the result of inconsistency between direct and indirect evidence to between-study variation.

To explore this further we plotted the contribution of each study arm to the total residual deviance for the inconsistency model vs the consistency model in a dev-dev plot for the full

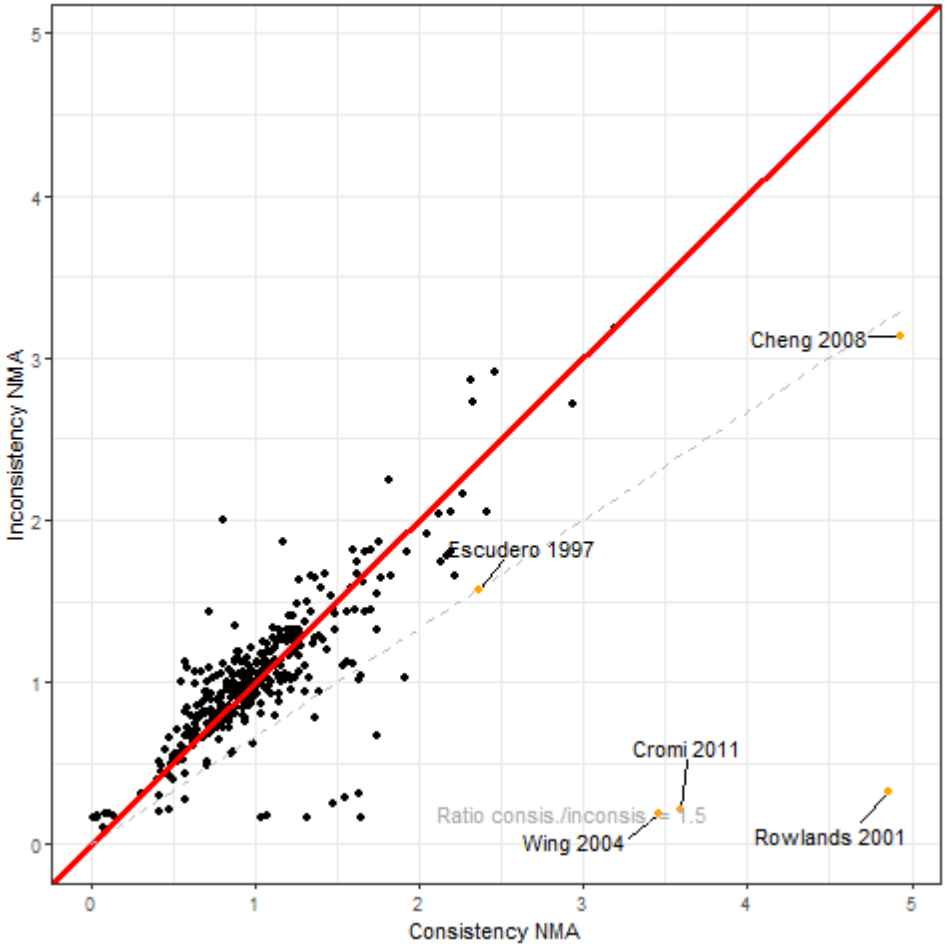
dataset and the unfavourable cervix subgroup. A simple rule was used to identify study arms with relatively high deviance in the consistency model: points with relatively high deviance were those with mean deviance in the consistency NMA model greater than 2, and where the residual deviance in the consistency NMA was at least 1.5 times that estimated under the inconsistency model.

Three studies were flagged in both the full and subgroup datasets as having higher deviance in the consistency model than in the inconsistency model:

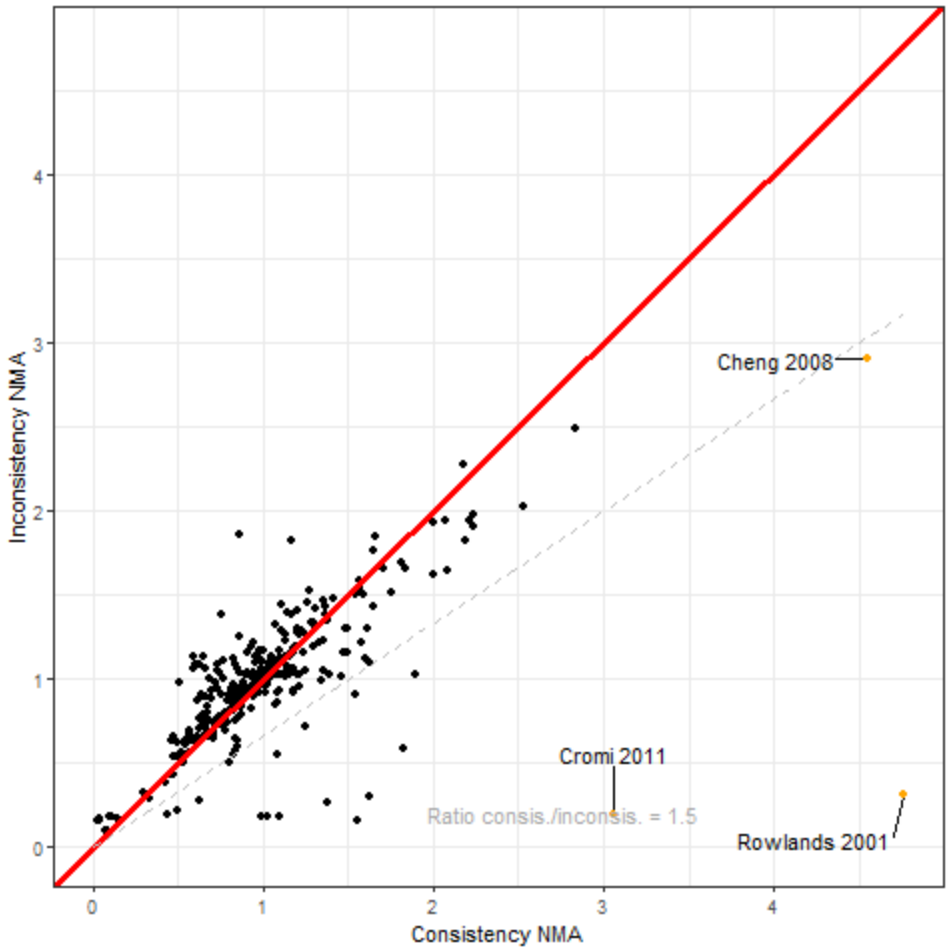
- Cromi 2011 was a two-armed trial comparing vaginal PGE2 (pessary – slow release) and Foley catheter with zero events in the Foley catheter arm.
- Rowlands 2001 (highlighted 2019) was a two-armed trial comparing vaginal PGE2 pessary (normal release) and vaginal misoprostol (dose 50 mcg or more) with zero events in the PGE2 pessary arm.
- Cheng 2008 (highlighted 2019) was a two-armed trial comparing vaginal misoprostol (dose less than 50 mcg) and sustained release misoprostol insert, with zero events in the vaginal misoprostol arm.

Two studies were flagged in the full dataset only:

- Escudero 1997 was a two-armed trial comparing vaginal misoprostol (dose 50 mcg or more) and IV oxytocin, whilst Wing 2004 was a two-armed trial comparing oral misoprostol tablet (dose 50mcg or more) and IV oxytocin. Both recorded zero events in the oxytocin arm.



Dev-dev plots of each study arm's deviance in the RE consistency and inconsistency NMA models of hyperstimulation, full dataset. Labelled orange points indicate studies with relatively high deviance in the consistency model. Red line indicates line of equivalence.



Dev-dev plots of each study arm's deviance in the RE consistency and inconsistency NMA models of hyperstimulation, unfavourable cervix subgroup. Labelled orange points indicate studies with relatively high deviance in the consistency model. Red line indicates line of equivalence.

Random-effect node-splitting NMA models were fitted to assess inconsistency between direct and indirect evidence for each treatment comparison. Where the indirect estimate consistently differs from the direct estimate, the p value will approach zero, with a threshold set at 0.05 to highlight comparisons that are likely to be inconsistent.

In the full dataset, there were 11 comparisons out of a possible 65 with potential inconsistency between the direct and indirect estimates. Given multiple testing, we would expect at least 3 comparisons to show inconsistency. In the unfavourable cervix dataset, there were 10 comparisons out of a possible 65 with potential inconsistency between the direct and indirect estimates. Given multiple testing, we would expect at least 3 comparisons to show inconsistency. The flagged comparisons indicate that there may be inconsistency in the following treatment effect estimates:

- Foley catheter against no treatment, vaginal PGE2 (slow-release pessary) and IV oxytocin
- Oral misoprostol tablet (dose 50mcg or more) against IV oxytocin and vaginal PGE2 (tablet)
- Placebo against vaginal PGE2 in three forms (tablet, gel or slow-release pessary)
- Treatment loop involving vaginal PGE2 (gel), vaginal PGE2 pessary (normal release) and vaginal misoprostol (dose 50 mcg or more)

  Taken together these suggest that is likely to be inconsistency in the central part of the network, in comparisons between placebo, vaginal PGE2 (tablet), vaginal PGE2 (gel), vaginal PGE2 (pessary – slow release), vaginal misoprostol (dose 50 mcg or more), oral misoprostol tablet (dose 50mcg or more), IV oxytocin and Foley catheter (treatment codes: 1, 3, 4, 5, 9, 11, 14 and 18). However, this inconsistency in this loop may in part be explained by the presence of studies with zero responders, leading to poorly defined estimates when evidence is compartmentalised as direct and indirect.

Direct and indirect estomates of treatment difference (LOR), hyperstimulation outcome, full dataset. Where direct and indirect esimates are inconsistent (p<0.05), treatment comparisons are highlighted in yellow.

Intervention 1	Intervention 2	p-value	Residual deviance	Direct			Indirect		
				Median	2.5% CrI	97.5% CrI	Median	2.5% CrI	97.5% CrI
Consistency model		-	380.9	-	-	-	-	-	-
No treatment	Mechanical methods – foley catheter	0.013	380.2	-27.140	-125.917	-2.145	-0.308	-1.869	1.201
Oral misoprostol tablet (dose 50mcg or more)	IV oxytocin	0.001	378	-29.410	-81.795	-3.248	-0.081	-0.863	0.701
Oral misoprostol tablet (dose 50mcg or more)	Vaginal PGE2 (tablet)	0.009	379.5	-32.173	-80.899	-2.629	-0.167	-0.986	0.632
IV oxytocin	Mechanical methods – foley catheter	0.016	380.5	-35.099	-105.208	-2.118	-0.655	-1.568	0.213
Mechanical methods – foley catheter	Vaginal PGE2 (pessary – slow release)	0.001	379.4	20.850	3.786	46.974	1.061	0.315	1.853
Placebo	Vaginal PGE2 (tablet)	0.012	377.7	-32.933	-93.027	-0.930	1.347	0.205	2.567
Placebo	Vaginal PGE2 (gel)	0.039	380.6	18.805	1.623	58.845	1.262	0.293	2.322
Placebo	Vaginal PGE2 (pessary – slow release)	0	378	24.800	5.616	58.481	1.111	0.045	2.243
Vaginal PGE2 (tablet)	Intracervical PGE2	0.042	378.1	18.275	0.001	64.191	-0.287	-1.104	0.549
Vaginal PGE2 (gel)	Vaginal PGE2 pessary (normal release)	0.015	378.3	27.467	1.406	88.776	-0.083	-1.310	1.083
Vaginal PGE2 pessary (normal release)	Vaginal misoprostol (dose 50 mcg or more)	0	378.7	35.730	3.790	79.841	-0.588	-1.963	0.701
No treatment	IV oxytocin	0.809	381	0.049	-2.372	2.162	0.370	-1.210	1.963
No treatment	Intracervical PGE2	0.486	380.6	0.278	-1.121	1.673	-0.514	-2.336	1.262
No treatment	Vaginal misoprostol (dose 50 mcg or more)	0.496	381.5	0.542	-1.536	2.535	1.389	-0.069	2.887
Oral misoprostol tablet (dose less than 50 mcg)	Titrated (low dose) oral misoprostol solution	0.352	380.7	1.401	-1.088	4.940	-0.023	-1.584	1.510
Oral misoprostol tablet (dose less than 50 mcg)	Mechanical methods – foley catheter	0.666	381.7	-0.910	-4.535	1.998	-0.197	-1.660	1.277

Oral misoprostol tablet (dose less than 50 mcg)	Vaginal PGE2 (gel)	0.614	380.5	0.511	-1.080	2.124	1.149	-0.771	3.151
Oral misoprostol tablet (dose 50mcg or more)	Mechanical methods – foley catheter	0.14	381	-0.173	-1.582	1.250	-1.336	-2.072	-0.651
Oral misoprostol tablet (dose 50mcg or more)	Buccal/sublingual misoprostol	0.899	381.2	0.592	-1.646	3.079	0.753	-0.009	1.545
Oral misoprostol tablet (dose 50mcg or more)	Vaginal PGE2 (gel)	0.869	379.4	0.089	-1.208	1.379	-0.031	-0.641	0.598
Oral misoprostol tablet (dose 50mcg or more)	Intracervical PGE2	0.48	379.7	-0.789	-1.914	0.254	-0.351	-0.960	0.249
Oral misoprostol tablet (dose 50mcg or more)	Vaginal misoprostol (dose less than 50 mcg)	0.064	375.2	0.527	-0.135	1.223	-0.331	-0.980	0.286
Oral misoprostol tablet (dose 50mcg or more)	Vaginal misoprostol (dose 50 mcg or more)	0.467	381.6	0.463	-0.180	1.127	0.787	0.199	1.381
Titrated (low dose) oral misoprostol solution	Sustained release misoprostol insert	0.557	380.4	1.806	-0.010	3.821	1.138	-0.145	2.464
Titrated (low dose) oral misoprostol solution	Mechanical methods – foley catheter	0.502	378.4	-0.118	-1.813	1.524	-0.754	-1.670	0.107
Titrated (low dose) oral misoprostol solution	Vaginal PGE2 (gel)	0.09	379.3	-0.228	-1.145	0.707	0.928	-0.028	1.898
Titrated (low dose) oral misoprostol solution	Vaginal PGE2 (pessary – slow release)	0.188	380.8	-0.386	-2.209	1.397	0.924	0.091	1.773
Titrated (low dose) oral misoprostol solution	Vaginal PGE2 pessary (normal release)	0.147	382.7	1.481	-0.128	3.186	-0.167	-1.703	1.356
Titrated (low dose) oral misoprostol solution	Vaginal misoprostol (dose less than 50 mcg)	0.41	380.2	0.901	-0.105	1.961	0.350	-0.503	1.212
Sustained release misoprostol insert	Vaginal PGE2 (pessary – slow release)	0.565	381	-0.539	-1.544	0.468	-1.199	-3.367	0.808
IV oxytocin	Vaginal PGE2 (pessary – slow release)	0.557	381	0.159	-1.539	1.882	0.730	-0.182	1.638
IV oxytocin	Intracervical PGE2	0.353	379.9	-0.827	-2.717	0.917	0.078	-0.738	0.907
IV oxytocin	Vaginal misoprostol (dose less than 50 mcg)	0.147	381.2	-0.544	-2.089	0.944	0.702	-0.109	1.531

IV oxytocin	Vaginal misoprostol (dose 50 mcg or more)	0.407	381	1.304	0.275	2.377	0.713	-0.216	1.673
Nitric oxide	Vaginal PGE2 (tablet)	0.728	381	23.690	1.403	64.774	31.390	4.313	66.293
Nitric oxide	Intracervical PGE2	0.607	381	28.854	0.912	107.650	16.399	2.892	34.380
Nitric oxide	Vaginal misoprostol (dose 50 mcg or more)	0.518	380.3	12.485	3.595	33.050	28.752	2.865	95.974
Mechanical methods – foley catheter	Mechanical methods – Double balloon or Cook's catheter	0.988	378.6	-35.353	-123.423	28.361	-32.588	-84.580	-3.073
Mechanical methods – foley catheter	Vaginal PGE2 (gel)	0.497	379.5	0.801	-0.192	1.875	1.245	0.474	2.073
Mechanical methods – foley catheter	Intracervical PGE2	0.737	380.9	0.405	-1.131	1.992	0.697	0.001	1.430
Mechanical methods – foley catheter	Vaginal PGE2 pessary (normal release)	0.441	379.5	0.029	-3.793	3.716	1.453	0.215	2.735
Mechanical methods – foley catheter	Vaginal misoprostol (dose less than 50 mcg)	0.359	381.5	1.596	0.557	2.779	0.999	0.324	1.728
Mechanical methods – foley catheter	Vaginal misoprostol (dose 50 mcg or more)	0.865	381.3	1.891	0.179	4.174	1.720	1.093	2.408
Mechanical methods – laminaria including dilapan	Vaginal PGE2 (gel)	0.913	381.1	21.117	0.324	82.638	19.003	2.140	49.677
Mechanical methods – laminaria including dilapan	Intracervical PGE2	0.804	380.9	22.818	2.011	65.922	27.403	0.377	89.158
Placebo	Intracervical PGE2	0.36	378.8	0.638	-0.511	1.854	1.504	0.127	3.190
Placebo	Vaginal misoprostol (dose less than 50 mcg)	0.223	379.8	0.398	-1.520	2.411	1.784	0.734	2.928
Placebo	Vaginal misoprostol (dose 50 mcg or more)	0.096	380.5	14.454	1.039	51.656	1.947	1.025	2.954
Mechanical methods – Double balloon or Cook's catheter	Vaginal PGE2 (gel)	0.993	379.5	23.343	2.910	60.045	21.692	2.745	72.830

Mechanical methods – Double balloon or Cook's catheter	Vaginal PGE2 (pessary – slow release)	0.882	381	30.461	2.999	96.169	28.085	2.940	135.058
Buccal/sublingual misoprostol	Vaginal misoprostol (dose less than 50 mcg)	0.523	380.6	-0.312	-1.614	0.969	-0.804	-1.673	0.021
Buccal/sublingual misoprostol	Vaginal misoprostol (dose 50 mcg or more)	0.476	380.7	-0.246	-1.044	0.521	0.255	-0.926	1.405
Vaginal PGE2 (tablet)	Vaginal PGE2 (gel)	0.945	380.8	0.233	-1.225	1.720	0.289	-0.603	1.224
Vaginal PGE2 (tablet)	Vaginal PGE2 (pessary – slow release)	0.818	381.1	0.326	-1.733	2.455	0.587	-0.329	1.540
Vaginal PGE2 (tablet)	Vaginal misoprostol (dose 50 mcg or more)	0.376	379.5	0.677	-0.210	1.602	1.330	0.210	2.536
Vaginal PGE2 (gel)	Intracervical PGE2	0.88	381.4	-0.552	-2.343	1.083	-0.422	-1.025	0.165
Vaginal PGE2 (gel)	Vaginal misoprostol (dose less than 50 mcg)	0.64	378.8	0.251	-0.573	1.037	0.012	-0.604	0.630
Vaginal PGE2 (gel)	Vaginal misoprostol (dose 50 mcg or more)	0.085	380.8	0.103	-0.688	0.894	0.961	0.373	1.552
Vaginal PGE2 (pessary – slow release)	Intracervical PGE2	0.433	380.2	-0.209	-1.662	1.185	-0.841	-1.571	-0.142
Vaginal PGE2 (pessary – slow release)	Vaginal misoprostol (dose less than 50 mcg)	0.133	379.5	-1.214	-2.816	0.223	0.003	-0.662	0.669
Vaginal PGE2 (pessary – slow release)	Vaginal misoprostol (dose 50 mcg or more)	0.085	377.2	0.977	0.091	1.909	-0.024	-0.787	0.716
Intracervical PGE2	Vaginal misoprostol (dose less than 50 mcg)	0.543	380.1	0.336	-0.430	1.126	0.637	0.063	1.223
Intracervical PGE2	Vaginal misoprostol (dose 50 mcg or more)	0.893	375.5	1.053	0.361	1.779	1.119	0.536	1.717
Vaginal PGE2 pessary (normal release)	Vaginal misoprostol (dose less than 50 mcg)	0.274	380.7	-1.607	-5.434	1.339	0.162	-1.034	1.371
Vaginal misoprostol (dose less than 50 mcg)	Vaginal misoprostol (dose 50 mcg or more)	0.409	379.5	0.871	0.049	1.754	0.471	-0.005	0.945

Direct and indirect estimates of treatment difference (LOR), hyperstimulation outcome, unfavourable cervix subgroup dataset. Where direct and indirect estimates are inconsistent (p<0.05), treatment comparisons are highlighted in yellow.

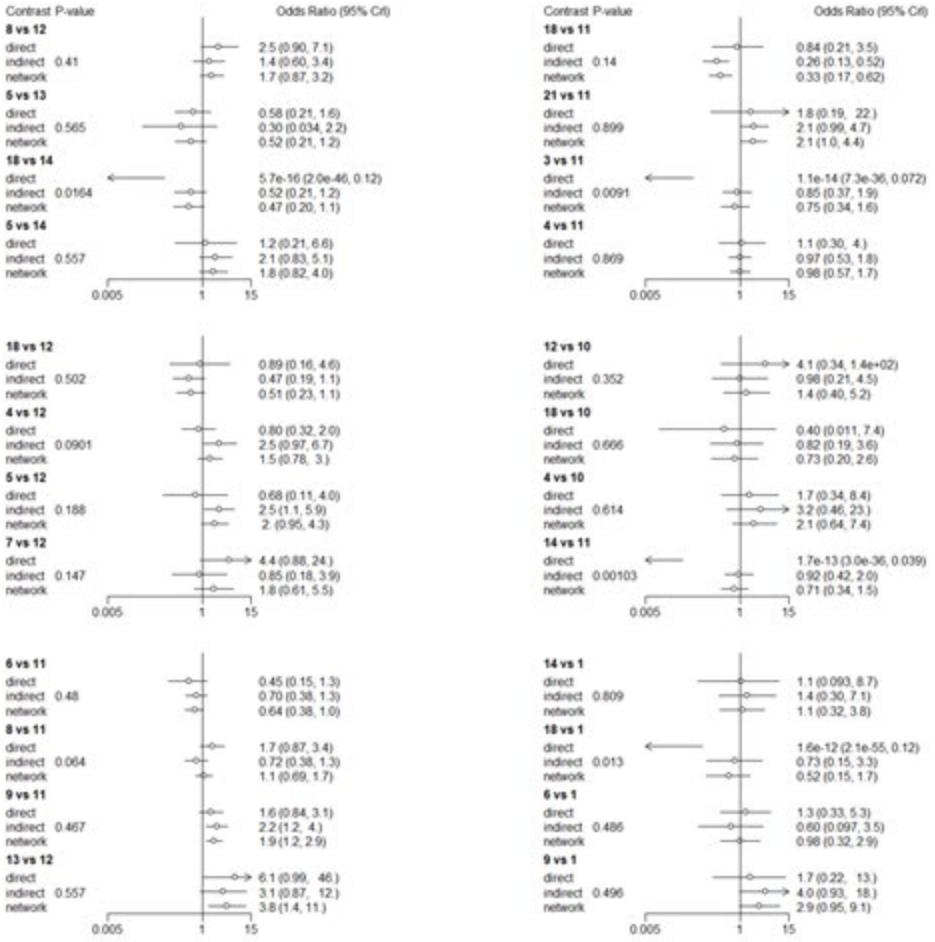
Intervention 1	Intervention 2	p-value	Residual deviance	Direct			Indirect		
				Median	2.5% CrI	97.5% CrI	Median	2.5% CrI	97.5% CrI
Consistency model	-	-	308.6	-	-	-	-	-	-
No treatment	Mechanical methods – foley catheter	0.014	307.3	-32.224	-95.345	-2.227	-0.335	-1.950	1.260
IV oxytocin	Mechanical methods – foley catheter	0.028	308.3	-34.276	-110.816	-2.583	-1.346	-2.532	-0.179
Mechanical methods – foley catheter	Vaginal PGE2 (pessary – slow release)	0.005	307.3	18.682	3.104	77.879	1.290	0.445	2.171
Placebo	Vaginal PGE2 (tablet)	0.003	305	-59.161	-147.908	-4.293	1.245	-0.095	2.634
Placebo	Vaginal PGE2 (gel)	0.030	307.5	23.561	2.004	67.254	1.200	0.107	2.368
Placebo	Vaginal PGE2 (pessary – slow release)	0.003	304.8	19.116	3.373	43.646	1.104	-0.101	2.389
Vaginal PGE2 (tablet)	Intracervical PGE2	0.044	304.9	21.010	-0.066	79.031	-0.283	-1.288	0.697
Vaginal PGE2 (gel)	Vaginal PGE2 pessary (normal release)	0.025	306.2	20.264	0.819	83.105	-0.127	-1.418	1.119
Vaginal PGE2 (pessary – slow release)	Vaginal misoprostol (Dose 50 mcg or more)	0.014	303.5	1.290	0.182	2.544	-0.434	-1.321	0.400
Vaginal PGE2 pessary (normal release)	Vaginal misoprostol (Dose 50 mcg or more)	<0.001	305.9	39.239	8.772	96.559	-0.713	-2.114	0.594
No treatment	IV oxytocin	0.504	308.5	0.056	-2.409	2.248	1.009	-0.764	2.831
No treatment	Intracervical PGE2	0.365	308.1	0.271	-1.165	1.719	-0.790	-2.651	1.035
No treatment	Vaginal misoprostol (Dose 50 mcg or more)	0.492	308.4	0.546	-1.627	2.583	1.422	-0.082	2.972
Oral misoprostol tablet (Dose less than 50 mcg)	Titrated (low dose) oral misoprostol solution	0.355	308.9	1.433	-1.083	4.894	0.000	-1.648	1.640
Oral misoprostol tablet (Dose less than 50 mcg)	Mechanical methods – foley catheter	0.744	308.9	-0.892	-4.493	2.041	-0.349	-1.901	1.216
Oral misoprostol tablet (Dose less than 50 mcg)	Vaginal PGE2 (gel)	0.582	308.3	0.518	-1.162	2.197	1.236	-0.715	3.384

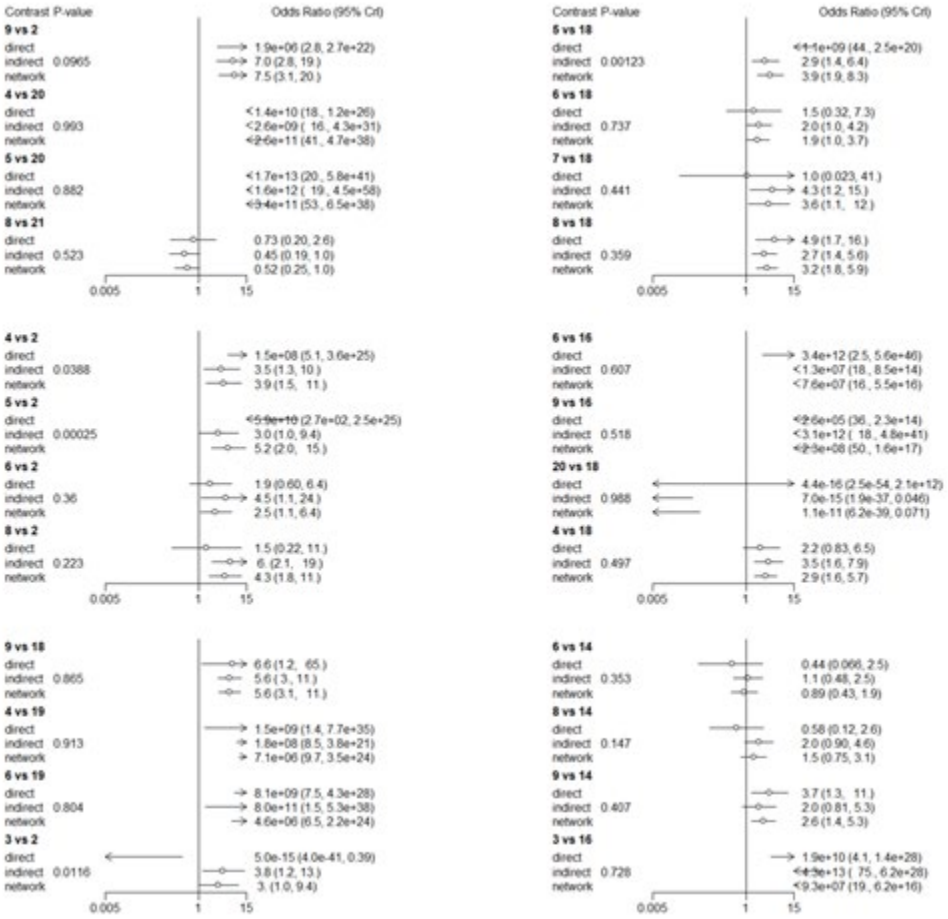
Oral misoprostol tablet (dose 50mcg or more)	Mechanical methods – foley catheter	0.134	308.2	-0.174	-1.664	1.317	-1.450	-2.302	-0.627
Oral misoprostol tablet (dose 50mcg or more)	Buccal/sublingual misoprostol	0.829	308.6	0.627	-1.626	3.082	0.899	0.002	1.837
Oral misoprostol tablet (dose 50mcg or more)	Vaginal PGE2 (gel)	0.919	309.2	-0.100	-3.966	3.962	0.089	-0.607	0.818
Oral misoprostol tablet (dose 50mcg or more)	Intracervical PGE2	0.45	307.1	-0.813	-1.982	0.268	-0.316	-1.052	0.411
Oral misoprostol tablet (dose 50mcg or more)	Vaginal misoprostol (Dose less than 50 mcg)	0.136	304.2	0.814	-0.079	1.824	-0.072	-0.838	0.663
Oral misoprostol tablet (dose 50mcg or more)	Vaginal misoprostol (Dose 50 mcg or more)	0.13	307.1	0.193	-0.610	1.001	1.022	0.309	1.776
Titrated (low dose) oral misoprostol solution	Sustained release misoprostol insert	0.621	308.5	1.828	-0.057	3.940	1.239	-0.139	2.660
Titrated (low dose) oral misoprostol solution	Vaginal PGE2 (gel)	0.219	308	-0.184	-1.386	1.056	0.819	-0.239	1.875
Titrated (low dose) oral misoprostol solution	Vaginal PGE2 (pessary – slow release)	0.159	308.1	-0.390	-2.265	1.448	1.089	0.135	2.062
Titrated (low dose) oral misoprostol solution	Vaginal PGE2 pessary (normal release)	0.143	309.6	1.481	-0.209	3.181	-0.230	-1.828	1.351
Titrated (low dose) oral misoprostol solution	Vaginal misoprostol (Dose less than 50 mcg)	0.569	307.4	0.896	-0.149	1.998	0.462	-0.633	1.539
Sustained release misoprostol insert	Vaginal PGE2 (pessary – slow release)	0.622	308.6	-0.540	-1.592	0.515	-1.121	-3.353	0.991
IV oxytocin	Vaginal PGE2 (pessary – slow release)	0.938	309	0.178	-1.589	1.958	0.261	-0.931	1.480
IV oxytocin	Intracervical PGE2	0.823	307.4	-0.815	-2.724	0.884	-0.583	-1.697	0.541
IV oxytocin	Vaginal misoprostol (Dose less than 50 mcg)	0.687	308.7	-0.350	-2.528	1.798	0.138	-0.925	1.208
IV oxytocin	Vaginal misoprostol (Dose 50 mcg or more)	0.794	308.3	0.588	-1.004	2.255	0.333	-0.857	1.516
Nitric oxide	Vaginal PGE2 (tablet)	0.74	308.6	20.001	1.043	65.870	31.233	3.837	84.597
Nitric oxide	Intracervical PGE2	0.73	307.5	23.388	0.633	67.203	14.487	2.568	43.990

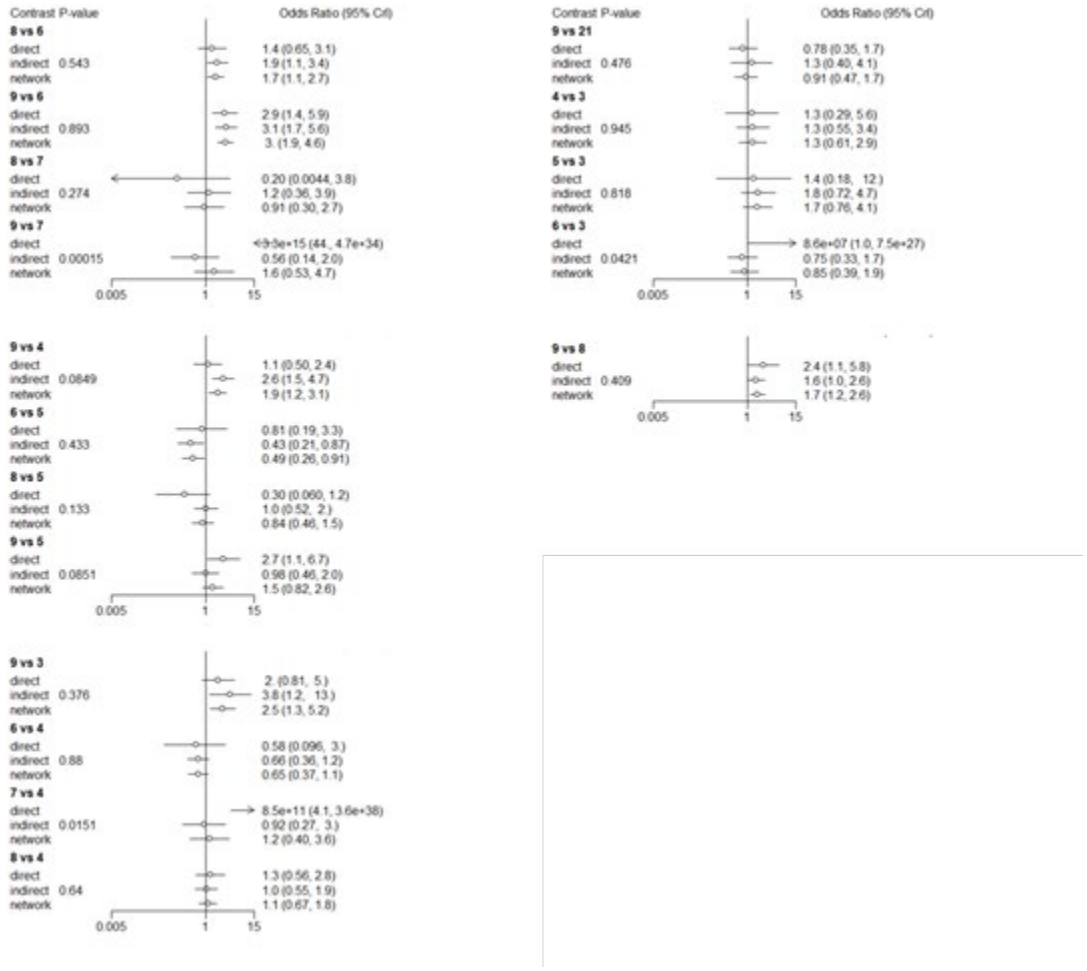
Nitric oxide	Vaginal misoprostol (Dose 50 mcg or more)	0.996	308.1	37.017	6.698	71.493	30.577	3.868	91.002
Mechanical methods – foley catheter	Mechanical methods – Double balloon or Cook's catheter	0.809	306.2	-42.538	-163.697	113.567	-24.881	-58.409	-2.004
Mechanical methods – foley catheter	Vaginal PGE2 (gel)	0.799	307.8	1.397	0.088	2.866	1.189	0.362	2.104
Mechanical methods – foley catheter	Intracervical PGE2	0.722	308.6	0.439	-1.150	2.100	0.756	-0.002	1.566
Mechanical methods – foley catheter	Vaginal PGE2 pessary (normal release)	0.374	306.7	-0.078	-4.009	3.648	1.627	0.297	3.003
Mechanical methods – foley catheter	Vaginal misoprostol (Dose less than 50 mcg)	0.686	308.4	1.623	0.544	2.813	1.339	0.559	2.208
Mechanical methods – foley catheter	Vaginal misoprostol (Dose 50 mcg or more)	0.905	308.7	1.930	0.173	4.084	1.812	1.100	2.608
Mechanical methods – laminaria including dilapan	Vaginal PGE2 (gel)	0.711	308.7	19.400	0.255	71.221	31.381	3.156	74.576
Mechanical methods – laminaria including dilapan	Intracervical PGE2	0.901	308.3	25.266	2.502	97.198	18.956	-0.737	99.724
Placebo	Intracervical PGE2	0.125	305.7	0.222	-1.053	1.541	1.875	0.200	3.923
Placebo	Vaginal misoprostol (Dose less than 50 mcg)	0.414	307.8	0.616	-1.760	3.171	1.738	0.627	2.986
Placebo	Vaginal misoprostol (Dose 50 mcg or more)	0.073	307.7	23.382	1.274	83.999	1.806	0.801	2.904
Mechanical methods – Double balloon or Cook's catheter	Vaginal PGE2 (gel)	0.358	307.7	40.041	7.494	114.580	18.509	2.284	65.895
Mechanical methods – Double balloon or Cook's catheter	Vaginal PGE2 (pessary – slow release)	0.939	308.8	29.071	3.123	90.211	36.374	3.613	98.297
Buccal/sublingual misoprostol	Vaginal misoprostol (Dose less than 50 mcg)	0.617	308	-0.307	-1.668	1.003	-0.722	-1.715	0.240

Buccal/sublingual misoprostol	Vaginal misoprostol (Dose 50 mcg or more)	0.535	307.8	-0.364	-1.305	0.527	0.116	-1.132	1.323
Vaginal PGE2 (tablet)	Vaginal PGE2 (gel)	0.715	308.6	0.227	-1.270	1.748	0.579	-0.566	1.791
Vaginal PGE2 (tablet)	Vaginal misoprostol (Dose 50 mcg or more)	0.729	308.3	0.911	-0.112	1.977	1.229	-0.238	2.776
Vaginal PGE2 (gel)	Intracervical PGE2	0.972	308.9	-0.527	-2.428	1.114	-0.566	-1.285	0.117
Vaginal PGE2 (gel)	Vaginal misoprostol (Dose less than 50 mcg)	0.385	307.5	0.552	-0.524	1.635	-0.007	-0.728	0.699
Vaginal PGE2 (gel)	Vaginal misoprostol (Dose 50 mcg or more)	0.105	307.7	-0.018	-0.939	0.881	0.920	0.217	1.629
Vaginal PGE2 (pessary – slow release)	Intracervical PGE2	0.519	307.6	-0.515	-2.082	0.987	-1.085	-1.928	-0.291
Vaginal PGE2 (pessary – slow release)	Vaginal misoprostol (Dose less than 50 mcg)	0.136	306.4	-1.249	-2.861	0.240	0.038	-0.754	0.832
Intracervical PGE2	Vaginal misoprostol (Dose less than 50 mcg)	0.316	307.9	0.380	-0.492	1.277	0.936	0.295	1.598
Intracervical PGE2	Vaginal misoprostol (Dose 50 mcg or more)	0.808	303.7	1.193	0.441	1.981	1.065	0.413	1.766
Vaginal PGE2 pessary (normal release)	Vaginal misoprostol (Dose less than 50 mcg)	0.245	308.3	-1.564	-5.207	1.364	0.306	-0.937	1.568
Vaginal misoprostol (Dose less than 50 mcg)	Vaginal misoprostol (Dose 50 mcg or more)	0.543	306.8	0.619	-0.296	1.572	0.291	-0.273	0.857

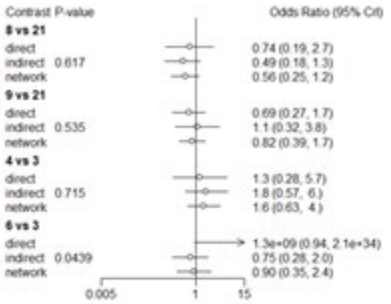
Forest plots for the outcome hyperstimulation, full dataset, showing direct, indirect and network estimates of treatment difference (contrast), odds ratio scale. Treatment codes: 1 - No treatment, 2 – Placebo, 3 - Vaginal PGE2 (tablet), 4 - Vaginal PGE2 (gel), 5 - Vaginal PGE2 (pessary – slow release), 6 - Intracervical PGE2, 7 - Vaginal PGE2 pessary (normal release), 8 - Vaginal misoprostol (Dose less than 50 mcg), 9 - Vaginal misoprostol (Dose 50 mcg or more), 10 - Oral misoprostol tablet (Dose less than 50 mcg), 11 - Oral misoprostol tablet (dose 50mcg or more), 12 - Titrated (low dose) oral misoprostol solution, 13 - Sustained release misoprostol insert, 14 - IV oxytocin, 15 - IV oxytocin plus amniotomy, 16 - Nitric oxide, 17 – Mifepristone, 18 - Mechanical methods – foley catheter, 19 - Mechanical methods – laminaria including dilapan, 20 - Mechanical methods – Double balloon or Cook's catheter, 21 - Buccal/sublingual misoprostol.

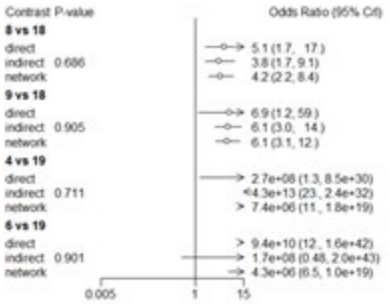


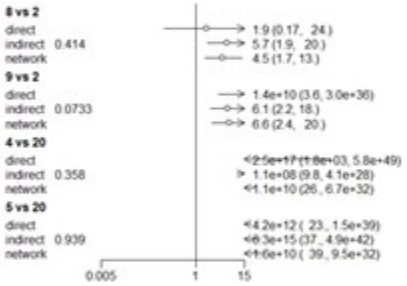

Contrast P-value
Odds Ratio (95% CrI)
9 vs 2
direct
indirect 0.0965
network
1.9e+06 (2.8, 2.7e+22)
7.0 (2.8, 19.)
7.5 (3.1, 20.)
4 vs 20
direct
indirect 0.993
network
<1.4e+10 (18., 1.2e+26)
<2.6e+09 (16., 4.3e+31)
<2.6e+11 (41., 4.7e+38)
5 vs 20
direct
indirect 0.882
network
<1.7e+13 (20., 5.8e+41)
<1.6e+12 (19., 4.5e+58)
<9.4e+11 (53., 6.5e+38)
8 vs 21
direct
indirect 0.523
network
0.73 (0.20, 2.6)
0.45 (0.19, 1.0)
0.52 (0.25, 1.0)
0.005
1
15
5 vs 18
direct
indirect 0.00123
network
<1.1e+09 (44., 2.5e+20)
2.9 (1.4, 6.4)
3.9 (1.9, 8.3)
6 vs 18
direct
indirect 0.737
network
1.5 (0.32, 7.3)
2.0 (1.0, 4.2)
1.9 (1.0, 3.7)
7 vs 18
direct
indirect 0.441
network
1.0 (0.023, 41.)
4.3 (1.2, 15.)
3.6 (1.1, 12.)
8 vs 18
direct
indirect 0.359
network
4.9 (1.7, 16.)
2.7 (1.4, 5.6)
3.2 (1.8, 5.9)
0.005
1
15
4 vs 2
direct
indirect 0.0388
network
1.5e+08 (5.1, 3.6e+25)
3.5 (1.3, 10.)
3.9 (1.5, 11.)
5 vs 2
direct
indirect 0.00025
network
<5.9e+10 (2.7e+02, 2.5e+25)
3.0 (1.0, 9.4)
5.2 (2.0, 15.)
6 vs 2
direct
indirect 0.36
network
1.9 (0.60, 6.4)
4.5 (1.1, 24.)
2.5 (1.1, 6.4)
8 vs 2
direct
indirect 0.223
network
1.5 (0.22, 11.)
6. (2.1, 19.)
4.3 (1.8, 11.)
0.005
1
15
6 vs 16
direct
indirect 0.607
network
3.4e+12 (2.5, 5.6e+46)
<1.3e+07 (18., 8.5e+14)
<7.6e+07 (16., 5.5e+16)
9 vs 16
direct
indirect 0.518
network
<2.6e+05 (36., 2.3e+14)
<3.1e+12 (18., 4.8e+41)
<2.3e+08 (50., 1.6e+17)
20 vs 18
direct
indirect 0.988
network
4.4e-16 (2.5e-54, 2.1e+12)
7.0e-15 (1.9e-37, 0.046)
1.1e-11 (6.2e-39, 0.071)
4 vs 18
direct
indirect 0.497
network
2.2 (0.83, 6.5)
3.5 (1.6, 7.9)
2.9 (1.6, 5.7)
0.005
1
15
9 vs 18
direct
indirect 0.865
network
6.6 (1.2, 65.)
5.6 (1., 11.)
5.6 (3.1, 11.)
4 vs 19
direct
indirect 0.913
network
1.5e+09 (1.4, 7.7e+35)
1.8e+08 (8.5, 3.8e+21)
7.1e+06 (9.7, 3.5e+24)
6 vs 19
direct
indirect 0.804
network
8.1e+09 (7.5, 4.3e+28)
8.0e+11 (1.5, 5.3e+38)
4.6e+06 (6.5, 2.2e+24)
3 vs 2
direct
indirect 0.0116
network
5.0e-15 (4.0e-41, 0.39)
3.8 (1.2, 13.)
3. (1.0, 9.4)
0.005
1
15
6 vs 14
direct
indirect 0.353
network
0.44 (0.066, 2.5)
1.1 (0.48, 2.5)
0.89 (0.43, 1.9)
8 vs 14
direct
indirect 0.147
network
0.58 (0.12, 2.6)
2.0 (0.90, 4.6)
1.5 (0.75, 3.1)
9 vs 14
direct
indirect 0.407
network
3.7 (1.3, 11.)
2.0 (0.81, 5.3)
2.6 (1.4, 5.3)
3 vs 16
direct
indirect 0.728
network
1.9e+10 (4.1, 1.4e+28)
<4.3e+13 (75., 6.2e+28)
<9.3e+07 (19., 6.2e+16)
0.005
1
15

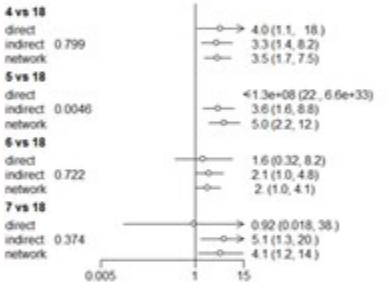


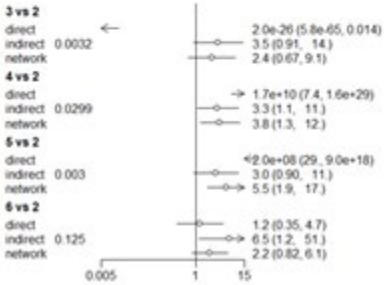
Forest plots for the outcome hyperstimulation, unfavourable cervix subgroup, showing direct, indirect and network estimates of treatment difference (contrast), odds ratio scale. Treatment codes: 1 - No treatment, 2 – Placebo, 3 - Vaginal PGE2 (tablet), 4 - Vaginal PGE2 (gel), 5 - Vaginal PGE2 (pessary – slow release), 6 - Intracervical PGE2, 7 - Vaginal PGE2 pessary (normal release), 8 - Vaginal misoprostol (Dose less than 50 mcg), 9 - Vaginal misoprostol (Dose 50 mcg or more), 10 - Oral misoprostol tablet (Dose less than 50 mcg), 11 - Oral misoprostol tablet (dose 50mcg or more), 12 - Titrated (low dose) oral misoprostol solution, 13 - Sustained release misoprostol insert, 14 - IV oxytocin, 15 - IV oxytocin plus amniotomy, 16 - Nitric oxide, 17 – Mifepristone, 18 - Mechanical methods – foley catheter, 19 - Mechanical methods – laminaria including dilapan, 20 - Mechanical methods – Double balloon or Cook's catheter, 21 - Buccal/sublingual misoprostol.

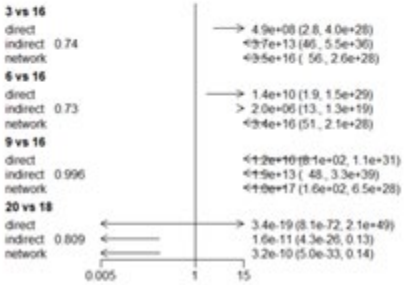

Contrast P-value
Odds Ratio (95% CrI)
8 vs 21
direct
indirect 0.617
network
0.74 (0.19, 2.7)
0.49 (0.18, 1.3)
0.56 (0.25, 1.2)
9 vs 21
direct
indirect 0.535
network
0.69 (0.27, 1.7)
1.1 (0.32, 3.8)
0.82 (0.39, 1.7)
4 vs 3
direct
indirect 0.715
network
1.3 (0.28, 5.7)
1.8 (0.57, 6.)
1.6 (0.63, 4.)
6 vs 3
direct
indirect 0.0439
network
1.3e+09 (0.94, 2.1e+34)
0.75 (0.28, 2.0)
0.90 (0.35, 2.4)
0.005
1
15

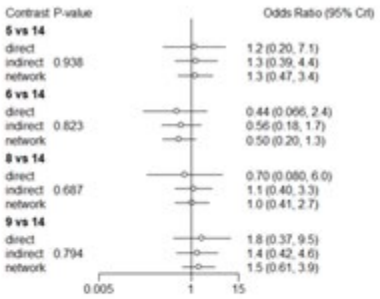

Contrast P-value
Odds Ratio (95% CrI)
8 vs 18
direct
indirect 0.686
network
5.1 (1.7, 17.)
3.8 (1.7, 9.1)
4.2 (2.2, 8.4)
9 vs 18
direct
indirect 0.905
network
6.9 (1.2, 59.)
6.1 (3.0, 14.)
6.1 (3.1, 12.)
4 vs 19
direct
indirect 0.711
network
2.7e+08 (1.3, 8.5e+30)
4.3e+13 (23., 2.4e+32)
7.4e+06 (11., 1.8e+19)
6 vs 19
direct
indirect 0.901
network
9.4e+10 (12., 1.6e+42)
1.7e+08 (0.48, 2.0e+43)
4.3e+06 (6.5, 1.0e+19)
0.005
1
15

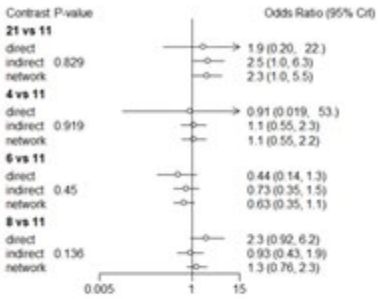

8 vs 2
direct
indirect 0.414
network
1.9 (0.17, 24.)
5.7 (1.9, 20.)
4.5 (1.7, 13.)
9 vs 2
direct
indirect 0.0733
network
1.4e+10 (3.6, 3.0e+36)
6.1 (2.2, 18.)
6.6 (2.4, 20.)
4 vs 20
direct
indirect 0.358
network
2.5e+17 (1.8e+03, 5.8e+49)
1.1e+08 (9.8, 4.1e+28)
1.1e+10 (26., 6.7e+32)
5 vs 20
direct
indirect 0.939
network
4.2e+12 (23., 1.5e+39)
6.3e+15 (37., 4.9e+42)
1.6e+10 (39., 9.5e+32)
0.005
1
15

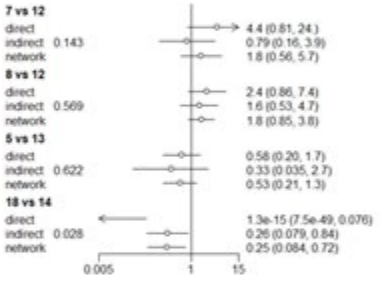

4 vs 18
direct
indirect 0.799
network
4.0 (1.1, 18.)
3.3 (1.4, 8.2)
3.5 (1.7, 7.5)
5 vs 18
direct
indirect 0.0046
network
1.3e+08 (22., 6.6e+33)
3.6 (1.6, 8.8)
5.0 (2.2, 12.)
6 vs 18
direct
indirect 0.722
network
1.6 (0.32, 8.2)
2.1 (1.0, 4.8)
2. (1.0, 4.1)
7 vs 18
direct
indirect 0.374
network
0.92 (0.018, 38.)
5.1 (1.3, 20.)
4.1 (1.2, 14.)
0.005
1
15

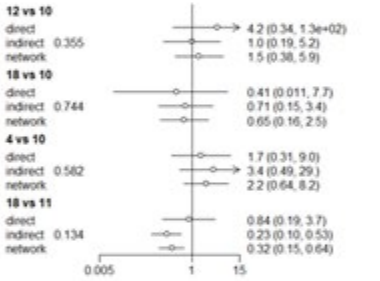

3 vs 2
direct
indirect 0.0032
network
2.0e-26 (5.8e-65, 0.014)
3.5 (0.91, 14.)
2.4 (0.67, 9.1)
4 vs 2
direct
indirect 0.0299
network
1.7e+10 (7.4, 1.6e+29)
3.3 (1.1, 11.)
3.8 (1.3, 12.)
5 vs 2
direct
indirect 0.003
network
2.0e+08 (29., 9.0e+18)
3.0 (0.90, 11.)
5.5 (1.9, 17.)
6 vs 2
direct
indirect 0.125
network
1.2 (0.35, 4.7)
6.5 (1.2, 51.)
2.2 (0.82, 6.1)
0.005
1
15

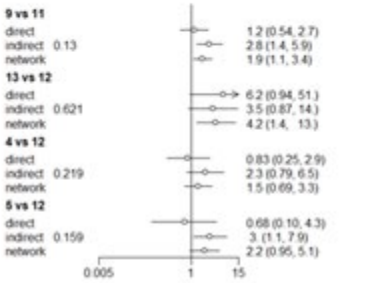

3 vs 16
direct
indirect 0.74
network
4.9e+08 (2.8, 4.0e+28)
3.7e+13 (46., 5.5e+36)
3.5e+16 (56., 2.6e+28)
6 vs 16
direct
indirect 0.73
network
1.4e+10 (1.9, 1.5e+29)
2.0e+06 (13., 1.3e+19)
3.4e+16 (51., 2.1e+28)
9 vs 16
direct
indirect 0.996
network
1.2e+10 (8.1e+02, 1.1e+31)
1.9e+13 (48., 3.3e+39)
1.0e+17 (1.6e+02, 6.5e+28)
20 vs 18
direct
indirect 0.809
network
3.4e-19 (8.1e-72, 2.1e+49)
1.6e-11 (4.3e-26, 0.13)
3.2e-10 (5.0e-33, 0.14)
0.005
1
15

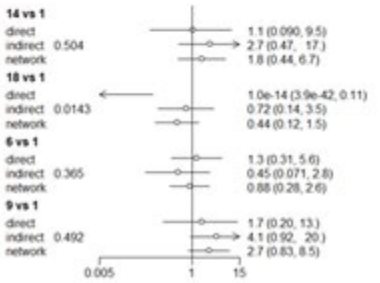

Contrast P-value
Odds Ratio (95% CrI)
5 vs 14
direct
indirect 0.938
network
1.2 (0.20, 7.1)
1.3 (0.39, 4.4)
1.3 (0.47, 3.4)
6 vs 14
direct
indirect 0.823
network
0.44 (0.066, 2.4)
0.56 (0.18, 1.7)
0.50 (0.20, 1.3)
8 vs 14
direct
indirect 0.687
network
0.70 (0.080, 6.0)
1.1 (0.40, 3.3)
1.0 (0.41, 2.7)
9 vs 14
direct
indirect 0.794
network
1.8 (0.37, 9.5)
1.4 (0.42, 4.6)
1.5 (0.61, 3.9)
0.005
1
15

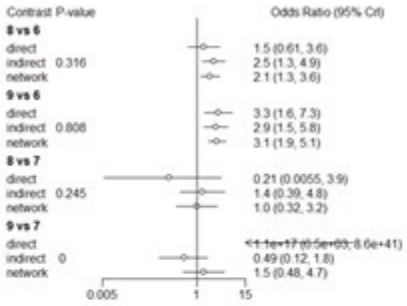

Contrast P-value
Odds Ratio (95% CrI)
21 vs 11
direct
indirect 0.829
network
1.9 (0.20, 22.)
2.5 (1.0, 6.3)
2.3 (1.0, 5.5)
4 vs 11
direct
indirect 0.919
network
0.91 (0.019, 53.)
1.1 (0.55, 2.3)
1.1 (0.55, 2.2)
6 vs 11
direct
indirect 0.45
network
0.44 (0.14, 1.3)
0.73 (0.35, 1.5)
0.63 (0.35, 1.1)
8 vs 11
direct
indirect 0.136
network
2.3 (0.92, 6.2)
0.93 (0.43, 1.9)
1.3 (0.76, 2.3)
0.005
1
15

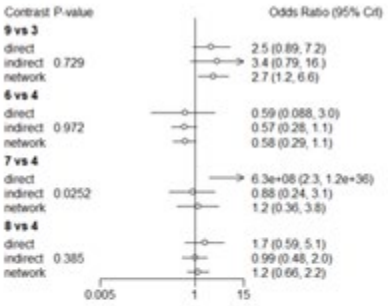

7 vs 12
direct
indirect 0.143
network
4.4 (0.81, 24.)
0.79 (0.16, 3.9)
1.8 (0.56, 5.7)
8 vs 12
direct
indirect 0.569
network
2.4 (0.86, 7.4)
1.6 (0.53, 4.7)
1.8 (0.85, 3.8)
5 vs 13
direct
indirect 0.622
network
0.58 (0.20, 1.7)
0.33 (0.035, 2.7)
0.53 (0.21, 1.3)
18 vs 14
direct
indirect 0.028
network
1.3e-15 (7.5e-49, 0.076)
0.26 (0.079, 0.84)
0.25 (0.084, 0.72)
0.005
1
15

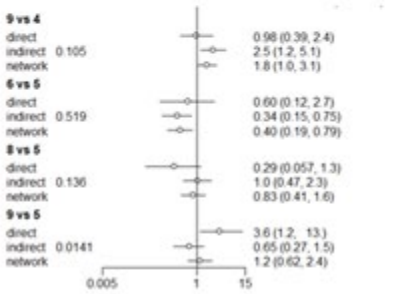

12 vs 10
direct
indirect 0.355
network
4.2 (0.34, 1.3e+02)
1.0 (0.19, 5.2)
1.5 (0.38, 5.9)
18 vs 10
direct
indirect 0.744
network
0.41 (0.011, 7.7)
0.71 (0.15, 3.4)
0.65 (0.16, 2.5)
4 vs 10
direct
indirect 0.582
network
1.7 (0.31, 9.0)
3.4 (0.49, 29.)
2.2 (0.64, 8.2)
18 vs 11
direct
indirect 0.134
network
0.84 (0.19, 3.7)
0.23 (0.10, 0.53)
0.32 (0.15, 0.64)
0.005
1
15


9 vs 11
direct
indirect 0.13
network
1.2 (0.54, 2.7)
2.8 (1.4, 5.9)
1.9 (1.1, 3.4)
13 vs 12
direct
indirect 0.621
network
6.2 (0.94, 51.)
3.5 (0.87, 14.)
4.2 (1.4, 13.)
4 vs 12
direct
indirect 0.219
network
0.83 (0.25, 2.9)
2.3 (0.79, 6.5)
1.5 (0.69, 3.3)
5 vs 12
direct
indirect 0.159
network
0.68 (0.10, 4.3)
3. (1.1, 7.9)
2.2 (0.95, 5.1)
0.005
1
15


14 vs 1
direct
indirect 0.504
network
1.1 (0.090, 9.5)
2.7 (0.47, 17.)
1.8 (0.44, 6.7)
18 vs 1
direct
indirect 0.0143
network
1.0e-14 (3.9e-42, 0.11)
0.72 (0.14, 3.5)
0.44 (0.12, 1.5)
6 vs 1
direct
indirect 0.365
network
1.3 (0.31, 5.6)
0.45 (0.071, 2.8)
0.88 (0.28, 2.6)
9 vs 1
direct
indirect 0.492
network
1.7 (0.20, 13.)
4.1 (0.92, 20.)
2.7 (0.83, 8.5)
0.005
1
15







NICU admission

Analysis of the full dataset included 186 trials of 25 treatments (386 arms) whilst analysis of the unfavourable cervix dataset included 146 trials of 23 treatments (303 arms). This dataset contained a substantial number of trials containing at least one zero-event arm. Where there are several zero-event arms, or where a treatment contrast is based entirely on zero event arms there will be less information available to the model. Whilst no treatment difference was based entirely on zero-event trials, where a zero-event arm could be contributing to inconsistency, this has been flagged.

Given the relatively high number of zero-event arms, two adjustments were made to the models fitted here. Fixed-effect models were run with increased precision on the uninformative priors given to parameters estimating trial baselines (mu) and treatment effects (d). Precision was increased from 0.001 (equivalent to variance of 1002) to 0.01 (equivalent to variance of 102). Whilst this restricts the range of the prior distribution, it can still be considered a vague, uninformative prior that covers the full range of potential parameter values. In random effect models, the standard, Un(0,5) uninformative prior on between-study standard deviation (SD) (as specified in TSD2 (1)) was replaced with an informative prior for between-study SD drawn from Turner et al. 2015 (2) for obstetric non-pharmacological vs pharmacological interventions. Results were based on 80,000 iterations following a burn-in of 40,000 iterations, which was sufficient to achieve convergence according to the Brooks Gelman-Rubin statistic (3).

Fixed-effect (FE) and random-effect (RE) models, which estimate a parameter for between-study standard deviation (SD), were fitted to both datasets. There was estimated to be low between-study SD, with estimates of 0.13 (95% credible interval [CrI] 0.04-0.25) in the full dataset and 0.14 (95% CrI 0.05-0.28) in the subgroup dataset. Whilst posterior mean residual deviance was slightly lower in the random-effects consistency NMA model than in the fixed-effects model, the increase in DIC supported use of the FE model structure in the inconsistency model.

Network meta-analysis (NMA) models of the outcome admission to NICU, comparison of fixed- (FE) and random-effect (RE) models. Residual deviance is the model's posterior mean residual deviance, to be compared to number of data points, lower values preferred. DIC is the Deviance information criteria – lower values preferred.

Dataset	Model	Between-study SD (mean)			Mean residual deviance	Data points (arms)	DIC
		Mean	2.5% CrI	97.5% CrI			
Full	Consistency NMA (FE)	-	-	-	417.40	386	1874.98
	Consistency NMA (RE)	0.13	0.04	0.25	410.50	386	1879.71
	Inconsistency NMA (FE)	-	-	-	403.40	386	1916.14
Subgroup (unfav. cervix)	Consistency NMA (FE)	-	-	-	331.10	303	1480.12
	Consistency NMA (RE)	0.14	0.05	0.28	325.90	303	1483.84
	Inconsistency NMA (FE)	-	-	-	319.70	303	1510.12

Consistency and inconsistency fixed-effects NMA models were fitted to the full and subgroup datasets. In both the full and subgroup datasets there was no evidence of inconsistency when comparing based on DIC.

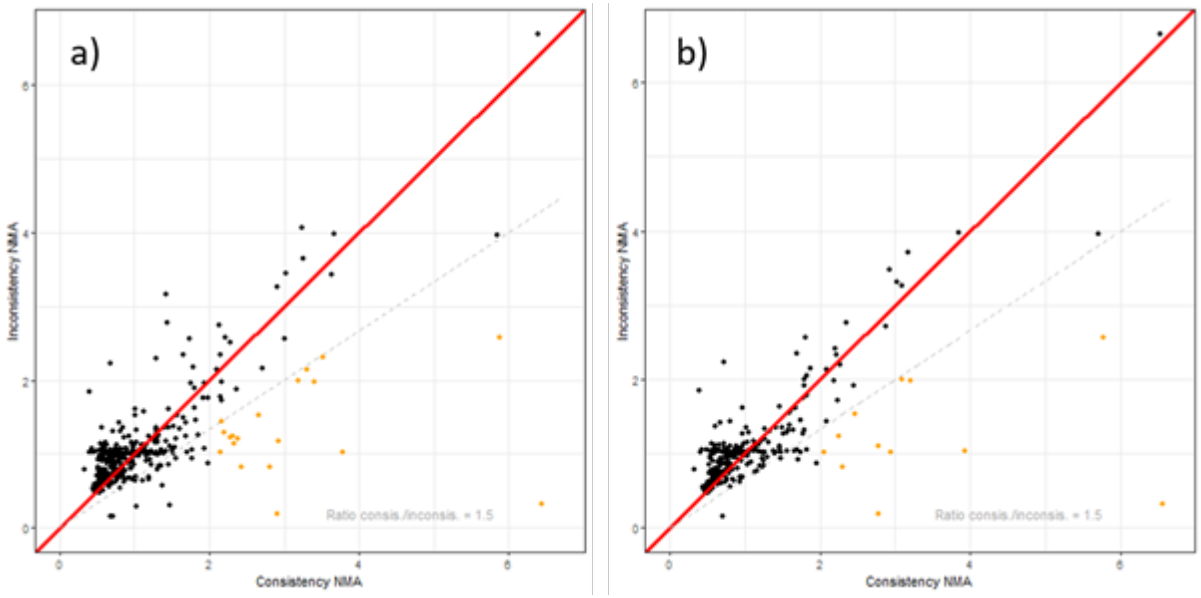
To explore this further we plotted the contribution of each study arm to the total residual deviance for the inconsistency model vs the consistency model in a dev-dev plot (Fig. 1). A simple rule was used to identify study arms with relatively high deviance in the consistency model: points with relatively high deviance were those with mean deviance in the consistency NMA model greater than 2, and where the residual deviance in the consistency NMA was at least 1.5 times that estimated under the inconsistency model.

Eight studies were flagged in both the full and subgroup datasets as having higher deviance in the consistency model than in the inconsistency model:

- Agarwal 2014 was a two-armed trial comparing intracervical PGE2 and nitric oxide with zero events in the nitric oxide arm.
- Akay 2012 was a two-armed trial comparing vaginal PGE2 (pessary – slow release) and IV oxytocin with zero events in the IV oxytocin arm.
- Guha 2015 was a two-armed trial comparing vaginal misoprostol (dose 50 mcg or more) and nitric oxide.
- Osman 2006 was a two-armed trial comparing vaginal PGE2 gel and nitric oxide.
- Cheng 2008 (highlighted 2019) was a two-armed trial comparing vaginal misoprostol (dose less than 50 mcg) and titrated (low dose) oral misoprostol solution with zero events in the oral misoprostol arm.
- O'Brien 1995 (highlighted 2019) was a relatively small two-armed trial comparing vaginal PGE2 against placebo.
- Razaq 2011 (highlighted 2019) was a two-armed trial comparing vaginal misoprostol (dose 50 mcg or more) and nitric oxide with zero events in the nitric oxide arm.
- Rouzi 2014 (highlighted 2019) was a two-armed trial comparing vaginal PGE2 (pessary – slow release) and titrated (low dose) oral misoprostol solution with zero events in the vaginal PGE2 arm.

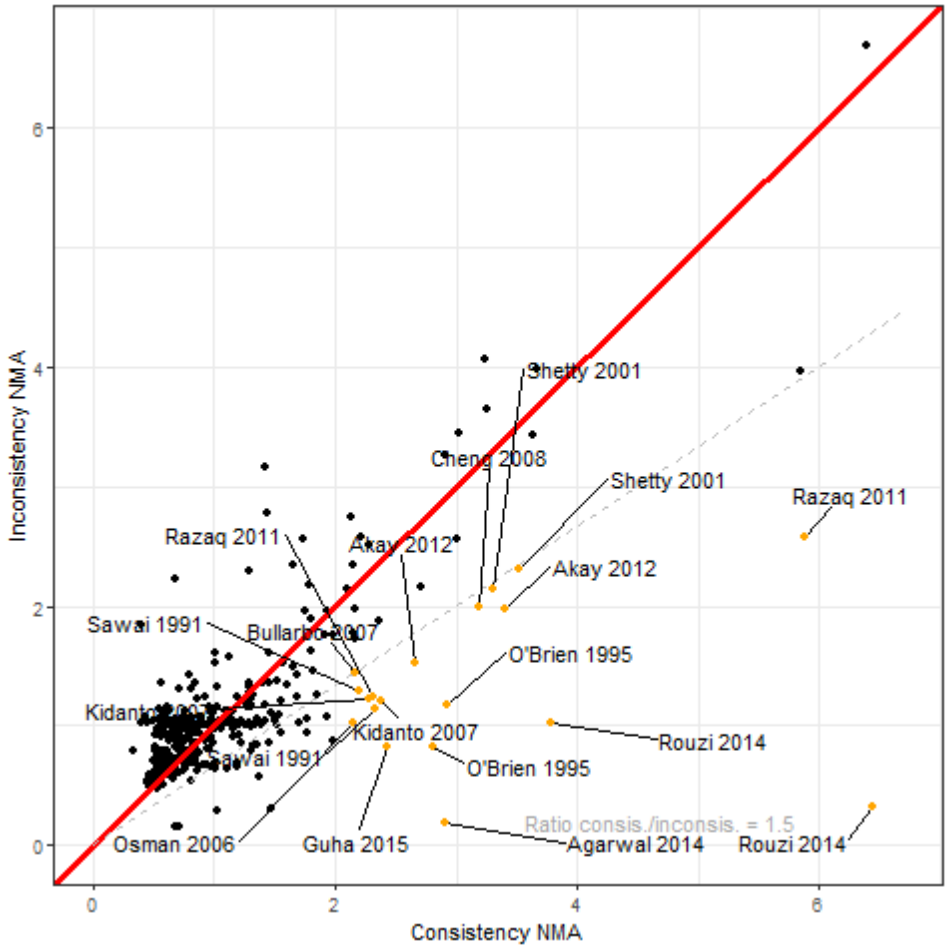
Four studies were flagged in the full dataset only:

- Bullarbo 2007 was a two-armed trial comparing nitric oxide against placebo.
- Kidanto 2007 was a two-armed trial comparing vaginal misoprostol (dose less than 50 mcg) and IV oxytocin.
- Sawai 1991 was a relatively small two-armed trial comparing vaginal PGE2 gel against placebo, with zero events in the vaginal PGE2 gel arm.
- Shetty 2001 was a two-armed trial comparing vaginal misoprostol (dose 50 mcg or more) and oral misoprostol tablet (dose 50 mcg or more).



Dev-dev plots of each study arm's deviance in the FE consistency (x-axis) and inconsistency NMA (y-axis) models of NICU admission. Deviance is shown for a) the full dataset and b) the unfavourable cervix subgroup dataset indicating study arms that were relatively poorly predicted by the consistency NMA in orange. Red line indicates line of equivalence.

Dev-dev plot of the outcome NICU admission, full dataset, indicating distribution of studies with relatively high deviance in the consistency model.



Fixed-effect node-splitting NMA models were used to assess the direct and indirect evidence for each treatment comparison. Where the indirect estimate consistently differs from the direct estimate, the p value will approach zero, with a threshold set at 0.05 to highlight comparisons that are likely to be inconsistent.

In the full dataset, there were 10 comparisons out of 84 with potential inconsistency between the direct and indirect estimates. Given multiple testing, we would expect at least 4 comparisons to show inconsistency. The flagged comparisons indicate that there may be inconsistency in the following treatment effect estimates:

- Vaginal misoprostol (dose 50 mcg or more) against oral misoprostol tablet (dose 50mcg or more) and nitric oxide
- Titrated (low dose) oral misoprostol solution against vaginal PGE2 (pessary – slow release) and vaginal misoprostol (dose less than 50 mcg)
- Amniotomy against IV oxytocin plus amniotomy and vaginal PGE2 gel
- Nitric oxide against placebo, intracervical PGE2 and vaginal misoprostol (dose 50 mcg or more)
- Vaginal PGE2 (gel) against buccal/sublingual misoprostol, placebo and amniotomy

Treatment differences based only on direct evidence were poorly estimated for comparisons involving nitric oxide (treatment code 17 in full dataset) and amniotomy (treatment code 15 in full dataset).

In the unfavourable cervix subgroup, 7 out of 65 treatment comparisons were potentially inconsistent, with at least 3 anticipated under multiple testing. Treatment differences based only on direct evidence were poorly estimated for nitric oxide (treatment code 15 in subgroup dataset).

- Titrated (low dose) oral misoprostol solution against vaginal PGE2 (pessary – slow release) and vaginal misoprostol (dose less than 50 mcg)
- Nitric oxide against placebo, vaginal PGE2 (tablet), intracervical PGE2 and vaginal misoprostol (dose 50 mcg or more)
- Placebo against vaginal PGE2 (gel) and nitric oxide

Direct and indirect estimates of treatment difference (LOR) for the outcome NICU admission, full dataset. Treatment comparisons where direct and indirect evidence were judged to be inconsistent ($p<0.05$) are highlighted in yellow. Residual deviance is the model's posterior mean residual deviance, to be compared to number of data points (386), lower values preferred.

Intervention 1	Intervention 2	p-value	Residual deviance	Direct			Indirect		
				Median	2.50%	97.50%	Median	2.50%	97.50%
Consistency			417.6						
Oral misoprostol tablet (dose 50mcg or more)	Vaginal misoprostol (dose 50 mcg or more)	0.017	413.1	-0.122	-0.385	0.137	0.338	0.055	0.621
Titrated (low dose) oral misoprostol solution	Vaginal PGE2 (pessary – slow release)	<0.001	407.9	-32.537	-103.332	-3.571	0.219	-0.175	0.613
Titrated (low dose) oral misoprostol solution	Vaginal misoprostol (dose less than 50 mcg)	0.014	411.5	0.711	0.104	1.341	-0.185	-0.557	0.188
Amniotomy	IV oxytocin plus amniotomy	0.01	414.4	16.788	1.772	54.384	0.120	-1.254	1.467
Amniotomy	Vaginal PGE2 (gel)	0.007	414.4	-0.171	-1.354	0.990	17.592	1.581	59.127
Nitric oxide	Placebo	0.037	414.4	0.137	-0.272	0.546	1.015	0.303	1.746
Nitric oxide	Intracervical PGE2	0.005	413.9	20.033	2.585	55.331	0.515	0.076	0.959
Nitric oxide	Vaginal misoprostol (dose 50 mcg or more)	0.001	407.9	1.963	1.133	2.983	0.346	-0.150	0.840
Placebo	Vaginal PGE2 (gel)	0.041	414.7	-1.008	-2.634	0.362	0.488	0.047	0.929
Buccal/sublingual misoprostol	Vaginal PGE2 (gel)	0.023	416.3	-31.162	-103.236	-1.188	0.042	-0.367	0.454
No treatment	IV oxytocin	0.314	418.1	-0.045	-1.224	0.951	0.565	-0.053	1.193

No treatment	IV oxytocin plus amniotomy	0.707	418.4	0.528	-0.423	1.528	0.795	-0.206	1.784
No treatment	Nitric oxide	0.736	418.6	-0.203	-1.881	1.621	-0.505	-1.107	0.090
No treatment	Mechanical methods – foley catheter	0.218	418	-0.624	-2.169	0.549	0.213	-0.349	0.777
No treatment	Intracervical PGE2	0.783	418.6	-0.074	-1.595	1.471	0.146	-0.358	0.654
No treatment	Vaginal PGE2 pessary (normal release)	0.182	416.8	0.344	-0.266	0.961	-0.305	-1.040	0.423
No treatment	Vaginal misoprostol (dose less than 50 mcg)	0.981	418.7	0.021	-3.654	3.676	0.060	-0.402	0.533
No treatment	Vaginal misoprostol (dose 50 mcg or more)	0.491	418.4	0.175	-0.699	0.988	0.525	-0.048	1.104
Oral misoprostol tablet (dose less than 50 mcg)	Oral misoprostol tablet (dose 50mcg or more)	0.691	418.6	0.670	-1.956	4.160	0.123	-0.348	0.590
Oral misoprostol tablet (dose less than 50 mcg)	Titrated (low dose) oral misoprostol solution	0.278	417.2	0.358	-0.587	1.356	-0.251	-0.820	0.315
Oral misoprostol tablet (dose less than 50 mcg)	Mechanical methods – foley catheter	0.163	416.6	-0.409	-1.032	0.195	0.209	-0.406	0.837
Oral misoprostol tablet (dose less than 50 mcg)	Vaginal PGE2 (gel)	0.517	418.2	0.411	-0.615	1.477	0.035	-0.468	0.537
Oral misoprostol tablet (dose less than 50 mcg)	Intracervical PGE2	0.992	418.5	-0.001	-1.165	1.168	0.005	-0.494	0.509
Oral misoprostol tablet (dose 50mcg or more)	IV oxytocin	0.917	418.5	0.143	-0.802	1.067	0.090	-0.278	0.456
Oral misoprostol tablet (dose 50mcg or more)	Placebo	0.734	418.6	-0.012	-2.286	2.270	-0.389	-0.825	0.049

Oral misoprostol tablet (dose 50mcg or more)	Mechanical methods – foley catheter	0.475	416.4	-0.068	-0.607	0.467	-0.287	-0.559	-0.015
Oral misoprostol tablet (dose 50mcg or more)	Buccal/sublingual misoprostol	0.632	418.4	-0.185	-0.867	0.484	0.012	-0.449	0.472
Oral misoprostol tablet (dose 50mcg or more)	Vaginal PGE2 (tablet)	0.843	418.6	0.001	-0.865	0.872	-0.097	-0.555	0.362
Oral misoprostol tablet (dose 50mcg or more)	Vaginal PGE2 (gel)	0.182	416.1	0.665	-0.365	1.847	-0.062	-0.318	0.192
Oral misoprostol tablet (dose 50mcg or more)	Intracervical PGE2	0.939	415.3	-0.102	-1.000	0.782	-0.135	-0.415	0.139
Oral misoprostol tablet (dose 50mcg or more)	Vaginal misoprostol (dose less than 50 mcg)	0.084	414.5	0.003	-0.293	0.296	-0.349	-0.618	-0.085
Titrated (low dose) oral misoprostol solution	Sustained release misoprostol insert	0.844	418.5	0.023	-1.500	1.546	-0.133	-0.621	0.358
Titrated (low dose) oral misoprostol solution	IV oxytocin	0.118	416.8	1.949	-0.073	5.253	0.254	-0.174	0.686
Titrated (low dose) oral misoprostol solution	Mechanical methods – foley catheter	0.223	416.1	-0.956	-2.972	0.477	0.002	-0.355	0.362
Titrated (low dose) oral misoprostol solution	Extra-amniotic PGE2 or PGF2	0.815	419.3	-0.556	-1.629	0.401	-0.411	-1.145	0.310
Titrated (low dose) oral misoprostol solution	Vaginal PGE2 (gel)	0.922	412.2	0.219	-0.284	0.749	0.187	-0.227	0.601
Titrated (low dose) oral misoprostol solution	Vaginal PGE2 pessary (normal release)	0.625	419.2	-0.038	-0.623	0.532	0.188	-0.528	0.916
Titrated (low dose) oral misoprostol solution	Vaginal misoprostol (dose 50 mcg or more)	0.94	419.3	0.302	-0.245	0.867	0.327	-0.042	0.703

Sustained release misoprostol insert	Vaginal PGE2 (pessary – slow release)	0.85	418.6	0.214	-0.070	0.498	0.064	-1.502	1.628
IV oxytocin	Mechanical methods – foley catheter	0.768	418.9	-0.579	-2.272	0.906	-0.349	-0.729	0.029
IV oxytocin	Mechanical methods – Double balloon or Cook's catheter	0.285	418	-1.745	-5.173	0.384	-0.490	-0.999	0.017
IV oxytocin	Vaginal PGE2 (pessary – slow release)	0.065	415.4	0.811	-0.370	2.177	-0.369	-0.797	0.057
IV oxytocin	Vaginal misoprostol (dose less than 50 mcg)	0.162	416.6	-0.673	-1.323	-0.044	-0.147	-0.532	0.246
IV oxytocin	Vaginal misoprostol (dose 50 mcg or more)	0.333	418.2	0.123	-0.318	0.566	-0.195	-0.670	0.272
IV oxytocin plus amniotomy	Vaginal PGE2 (gel)	0.688	418.4	-0.303	-1.205	0.656	-0.579	-1.641	0.433
Nitric oxide	Vaginal PGE2 (tablet)	0.063	416.8	18.965	0.259	68.090	0.625	0.079	1.179
Nitric oxide	Vaginal PGE2 (gel)	0.077	415.5	0.073	-0.722	0.877	0.919	0.441	1.407
Mifepristone	Placebo	0.239	417.3	-0.169	-0.961	0.606	0.846	-0.617	2.557
Mifepristone	Intracervical PGE2	0.232	417.5	1.020	-0.372	2.667	-0.003	-0.912	0.887
Placebo	Vaginal PGE2 (pessary – slow release)	0.282	418	1.509	-0.789	4.921	0.183	-0.299	0.671
Placebo	Intracervical PGE2	0.469	417.1	-0.444	-2.628	1.476	0.274	-0.166	0.718
Placebo	Vaginal PGE2 pessary (normal release)	0.282	417.4	-0.726	-2.861	1.038	0.302	-0.294	0.892

Placebo	Vaginal misoprostol (dose less than 50 mcg)	0.33	417.7	-0.119	-0.857	0.608	0.317	-0.174	0.814
Mechanical methods – foley catheter	Mechanical methods – Double balloon or Cook's catheter	0.179	416.4	-0.580	-1.249	0.067	0.002	-0.536	0.541
Mechanical methods – foley catheter	Extra-amniotic PGE2 or PGF2	0.633	418.2	-0.272	-1.130	0.560	-0.539	-1.296	0.156
Mechanical methods – foley catheter	Vaginal PGE2 (tablet)	0.331	417.5	-0.271	-1.269	0.704	0.259	-0.182	0.695
Mechanical methods – foley catheter	Vaginal PGE2 (gel)	0.659	417.4	0.287	-0.142	0.720	0.172	-0.121	0.460
Mechanical methods – foley catheter	Vaginal PGE2 (pessary – slow release)	0.383	417.8	0.251	-0.187	0.694	-0.007	-0.394	0.380
Mechanical methods – foley catheter	Intracervical PGE2	0.804	418.5	0.152	-0.283	0.593	0.087	-0.222	0.396
Mechanical methods – foley catheter	Vaginal misoprostol (dose less than 50 mcg)	0.589	417.2	-0.042	-0.427	0.346	0.086	-0.172	0.345
Mechanical methods – foley catheter	Vaginal misoprostol (dose 50 mcg or more)	0.458	418.2	-0.001	-0.898	0.899	0.349	0.108	0.590
Mechanical methods – laminaria including dilapan	Vaginal PGE2 (gel)	0.25	417.4	0.443	-1.501	2.629	-0.936	-2.585	0.444
Mechanical methods – laminaria including dilapan	Intracervical PGE2	0.263	417.5	-1.014	-2.640	0.342	0.345	-1.612	2.543
Mechanical methods – Double balloon or Cook's catheter	Vaginal PGE2 (tablet)	0.639	418.4	0.337	-0.038	0.719	0.526	-0.165	1.226

Mechanical methods – Double balloon or Cook's catheter	Vaginal PGE2 (gel)	0.678	417	0.509	-0.229	1.298	0.320	-0.199	0.840
Mechanical methods – Double balloon or Cook's catheter	Vaginal PGE2 (pessary – slow release)	0.128	416.4	-0.509	-1.763	0.645	0.464	-0.022	0.955
Extra-amniotic PGE2 or PGF2	Vaginal PGE2 pessary (normal release)	0.76	419.3	0.339	-0.799	1.531	0.560	-0.248	1.385
Extra-amniotic PGE2 or PGF2	Vaginal misoprostol (dose 50 mcg or more)	0.645	419.3	0.853	0.169	1.593	0.590	-0.275	1.484
Buccal/sublingual misoprostol	Vaginal misoprostol (dose less than 50 mcg)	0.77	418.5	-0.075	-0.682	0.530	-0.188	-0.669	0.292
Buccal/sublingual misoprostol	Vaginal misoprostol (dose 50 mcg or more)	0.591	418.1	0.001	-0.618	0.629	0.217	-0.261	0.693
Vaginal PGE2 (tablet)	Vaginal PGE2 (gel)	0.474	418.3	-0.882	-4.377	1.679	0.072	-0.348	0.494
Vaginal PGE2 (tablet)	Vaginal PGE2 (pessary – slow release)	0.297	417.6	-0.785	-2.446	0.610	0.014	-0.451	0.482
Vaginal PGE2 (tablet)	Vaginal misoprostol (dose 50 mcg or more)	0.866	418.5	0.098	-0.780	0.981	0.182	-0.264	0.635
Vaginal PGE2 (gel)	Intracervical PGE2	0.796	418.6	-0.171	-0.727	0.385	-0.088	-0.376	0.204
Vaginal PGE2 (gel)	Vaginal misoprostol (dose less than 50 mcg)	0.44	416.7	-0.235	-0.532	0.060	-0.076	-0.358	0.206
Vaginal PGE2 (gel)	Vaginal misoprostol (dose 50 mcg or more)	0.693	416.8	0.202	-0.233	0.638	0.100	-0.161	0.363
Vaginal PGE2 (pessary – slow release)	Intracervical PGE2	0.21	416.5	1.504	-0.787	4.920	-0.023	-0.363	0.318

Vaginal PGE2 (pessary – slow release)	Vaginal misoprostol (dose less than 50 mcg)	0.493	415.2	0.123	-0.468	0.713	-0.115	-0.451	0.222
Vaginal PGE2 (pessary – slow release)	Vaginal misoprostol (dose 50 mcg or more)	0.437	415.2	0.028	-0.528	0.589	0.290	-0.059	0.642
Intracervical PGE2	Vaginal misoprostol (dose less than 50 mcg)	0.966	417.6	-0.050	-0.398	0.301	-0.061	-0.362	0.236
Intracervical PGE2	Vaginal misoprostol (dose 50 mcg or more)	0.698	418	0.312	-0.197	0.837	0.196	-0.082	0.477
Vaginal PGE2 pessary (normal release)	Vaginal misoprostol (dose less than 50 mcg)	0.663	418.6	-0.723	-4.389	2.930	0.000	-0.448	0.455
Vaginal PGE2 pessary (normal release)	Vaginal misoprostol (dose 50 mcg or more)	0.41	418.6	0.506	-0.230	1.295	0.118	-0.431	0.669
Vaginal misoprostol (dose less than 50 mcg)	Vaginal misoprostol (dose 50 mcg or more)	0.313	416.8	0.472	0.053	0.901	0.229	0.016	0.445

Direct and indirect estimates of treatment difference (LOR) for the outcome NICU admission, unfavourable cervix subgroup. Treatment comparisons where direct and indirect evidence were judged to be inconsistent ($p<0.05$) are highlighted in yellow. Residual deviance is the model's posterior mean residual deviance, to be compared to number of data points (303), lower values preferred.

Intervention 1	Intervention 2	p-value	Residual deviance	Direct			Indirect		
				Median	2.50%	97.50%	Median	2.50%	97.50%
Consistency		-	332.7	-	-	-	-	-	-
Titrated (low dose) oral misoprostol solution	Vaginal PGE2 (pessary – slow release)	0	322.7	-32.497	-103.280	-3.586	0.331	-0.154	0.820
Titrated (low dose) oral misoprostol solution	Vaginal misoprostol (dose less than 50 mcg)	0.011	326	0.710	0.105	1.343	-0.408	-1.020	0.194
Nitric oxide	Placebo	0.038	329.5	0.138	-0.270	0.543	1.070	0.284	1.878

Nitric oxide	Vaginal PGE2 (tablet)	0.043	331.8	24.635	0.807	73.065	0.574	-0.045	1.184
Nitric oxide	Intracervical PGE2	0.005	329.3	21.374	2.566	59.985	0.584	0.112	1.061
Nitric oxide	Vaginal misoprostol (dose 50 mcg or more)	0.001	323.2	1.959	1.121	2.985	0.323	-0.209	0.849
Placebo	Vaginal PGE2 (gel)	0.019	328.7	-1.997	-5.406	0.048	0.490	0.013	0.982
No treatment	IV oxytocin	0.660	334	-0.043	-1.213	0.956	0.271	-0.723	1.304
No treatment	Nitric oxide	0.553	333.4	-0.207	-1.891	1.639	-0.769	-1.525	-0.019
No treatment	Mechanical methods – Foley catheter	0.341	334	-0.616	-2.167	0.551	0.117	-0.791	1.065
No treatment	Intracervical PGE2	0.932	333.7	-0.061	-1.589	1.458	0.009	-0.673	0.700
No treatment	Vaginal misoprostol (dose 50 mcg or more)	0.819	334.4	0.172	-0.687	0.978	0.330	-0.799	1.482
Oral misoprostol tablet (dose less than 50 mcg)	Oral misoprostol tablet (dose 50mcg or more)	0.696	333.6	0.660	-1.952	4.166	0.126	-0.363	0.612
Oral misoprostol tablet (dose less than 50 mcg)	Titrated (low dose) oral misoprostol solution	0.208	332.1	0.355	-0.593	1.345	-0.378	-1.026	0.258
Oral misoprostol tablet (dose less than 50 mcg)	Mechanical methods – Foley catheter	0.120	331.3	-0.413	-1.037	0.195	0.278	-0.348	0.918
Oral misoprostol tablet (dose less than 50 mcg)	Vaginal PGE2 (gel)	0.464	333	0.400	-0.616	1.457	-0.023	-0.538	0.490
Oral misoprostol tablet (dose less than 50 mcg)	Intracervical PGE2	0.928	333.6	0.004	-1.164	1.167	0.063	-0.457	0.579
Oral misoprostol tablet (dose 50mcg or more)	Mechanical methods – Foley catheter	0.518	331.8	-0.069	-0.610	0.465	-0.275	-0.587	0.032

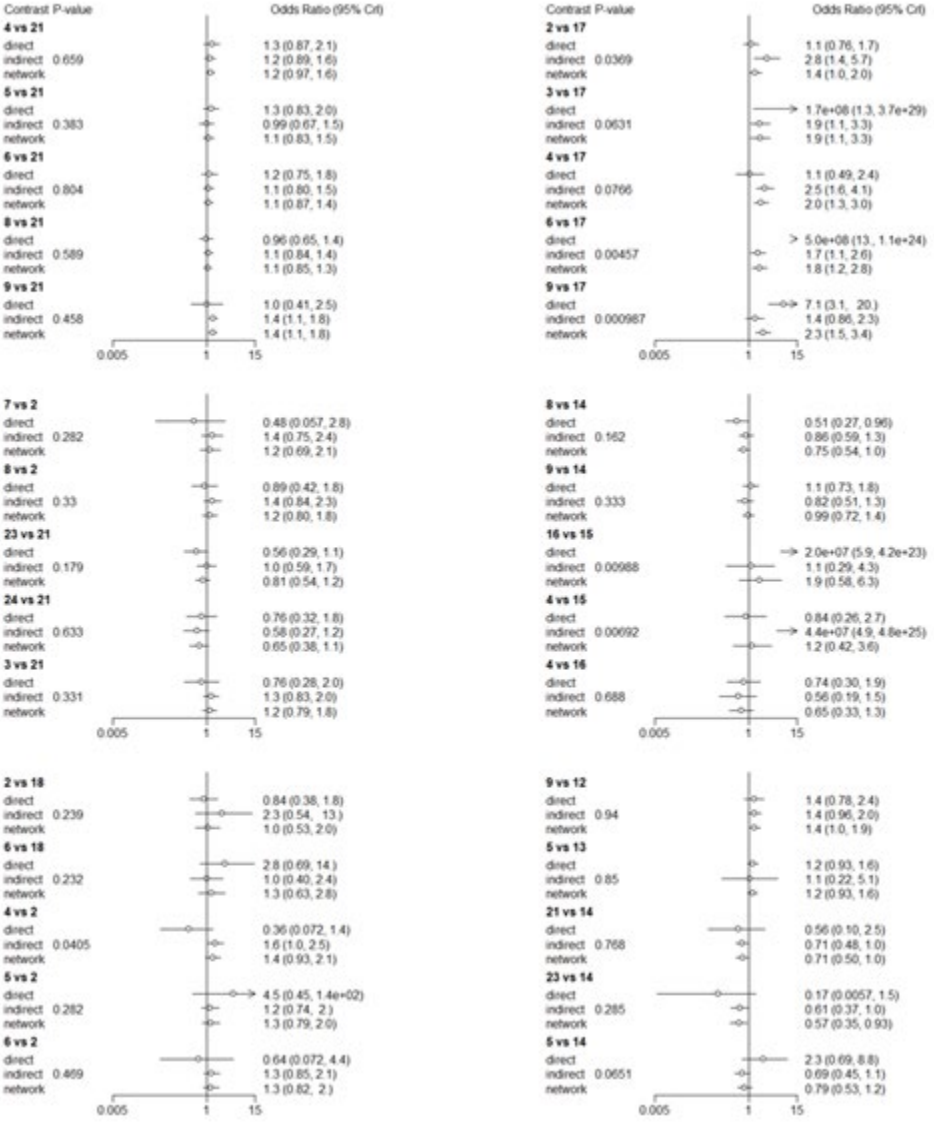
Oral misoprostol tablet (dose 50mcg or more)	Placebo	0.697	333.5	-0.009	-2.282	2.232	-0.442	-0.935	0.041
Oral misoprostol tablet (dose 50mcg or more)	Buccal/sublingual misoprostol	0.716	333.3	-0.180	-0.862	0.494	-0.024	-0.516	0.468
Oral misoprostol tablet (dose 50mcg or more)	Vaginal PGE2 (gel)	0.227	331.9	0.855	-0.620	2.902	-0.103	-0.397	0.188
Oral misoprostol tablet (dose 50mcg or more)	Intracervical PGE2	0.970	330	-0.101	-0.992	0.781	-0.082	-0.406	0.239
Oral misoprostol tablet (dose 50mcg or more)	Vaginal misoprostol (dose less than 50 mcg)	0.365	331.8	-0.078	-0.442	0.286	-0.295	-0.595	0.008
Oral misoprostol tablet (dose 50mcg or more)	Vaginal misoprostol (dose 50 mcg or more)	0.236	332.1	-0.030	-0.328	0.267	0.247	-0.099	0.592
Titrated (low dose) oral misoprostol solution	Sustained release misoprostol insert	0.889	333.6	0.016	-1.502	1.536	-0.093	-0.657	0.481
Titrated (low dose) oral misoprostol solution	IV oxytocin	0.091	331.3	1.921	-0.082	5.329	0.087	-0.518	0.690
Titrated (low dose) oral misoprostol solution	Vaginal PGE2 (gel)	0.722	329.6	0.079	-0.547	0.738	0.237	-0.327	0.799
Titrated (low dose) oral misoprostol solution	Vaginal PGE2 pessary (normal release)	0.711	333.7	0.069	-0.686	0.831	-0.222	-1.694	1.113
Sustained release misoprostol insert	Vaginal PGE2 (pessary – slow release)	0.891	333.7	0.215	-0.072	0.502	0.104	-1.499	1.708
IV oxytocin	Mechanical methods – Foley catheter	0.589	334.3	-0.586	-2.250	0.895	-0.150	-0.657	0.360

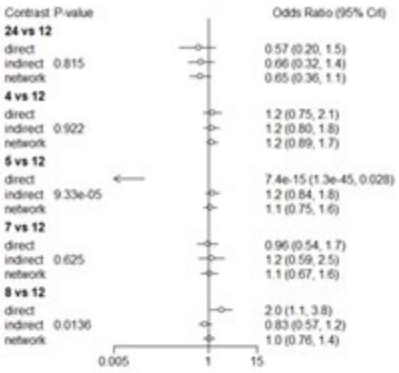
IV oxytocin	Mechanical methods – Double balloon or Cook's catheter	0.241	332.7	-1.734	-5.160	0.397	-0.343	-0.964	0.276
IV oxytocin	Vaginal PGE2 (pessary – slow release)	0.092	331	0.810	-0.375	2.164	-0.311	-0.857	0.239
IV oxytocin	Vaginal misoprostol (dose less than 50 mcg)	0.317	332.6	0.558	-0.919	2.233	-0.234	-0.719	0.251
IV oxytocin	Vaginal misoprostol (dose 50 mcg or more)	0.558	334.2	0.038	-0.506	0.586	0.317	-0.448	1.074
Nitric oxide	Vaginal PGE2 (gel)	0.080	330.7	0.076	-0.715	0.881	0.926	0.419	1.448
Mechanical methods – Foley catheter	Mechanical methods – Double balloon or Cook's catheter	0.223	332.2	-0.576	-1.254	0.067	-0.024	-0.640	0.582
Mechanical methods – Foley catheter	Vaginal PGE2 (tablet)	0.410	333	-0.275	-1.277	0.694	0.188	-0.336	0.711
Mechanical methods – Foley catheter	Vaginal PGE2 (gel)	0.915	332.3	0.156	-0.300	0.619	0.126	-0.189	0.445
Mechanical methods – Foley catheter	Vaginal PGE2 (pessary – slow release)	0.251	332.3	0.251	-0.189	0.692	-0.100	-0.511	0.310
Mechanical methods – Foley catheter	Intracervical PGE2	0.914	333.7	0.152	-0.283	0.587	0.121	-0.230	0.471
Mechanical methods – Foley catheter	Vaginal misoprostol (dose less than 50 mcg)	0.744	332.1	-0.043	-0.423	0.342	0.036	-0.244	0.316
Mechanical methods – Foley catheter	Vaginal misoprostol (dose 50 mcg or more)	0.483	333.7	0.001	-0.899	0.906	0.335	0.065	0.604

Placebo	Vaginal PGE2 (pessary – slow release)	0.294	332.8	1.509	-0.795	5.057	0.200	-0.327	0.732
Placebo	Intracervical PGE2	0.868	332.7	0.070	-3.616	3.731	0.339	-0.157	0.843
Placebo	Vaginal misoprostol (dose less than 50 mcg)	0.252	332.3	-0.116	-0.856	0.606	0.418	-0.146	0.995
Mechanical methods – laminaria including dilapan	Vaginal PGE2 (gel)	0.227	332.3	0.436	-1.508	2.598	-1.031	-2.676	0.353
Mechanical methods – laminaria including dilapan	Intracervical PGE2	0.227	332.5	-1.019	-2.637	0.337	0.441	-1.538	2.668
Mechanical methods – Double balloon or Cook's catheter	Vaginal PGE2 (tablet)	0.650	333.4	0.311	-0.069	0.692	0.518	-0.294	1.337
Mechanical methods – Double balloon or Cook's catheter	Vaginal PGE2 (gel)	0.641	332.4	0.513	-0.232	1.275	0.288	-0.307	0.877
Mechanical methods – Double balloon or Cook's catheter	Vaginal PGE2 (pessary – slow release)	0.120	331.4	-0.506	-1.756	0.644	0.498	-0.024	1.026
Buccal/sublingual misoprostol	Vaginal misoprostol (dose less than 50 mcg)	0.824	333.4	-0.073	-0.673	0.527	-0.164	-0.676	0.352
Buccal/sublingual misoprostol	Vaginal misoprostol (dose 50 mcg or more)	0.550	333.4	0.002	-0.677	0.679	0.257	-0.232	0.744
Vaginal PGE2 (tablet)	Vaginal PGE2 (gel)	0.462	333.3	-0.886	-4.377	1.693	0.098	-0.394	0.598
Vaginal PGE2 (tablet)	Vaginal PGE2 (pessary – slow release)	0.260	332.6	-0.789	-2.441	0.612	0.091	-0.440	0.633

Vaginal PGE2 (tablet)	Vaginal misoprostol (dose 50 mcg or more)	0.973	333.7	0.211	-1.059	1.528	0.236	-0.286	0.761
Vaginal PGE2 (gel)	Vaginal misoprostol (dose less than 50 mcg)	0.253	331	-0.227	-0.527	0.070	0.036	-0.302	0.375
Vaginal PGE2 (gel)	Vaginal misoprostol (dose 50 mcg or more)	0.904	331.8	0.200	-0.238	0.639	0.167	-0.142	0.477
Vaginal PGE2 (pessary – slow release)	Intracervical PGE2	0.227	331.5	1.502	-0.783	4.951	0.040	-0.322	0.402
Vaginal PGE2 (pessary – slow release)	Vaginal misoprostol (dose less than 50 mcg)	0.505	330.3	0.123	-0.470	0.724	-0.113	-0.474	0.248
Vaginal PGE2 (pessary – slow release)	Vaginal misoprostol (dose 50 mcg or more)	0.434	330.3	0.013	-0.649	0.679	0.317	-0.054	0.689
Intracervical PGE2	Vaginal misoprostol (dose less than 50 mcg)	0.763	332.6	-0.072	-0.442	0.296	-0.152	-0.505	0.200
Intracervical PGE2	Vaginal misoprostol (dose 50 mcg or more)	0.850	333.2	0.129	-0.456	0.724	0.194	-0.132	0.517
Vaginal PGE2 pessary (normal release)	Vaginal misoprostol (dose less than 50 mcg)	0.624	333.6	-0.686	-4.381	2.950	0.133	-0.609	0.880
Vaginal PGE2 pessary (normal release)	Vaginal misoprostol (dose 50 mcg or more)	0.496	333.3	0.809	-0.597	2.439	0.232	-0.620	1.083
Vaginal misoprostol (dose less than 50 mcg)	Vaginal misoprostol (dose 50 mcg or more)	0.237	331.5	0.559	0.071	1.060	0.229	-0.019	0.474

Forest plots for NICU admission, full dataset, showing direct, indirect and network estimates of treatment difference (contrast), odds ratio scale. Treatment codes: 1 - No treatment, 2 – Placebo, 3 - Vaginal PGE2 (tablet), 4 - Vaginal PGE2 (gel), 5 - Vaginal PGE2 (pessary – slow release), 6 - Intracervical PGE2, 7 - Vaginal PGE2 pessary (normal release), 8 - Vaginal misoprostol (dose less than 50 mcg), 9 - Vaginal misoprostol (dose 50 mcg or more), 10 - Oral misoprostol tablet (dose less than 50 mcg), 11 - Oral misoprostol tablet (dose 50mcg or more), 12 - Titrated (low dose) oral misoprostol solution, 13 - Sustained release misoprostol insert, 14 - IV oxytocin, 15 – Amniotomy, 16 - IV oxytocin plus amniotomy, 17 - Nitric oxide, 18 – Mifepristone, 19 – Oestrogens, 20 – Relaxin, 21 - Mechanical methods – foley catheter, 22 - Mechanical methods – laminaria including dilapan, 23 - Mechanical methods – Double balloon or Cook's catheter, 24 - Extra-amniotic PGE2 or PGF2, 25 - Buccal/sublingual misoprostol.




Contrast P-value
Odds Ratio (95% CrI)
24 vs 12
direct
indirect 0.815
network
0.57 (0.20, 1.5)
0.66 (0.32, 1.4)
0.65 (0.36, 1.1)
4 vs 12
direct
indirect 0.922
network
1.2 (0.75, 2.1)
1.2 (0.80, 1.8)
1.2 (0.89, 1.7)
5 vs 12
direct
indirect 9.33e-05
network
7.4e-15 (1.3e-45, 0.028)
1.2 (0.84, 1.8)
1.1 (0.75, 1.6)
7 vs 12
direct
indirect 0.625
network
0.96 (0.54, 1.7)
1.2 (0.59, 2.5)
1.1 (0.67, 1.6)
8 vs 12
direct
indirect 0.0136
network
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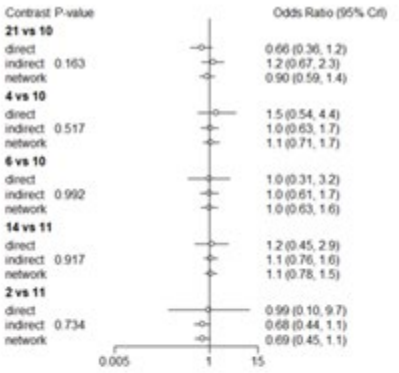
0.83 (0.57, 1.2)
1.0 (0.76, 1.4)
0.005
1
15


Contrast P-value
Odds Ratio (95% CrI)
21 vs 10
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indirect 0.163
network
0.66 (0.36, 1.2)
1.2 (0.67, 2.3)
0.90 (0.59, 1.4)
4 vs 10
direct
indirect 0.517
network
1.5 (0.54, 4.4)
1.0 (0.63, 1.7)
1.1 (0.71, 1.7)
6 vs 10
direct
indirect 0.992
network
1.0 (0.31, 3.2)
1.0 (0.61, 1.7)
1.0 (0.63, 1.6)
14 vs 11
direct
indirect 0.917
network
1.2 (0.45, 2.9)
1.1 (0.76, 1.6)
1.1 (0.78, 1.5)
2 vs 11
direct
indirect 0.734
network
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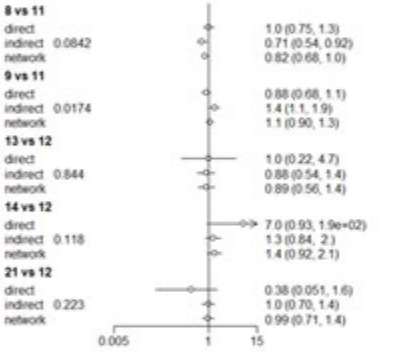
0.69 (0.45, 1.1)
0.005
1
15


8 vs 11
direct
indirect 0.0842
network
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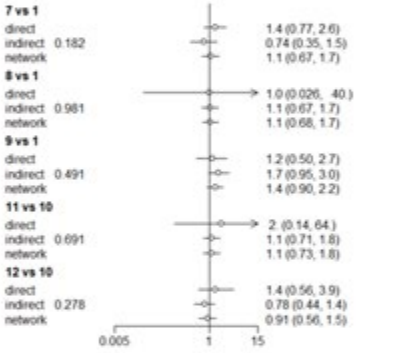
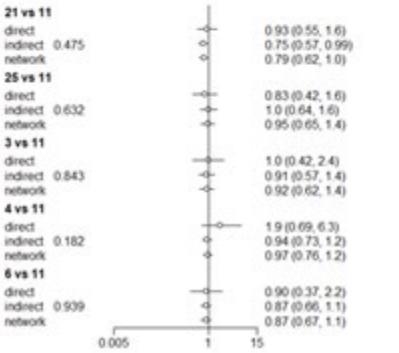
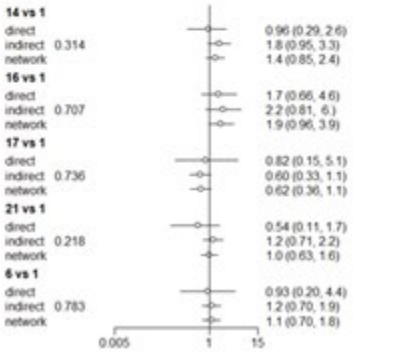
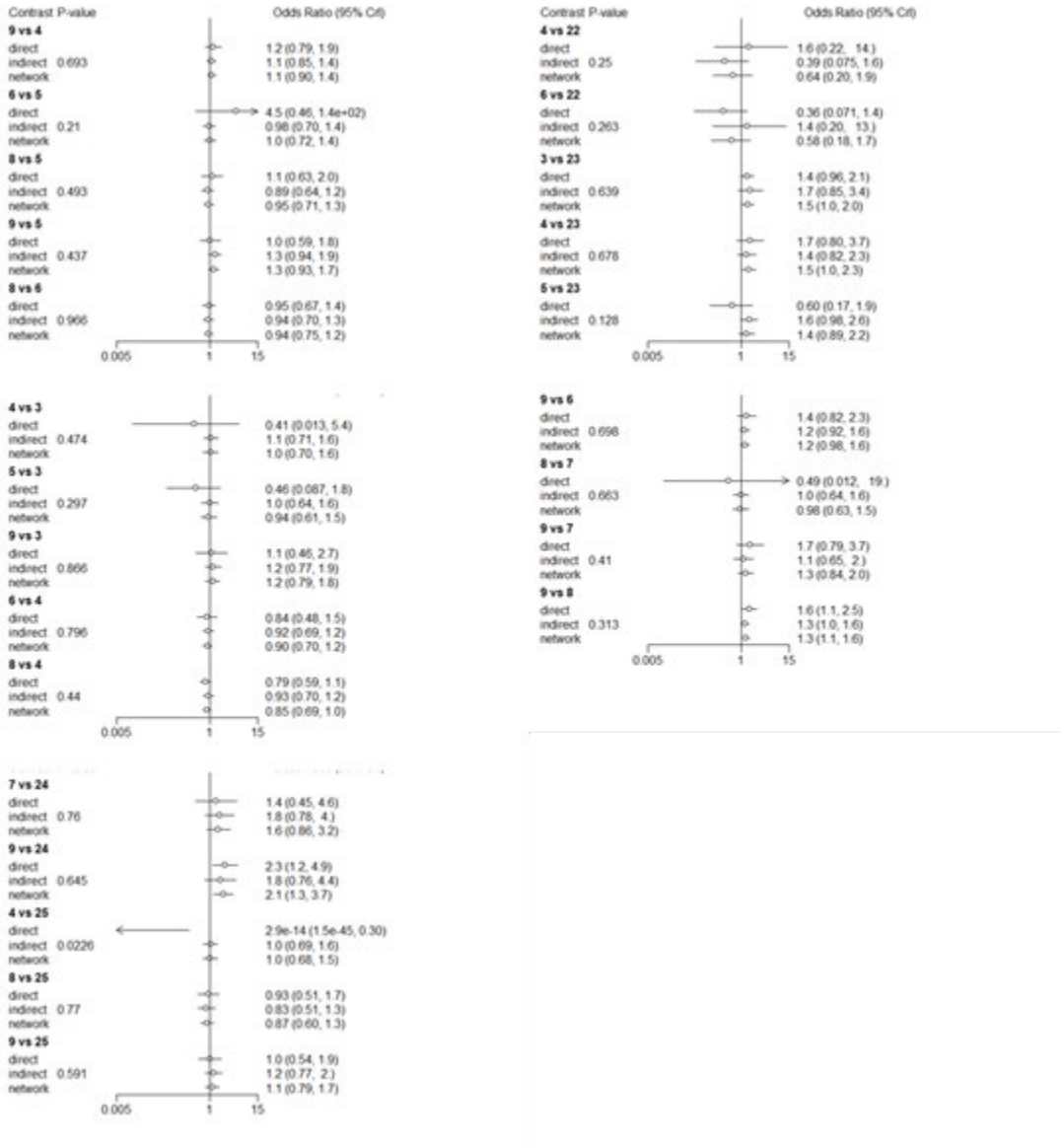
0.71 (0.54, 0.92)
0.82 (0.68, 1.0)
9 vs 11
direct
indirect 0.0174
network
0.88 (0.68, 1.1)
1.4 (1.1, 1.9)
1.1 (0.90, 1.3)
13 vs 12
direct
indirect 0.844
network
1.0 (0.22, 4.7)
0.88 (0.54, 1.4)
0.89 (0.56, 1.4)
14 vs 12
direct
indirect 0.118
network
7.0 (0.93, 1.9e+02)
1.3 (0.84, 2.)
1.4 (0.92, 2.1)
21 vs 12
direct
indirect 0.223
network
0.38 (0.051, 1.6)
1.0 (0.70, 1.4)
0.99 (0.71, 1.4)
0.005
1
15

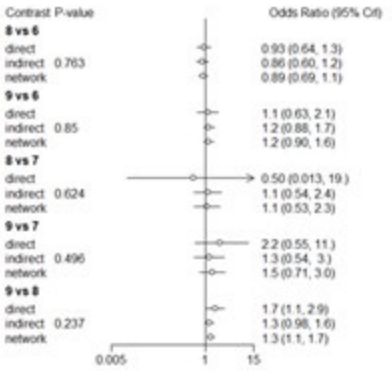

7 vs 1
direct
indirect 0.182
network
1.4 (0.77, 2.6)
0.74 (0.35, 1.5)
1.1 (0.67, 1.7)
8 vs 1
direct
indirect 0.981
network
1.0 (0.026, 40.)
1.1 (0.67, 1.7)
1.1 (0.68, 1.7)
9 vs 1
direct
indirect 0.491
network
1.2 (0.50, 2.7)
1.7 (0.95, 3.0)
1.4 (0.90, 2.2)
11 vs 10
direct
indirect 0.691
network
2. (0.14, 64.)
1.1 (0.71, 1.8)
1.1 (0.73, 1.8)
12 vs 10
direct
indirect 0.278
network
1.4 (0.56, 3.9)
0.78 (0.44, 1.4)
0.91 (0.56, 1.5)
0.005
1
15

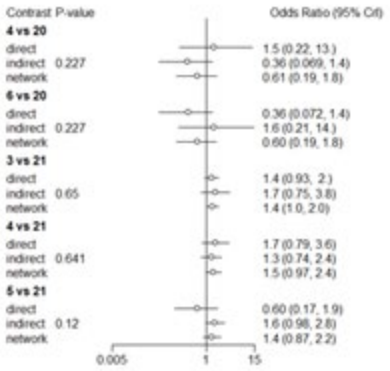

21 vs 11
direct
indirect 0.475
network
0.93 (0.55, 1.6)
0.75 (0.57, 0.99)
0.79 (0.62, 1.0)
25 vs 11
direct
indirect 0.632
network
0.83 (0.42, 1.6)
1.0 (0.64, 1.6)
0.95 (0.65, 1.4)
3 vs 11
direct
indirect 0.843
network
1.0 (0.42, 2.4)
0.91 (0.57, 1.4)
0.92 (0.62, 1.4)
4 vs 11
direct
indirect 0.182
network
1.9 (0.69, 6.3)
0.94 (0.73, 1.2)
0.97 (0.76, 1.2)
6 vs 11
direct
indirect 0.939
network
0.90 (0.37, 2.2)
0.87 (0.66, 1.1)
0.87 (0.67, 1.1)
0.005
1
15

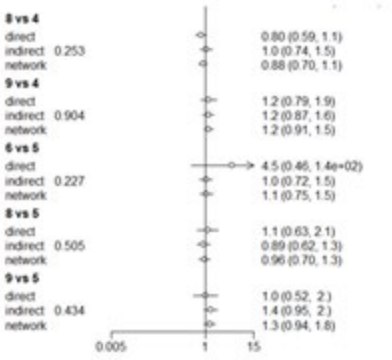

14 vs 1
direct
indirect 0.314
network
0.96 (0.29, 2.6)
1.8 (0.95, 3.3)
1.4 (0.85, 2.4)
16 vs 1
direct
indirect 0.707
network
1.7 (0.66, 4.6)
2.2 (0.81, 6.)
1.9 (0.96, 3.9)
17 vs 1
direct
indirect 0.736
network
0.82 (0.15, 5.1)
0.60 (0.33, 1.1)
0.62 (0.36, 1.1)
21 vs 1
direct
indirect 0.218
network
0.54 (0.11, 1.7)
1.2 (0.71, 2.2)
1.0 (0.63, 1.6)
6 vs 1
direct
indirect 0.783
network
0.93 (0.20, 4.4)
1.2 (0.70, 1.9)
1.1 (0.70, 1.8)
0.005
1
15

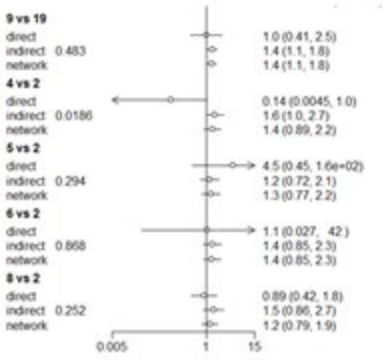


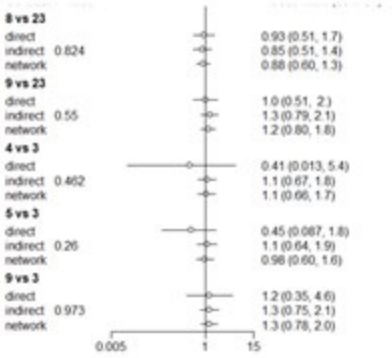
Forest plots for NICU admission, unfavourable cervix subgroup, showing direct, indirect and network estimates of treatment difference (contrast), odds ratio scale. Treatment codes: 1 - No treatment, 2 – Placebo, 3 - Vaginal PGE2 (tablet), 4 - Vaginal PGE2 (gel), 5 - Vaginal PGE2 (pessary – slow release), 6 - Intracervical PGE2, 7 - Vaginal PGE2 pessary (normal release), 8 - Vaginal misoprostol (dose less than 50 mcg), 9 - Vaginal misoprostol (dose 50 mcg or more), 10 - Oral misoprostol tablet (dose less than 50 mcg), 11 - Oral misoprostol tablet (dose 50mcg or more), 12 - Titrated (low dose) oral misoprostol solution, 13 - Sustained release misoprostol insert, 14 - IV oxytocin, 15 – Nitric oxide, 16 – Mifepristone, 17 – Oestrogens, 18 – Relaxin, 19 - Mechanical methods – foley catheter, 20 - Mechanical methods – laminaria including dilapan, 21 - Mechanical methods – Double balloon or Cook's catheter, 22 - Extra-amniotic PGE2 or PGF2, 23 - Buccal/sublingual misoprostol.

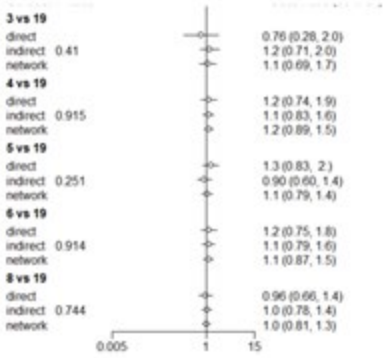

Contrast P-value
Odds Ratio (95% CrI)
8 vs 6
direct
indirect 0.763
network
0.93 (0.64, 1.3)
0.86 (0.60, 1.2)
0.89 (0.69, 1.1)
9 vs 6
direct
indirect 0.85
network
1.1 (0.63, 2.1)
1.2 (0.88, 1.7)
1.2 (0.90, 1.6)
8 vs 7
direct
indirect 0.624
network
0.50 (0.013, 19.)
1.1 (0.54, 2.4)
1.1 (0.53, 2.3)
9 vs 7
direct
indirect 0.496
network
2.2 (0.55, 11.)
1.3 (0.54, 3.)
1.5 (0.71, 3.0)
9 vs 8
direct
indirect 0.237
network
1.7 (1.1, 2.9)
1.3 (0.98, 1.6)
1.3 (1.1, 1.7)
0.005
1
15

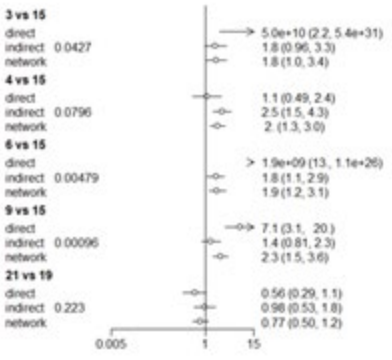

Contrast P-value
Odds Ratio (95% CrI)
4 vs 20
direct
indirect 0.227
network
1.5 (0.22, 13.)
0.36 (0.069, 1.4)
0.61 (0.19, 1.8)
6 vs 20
direct
indirect 0.227
network
0.36 (0.072, 1.4)
1.6 (0.21, 14.)
0.60 (0.19, 1.8)
3 vs 21
direct
indirect 0.65
network
1.4 (0.93, 2.)
1.7 (0.75, 3.8)
1.4 (1.0, 2.0)
4 vs 21
direct
indirect 0.641
network
1.7 (0.79, 3.6)
1.3 (0.74, 2.4)
1.5 (0.97, 2.4)
5 vs 21
direct
indirect 0.12
network
0.60 (0.17, 1.9)
1.6 (0.98, 2.8)
1.4 (0.87, 2.2)
0.005
1
15

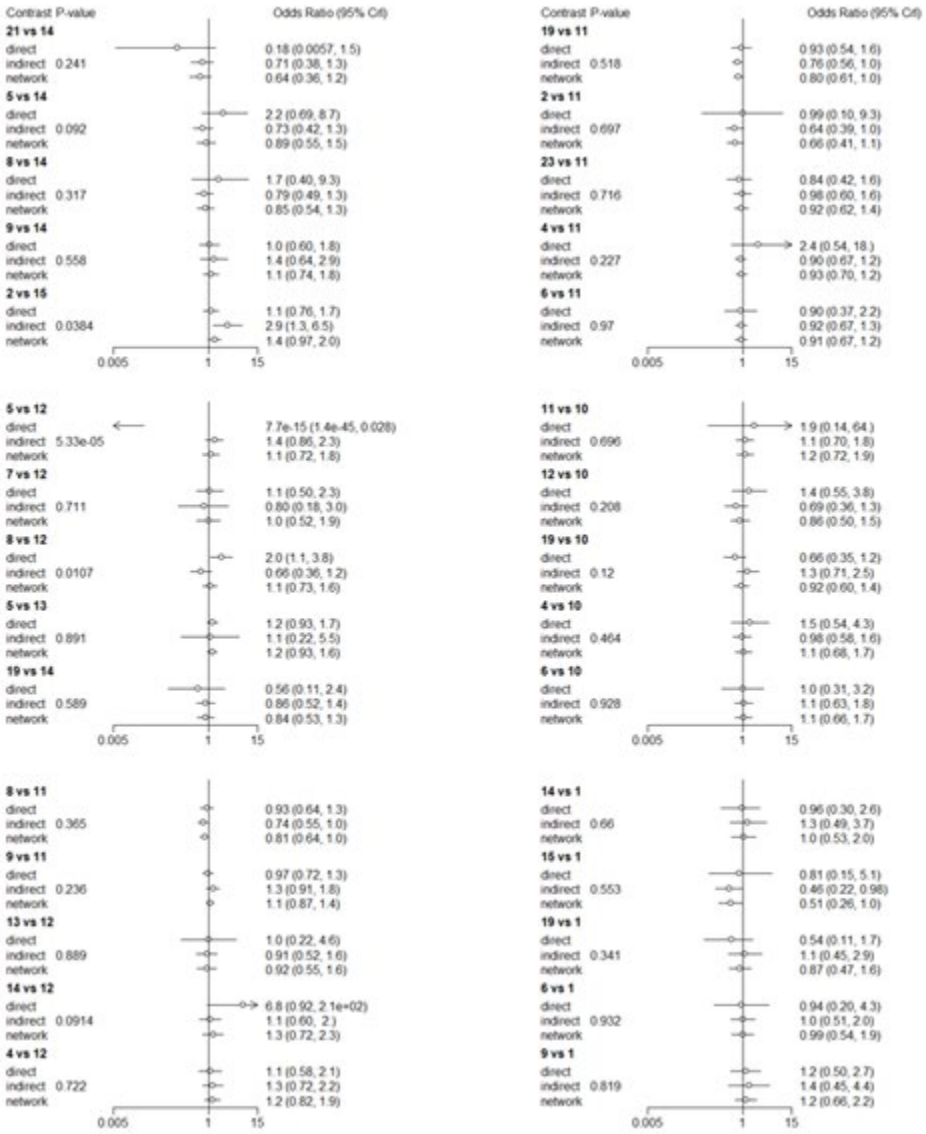

8 vs 4
direct
indirect 0.253
network
0.80 (0.59, 1.1)
1.0 (0.74, 1.5)
0.88 (0.70, 1.1)
9 vs 4
direct
indirect 0.904
network
1.2 (0.79, 1.9)
1.2 (0.87, 1.6)
1.2 (0.91, 1.5)
6 vs 5
direct
indirect 0.227
network
4.5 (0.46, 1.4e+02)
1.0 (0.72, 1.5)
1.1 (0.75, 1.5)
8 vs 5
direct
indirect 0.505
network
1.1 (0.63, 2.1)
0.89 (0.62, 1.3)
0.96 (0.70, 1.3)
9 vs 5
direct
indirect 0.434
network
1.0 (0.52, 2.)
1.4 (0.95, 2.)
1.3 (0.94, 1.8)
0.005
1
15


9 vs 19
direct
indirect 0.483
network
1.0 (0.41, 2.5)
1.4 (1.1, 1.8)
1.4 (1.1, 1.8)
4 vs 2
direct
indirect 0.0186
network
0.14 (0.0045, 1.0)
1.6 (1.0, 2.7)
1.4 (0.89, 2.2)
5 vs 2
direct
indirect 0.294
network
4.5 (0.45, 1.6e+02)
1.2 (0.72, 2.1)
1.3 (0.77, 2.2)
6 vs 2
direct
indirect 0.868
network
1.1 (0.027, 42.)
1.4 (0.85, 2.3)
1.4 (0.85, 2.3)
8 vs 2
direct
indirect 0.252
network
0.89 (0.42, 1.8)
1.5 (0.86, 2.7)
1.2 (0.79, 1.9)
0.005
1
15


8 vs 23
direct
indirect 0.824
network
0.93 (0.51, 1.7)
0.85 (0.51, 1.4)
0.88 (0.60, 1.3)
9 vs 23
direct
indirect 0.55
network
1.0 (0.51, 2.)
1.3 (0.79, 2.1)
1.2 (0.80, 1.8)
4 vs 3
direct
indirect 0.462
network
0.41 (0.013, 5.4)
1.1 (0.67, 1.8)
1.1 (0.66, 1.7)
5 vs 3
direct
indirect 0.26
network
0.45 (0.087, 1.8)
1.1 (0.64, 1.9)
0.98 (0.60, 1.6)
9 vs 3
direct
indirect 0.973
network
1.2 (0.35, 4.6)
1.3 (0.75, 2.1)
1.3 (0.78, 2.0)
0.005
1
15


3 vs 19
direct
indirect 0.41
network
0.76 (0.28, 2.0)
1.2 (0.71, 2.0)
1.1 (0.69, 1.7)
4 vs 19
direct
indirect 0.915
network
1.2 (0.74, 1.9)
1.1 (0.83, 1.6)
1.2 (0.89, 1.5)
5 vs 19
direct
indirect 0.251
network
1.3 (0.83, 2.)
0.90 (0.60, 1.4)
1.1 (0.79, 1.4)
6 vs 19
direct
indirect 0.914
network
1.2 (0.75, 1.8)
1.1 (0.79, 1.6)
1.1 (0.87, 1.5)
8 vs 19
direct
indirect 0.744
network
0.96 (0.66, 1.4)
1.0 (0.78, 1.4)
1.0 (0.81, 1.3)
0.005
1
15


3 vs 15
direct
indirect 0.0427
network
5.0e+10 (2.2, 5.4e+31)
1.8 (0.96, 3.3)
1.8 (1.0, 3.4)
4 vs 15
direct
indirect 0.0796
network
1.1 (0.49, 2.4)
2.5 (1.5, 4.3)
2. (1.3, 3.0)
6 vs 15
direct
indirect 0.00479
network
> 1.9e+09 (13., 1.1e+26)
1.8 (1.1, 2.9)
1.9 (1.2, 3.1)
9 vs 15
direct
indirect 0.00096
network
7.1 (3.1, 20.)
1.4 (0.81, 2.3)
2.3 (1.5, 3.6)
21 vs 19
direct
indirect 0.223
network
0.56 (0.29, 1.1)
0.98 (0.53, 1.8)
0.77 (0.50, 1.2)
0.005
1
15



Caesarean birth

Analysis of the full dataset included 485 trials of 30 treatments (1011 arms) whilst analysis of the unfavourable cervix dataset included 363 trials of 28 treatments (758 arms). Inconsistency checks were performed using the random effects model, as this had lower DIC than the fixed effects model and there was evidence of heterogeneity. There was estimated to be moderate between-study SD, with estimates of 0.27 (95% credible interval [CrI] 0.21, 0.33) in the full dataset and 0.24 (95% CrI 0.17, 0.31) in the subgroup dataset.

Convergence was satisfactory for the random effects model assuming inconsistency after 20,000 iterations, and the consistency and inconsistency models were compared using results based on samples from a further 40,000 iterations on three chains. WinBUGS code for the inconsistency model is provided below.

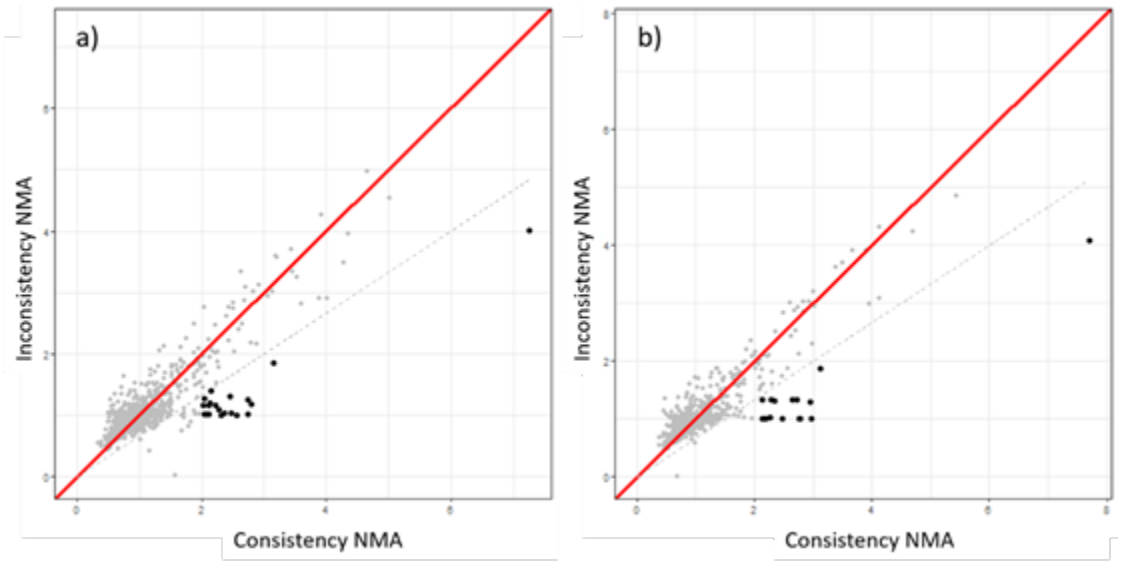
Network meta-analysis (NMA) models of the C-section outcome, comparison of fixed- (FE) and random-effect (RE) models.

Dataset	Model	Between-study SD (mean)			Mean residual deviance	Data points (arms)	DIC
		Mean	2.5% CrI	97.5% CrI			
Full	Consistency NMA (FE)	-	-	-	1243.0	1011	5741.25
	Consistency NMA (RE)	0.27	0.21	0.33	1043.0	1011	5668.63
	Inconsistency NMA (RE)	0.26	0.19	0.33	1038.0	1011	5742.93
Subgroup (unfav. cervix)	Consistency NMA (FE)	-	-	-	909.0	758	4366.38
	Consistency NMA (RE)	0.24	0.17	0.31	783.9	758	4327.71
	Inconsistency NMA (RE)	0.24	0.16	0.33	783.0	758	4394.14

Consistency and inconsistency random-effects NMA models were fitted to the full and subgroup datasets. In both cases there was no global evidence of inconsistency when model complexity was taken into account; the consistency models were preferred based on DIC.

To explore inconsistency within each dataset further we plotted the contribution of each study arm to the total residual deviance for the inconsistency model vs the consistency model in a dev-dev plot. A simple rule was used to identify study arms with relatively high deviance in the consistency model: points with relatively high deviance were those with mean deviance in the consistency NMA model greater than 2, and where the residual deviance in the consistency NMA was at least 1.5 times that estimated under the inconsistency model.

Seven studies were flagged as potentially inconsistent in both the full and unfavourable cervix subgroup analyses. These included both recent and older studies, and both mechanical and pharmacological interventions. Surita 2005, Rouzi 2017 and Souizi 2018 were those with the highest relative deviance under the consistency model.

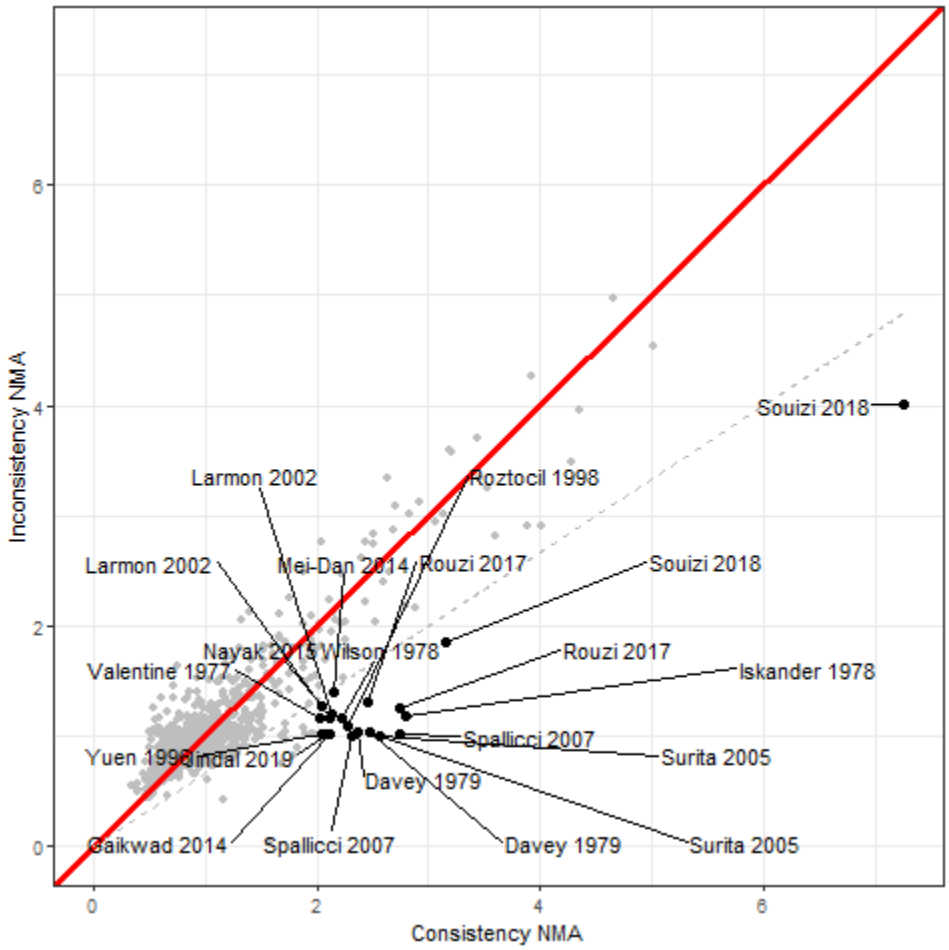


Dev-dev plots of each study arm's deviance in the consistency and inconsistency NMA models. Deviance is shown for a) the full dataset and b) the unfavourable cervix subgroup dataset indicating study arms that were relatively poorly predicted by the consistency NMA in black. Red line indicates line of equivalence.

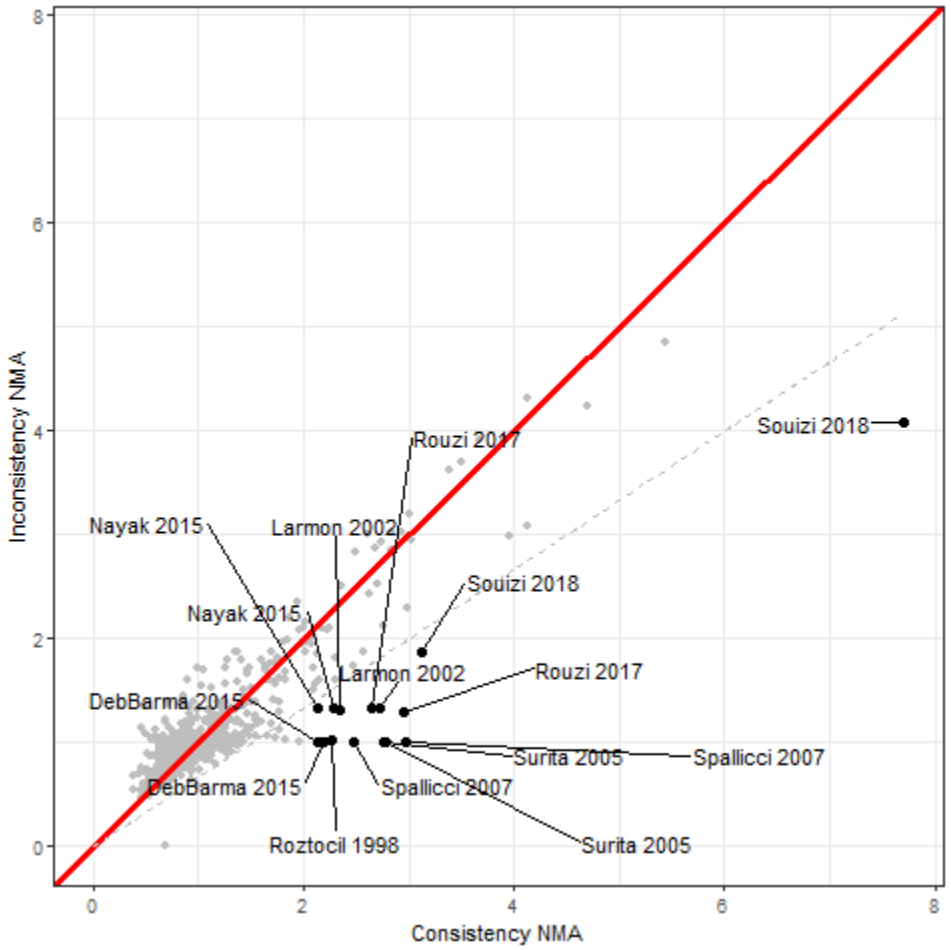
Studies flagged by comparison of the consistency and inconsistency models within the full and unfavourable cervix subgroup datasets.

Dataset	Study	Treatment
Both	Larmon 2002	Placebo
		Intracervical PGE2
		Oestrogens
	Roztocil 1998	Vaginal PGE2 (gel)
		Oestrogens
		Mechanical methods – laminaria including dilapan
	Souizi 2018	Vaginal misoprostol (dose less than 50 mcg)
		Nitric oxide
		Mechanical methods – laminaria including dilapan
	Nayak 2015	Vaginal PGE2 (tablet)
		Intracervical PGE2
	Spallicci 2007	Placebo
		Hyaluronidase
	Rouzi 2017	Oral misoprostol tablet (dose less than 50 mcg)

		Titrated (low dose) oral misoprostol solution
	Surita 2005	Hyaluronidase
		Mechanical methods – foley catheter
Full dataset only	Wilson 1978	Vaginal PGE2 (tablet)
		IV oxytocin
		Extra-amniotic PGE2 or PGF2
		Oral prostaglandins
	Valentine 1977	No treatment
		IV oxytocin
		Oral prostaglandins
	Yuen 1996	Intracervical PGE2
		Vaginal PGE2 pessary (normal release)
		Mechanical methods – Double balloon or Cook's catheter
	Davey 1979	Vaginal PGE2 (gel)
		Oral prostaglandins
	Mei-Dan 2014	Mechanical methods – foley catheter
		Mechanical methods – Double balloon or Cook's catheter
	Jindal 2019	Vaginal PGE2 (gel)
		Mifepristone
	Gaikwad 2014	Intracervical PGE2
		Mifepristone
	Iskander 1978	Extra-amniotic PGE2 or PGF2
		IV prostaglandin
Unfavourable cervix subgroup only	DebBarma 2015	Vaginal misoprostol (dose less than 50 mcg)
		Oral misoprostol tablet (dose less than 50 mcg)



Dev-dev plot of the outcome C-section, full dataset, indicating distribution of studies with relatively high deviance in the consistency model.



Dev-dev plot of the outcome C-section, unfavourable cervix dataset, indicating distribution of studies with relatively high deviance in the consistency model.

Further checks for inconsistency using the node-splitting method evaluate the relative direct and indirect evidence for each treatment comparison. For the full dataset, 14 treatment comparisons were judged to be inconsistent, with substantial differences between the estimates made from direct and indirect evidence. With multiple testing we would expect p-values to be <0.05 by chance in at least 7 out of these 152 comparisons.

Taken together these suggest that there may be inconsistency in the following loops of treatments:

- IV oxytocin, Extra-amniotic PGE2 or PGF2, IV prostaglandin and Vaginal misoprostol (Dose 50 mcg or more)
- IV oxytocin, Oral prostaglandins and Vaginal PGE2 (gel)
- Oral misoprostol tablet (dose less than 50 mcg), vaginal misoprostol (dose less than 50 mcg) and titrated (low dose) oral misoprostol solution

Inconsistency between direct and indirect estimates can occur where indirect trial evidence and direct trial evidence does not agree, for example evidence for hyaluronidase (treatment 23) when compared with placebo (treatment code 2) and Foley catheter (treatment code 24). Inconsistency can also occur where there is little direct evidence in the network, as can be seen in the difficulties of the node-splitting model in estimating effect sizes for IV prostaglandin (treatment 28).

For the unfavourable cervix subgroup, 9 of 119 treatment comparisons were judged to be inconsistent. With multiple testing we would expect p-values to be <0.05 by chance in at least 6 out of these comparisons.

This suggests that that there may be inconsistency in the following loops of treatments:

- Oral misoprostol tablet (dose less than 50 mcg), titrated (low dose) oral misoprostol solution and vaginal misoprostol (dose less than 50 mcg)
- Nitric oxide, vaginal misoprostol (dose less than 50 mcg) and oral misoprostol tablet (dose less than 50 mcg)

  Oestrogens, vaginal PGE2 (gel) and intracervical PGE2
- Hyaluronidase against placebo and foley catheter

Direct and indirect estimates of the treatment difference (log-odds ratio [LOR]) between pairs of interventions from node-splitting models of the outcome C-Section, full dataset. Treatment comparisons where the difference between indirect and direct estimates indicates inconsistency (p value below 0.05) are presented at the top of the table, highlighted in yellow.

Intervention 1	Intervention 2	p-value	Residual deviance[1]	Direct			Indirect		
				Median	2.5% CrI	97.5% CrI	Median	2.5% CrI	97.5% CrI
Consistency model		-	1042.9	-	-	-	-	-	-
No treatment	Amniotomy	0.002	1038.2	17.514	2.844	42.854	0.323	-0.307	0.939
Vaginal misoprostol (Dose 50 mcg or more)	Extra-amniotic PGE2 or PGF2	0.026	1042.6	0.934	0.193	1.687	-0.122	-0.690	0.435
Oral misoprostol tablet (Dose less than 50 mcg)	Titrated (low dose) oral misoprostol solution	0.044	1041.5	0.583	-0.119	1.309	-0.282	-0.741	0.179
Oral misoprostol tablet (Dose less than 50 mcg)	Vaginal misoprostol (Dose less than 50 mcg)	0.035	1044.2	-0.894	-1.849	0.023	0.185	-0.202	0.569
Oral misoprostol tablet (dose 50mcg or more)	Vaginal PGE2 (gel)	0.044	1039.4	-0.169	-0.567	0.228	0.279	0.099	0.461
IV oxytocin	IV prostaglandin	0.012	1039.9	1.725	0.228	3.758	-19.155	-59.381	-0.298
IV oxytocin	Oral prostaglandins	0.038	1037.5	0.451	-0.294	1.226	-0.590	-1.273	0.071
Nitric oxide	Vaginal misoprostol (Dose less than 50 mcg)	0.009	1040.5	1.019	0.142	1.955	-0.173	-0.398	0.055
Mifepristone	Intracervical PGE2	0.039	1041.8	1.456	0.386	2.590	0.248	-0.154	0.650
Placebo	Hyaluronidase	0.001	1043.6	-1.510	-2.396	-0.641	0.615	-0.246	1.483
Oestrogens	Intracervical PGE2	0.050	1041.5	-0.512	-1.352	0.309	0.478	-0.098	1.059
Hyaluronidase	Mechanical methods – foley catheter	0.001	1046.1	-0.704	-1.555	0.125	1.409	0.546	2.315
Extra-amniotic PGE2 or PGF2	IV prostaglandin	0.012	1039.9	-26.168	-75.228	-0.909	1.875	0.293	4.108
Oral prostaglandins	Vaginal PGE2 (gel)	0.023	1040.4	1.547	0.027	3.264	-0.296	-0.778	0.205
No treatment	IV oxytocin	0.889	1040.9	0.106	-0.457	0.655	0.149	-0.112	0.414
No treatment	IV oxytocin plus amniotomy	0.065	1042.7	0.469	-0.075	1.022	-0.152	-0.540	0.233
No treatment	Nitric oxide	0.882	1043.4	-0.268	-1.029	0.491	-0.203	-0.497	0.084
No treatment	Placebo	0.964	1042.9	0.043	-0.594	0.671	0.026	-0.239	0.293
No treatment	Corticosteroids	0.115	1041.9	-1.987	-5.499	0.142	-0.117	-0.948	0.710

No treatment	Mechanical methods – foley catheter	0.426	1039.4	0.425	-0.899	1.779	-0.113	-0.360	0.128
No treatment	Mechanical methods – laminaria including dilapan	0.773	1044.7	-0.039	-0.671	0.581	0.069	-0.285	0.425
No treatment	Oral prostaglandins	0.06	1040.5	-0.956	-2.073	0.146	0.232	-0.337	0.784
No treatment	Vaginal PGE2 (tablet)	0.861	1045.1	-0.070	-1.579	1.367	0.058	-0.209	0.328
No treatment	Vaginal PGE2 (gel)	0.279	1041.4	-0.639	-1.633	0.333	-0.089	-0.326	0.158
No treatment	Intracervical PGE2	0.734	1041	-0.088	-0.434	0.255	-0.011	-0.286	0.272
No treatment	Vaginal PGE2 pessary (normal release)	0.361	1041.4	0.136	-0.413	0.684	-0.154	-0.456	0.161
No treatment	Vaginal misoprostol (Dose less than 50 mcg)	0.367	1042.2	-1.011	-2.770	0.561	-0.289	-0.521	-0.056
Vaginal misoprostol (Dose 50 mcg or more)	Oral misoprostol tablet (dose 50mcg or more)	0.845	1041.4	-0.108	-0.310	0.094	-0.080	-0.278	0.116
Vaginal misoprostol (Dose 50 mcg or more)	Titrated (low dose) oral misoprostol solution	0.339	1042.7	0.280	-0.548	1.141	-0.144	-0.396	0.110
Vaginal misoprostol (Dose 50 mcg or more)	IV oxytocin	0.518	1043.7	0.287	-0.007	0.575	0.404	0.196	0.611
Vaginal misoprostol (Dose 50 mcg or more)	Nitric oxide	0.9	1042.8	0.045	-0.373	0.464	0.014	-0.238	0.261
Vaginal misoprostol (Dose 50 mcg or more)	Placebo	0.656	1043.9	0.511	-0.572	1.648	0.261	0.082	0.440
Vaginal misoprostol (Dose 50 mcg or more)	Mechanical methods – foley catheter	0.766	1042.4	0.050	-0.515	0.615	0.139	-0.023	0.305
Vaginal misoprostol (Dose 50 mcg or more)	Vaginal PGE2 (tablet)	0.536	1040.9	0.376	0.032	0.720	0.244	0.022	0.469
Vaginal misoprostol (Dose 50 mcg or more)	Buccal/sublingual misoprostol	0.89	1049.2	-0.092	-0.374	0.190	-0.119	-0.382	0.143
Vaginal misoprostol (Dose 50 mcg or more)	Vaginal PGE2 (gel)	0.787	1042.3	0.137	-0.141	0.420	0.093	-0.068	0.258
Vaginal misoprostol (Dose 50 mcg or more)	Vaginal PGE2 (pessary – slow release)	0.9	1040.9	0.073	-0.338	0.478	0.101	-0.090	0.293

Vaginal misoprostol (Dose 50 mcg or more)	Intracervical PGE2	0.316	1038.9	0.076	-0.167	0.315	0.223	0.067	0.379
Vaginal misoprostol (Dose 50 mcg or more)	Vaginal PGE2 pessary (normal release)	0.344	1041.9	0.427	-0.176	1.025	0.114	-0.128	0.356
Vaginal misoprostol (Dose 50 mcg or more)	Vaginal misoprostol (Dose less than 50 mcg)	0.696	1040.9	-0.121	-0.374	0.135	-0.061	-0.208	0.088
Oral misoprostol tablet (Dose less than 50 mcg)	Oral misoprostol tablet (dose 50mcg or more)	0.95	1043.2	-0.046	-1.520	1.432	0.005	-0.378	0.388
Oral misoprostol tablet (Dose less than 50 mcg)	Mechanical methods – foley catheter	0.552	1043.3	0.377	-0.245	1.008	0.150	-0.288	0.593
Oral misoprostol tablet (Dose less than 50 mcg)	Vaginal PGE2 (gel)	0.757	1043.3	0.071	-0.829	0.971	0.228	-0.168	0.619
Oral misoprostol tablet (Dose less than 50 mcg)	Intracervical PGE2	0.453	1042.5	-0.109	-1.183	0.950	0.325	-0.067	0.714
Oral misoprostol tablet (dose 50mcg or more)	Titrated (low dose) oral misoprostol solution	0.339	1043.7	0.503	-0.602	1.658	-0.062	-0.321	0.202
Oral misoprostol tablet (dose 50mcg or more)	IV oxytocin	0.335	1042.8	-0.022	-1.032	0.961	0.478	0.277	0.680
Oral misoprostol tablet (dose 50mcg or more)	Placebo	0.18	1043.4	1.016	0.061	2.034	0.339	0.135	0.550
Oral misoprostol tablet (dose 50mcg or more)	Mechanical methods – foley catheter	0.623	1041.4	0.117	-0.360	0.597	0.245	0.058	0.431
Oral misoprostol tablet (dose 50mcg or more)	Vaginal PGE2 (tablet)	0.501	1042.7	0.108	-0.716	0.939	0.399	0.182	0.615
Oral misoprostol tablet (dose 50mcg or more)	Buccal/sublingual misoprostol	0.575	1044.4	0.138	-0.288	0.549	0.001	-0.249	0.251
Oral misoprostol tablet (dose 50mcg or more)	Intracervical PGE2	0.793	1041.9	0.212	-0.266	0.697	0.280	0.108	0.454
Oral misoprostol tablet (dose 50mcg or more)	Vaginal misoprostol (Dose less than 50 mcg)	0.126	1038	0.165	-0.069	0.398	-0.070	-0.260	0.121
Titrated (low dose) oral misoprostol solution	Sustained release misoprostol insert	0.742	1043.4	0.390	-0.524	1.326	0.218	-0.278	0.711

Titrated (low dose) oral misoprostol solution	IV oxytocin	0.643	1043.2	0.639	-0.042	1.307	0.461	0.175	0.748
Titrated (low dose) oral misoprostol solution	Mechanical methods – foley catheter	0.815	1040.2	0.338	-0.379	1.052	0.246	-0.021	0.514
Titrated (low dose) oral misoprostol solution	Extra-amniotic PGE2 or PGF2	0.42	1042	0.679	-0.301	1.669	0.226	-0.313	0.769
Titrated (low dose) oral misoprostol solution	Vaginal PGE2 (gel)	0.814	1038.1	0.190	-0.204	0.579	0.252	-0.061	0.556
Titrated (low dose) oral misoprostol solution	Vaginal PGE2 (pessary – slow release)	0.208	1043.4	0.855	-0.164	1.921	0.178	-0.093	0.447
Titrated (low dose) oral misoprostol solution	Vaginal PGE2 pessary (normal release)	0.65	1043.1	0.405	-0.190	1.000	0.247	-0.081	0.576
Titrated (low dose) oral misoprostol solution	Vaginal misoprostol (Dose less than 50 mcg)	0.484	1040.5	0.207	-0.278	0.693	0.007	-0.274	0.284
Sustained release misoprostol insert	Vaginal PGE2 (pessary – slow release)	0.746	1042.9	-0.012	-0.427	0.403	-0.186	-1.150	0.779
IV oxytocin	Amniotomy	0.574	1043.9	0.526	-0.678	1.829	0.138	-0.527	0.809
IV oxytocin	IV oxytocin plus amniotomy	0.529	1041	0.113	-0.540	0.779	-0.128	-0.472	0.226
IV oxytocin	Mifepristone	0.551	1044	-0.912	-2.050	0.224	-0.536	-0.958	-0.119
IV oxytocin	Oestrogens	0.742	1042	-0.147	-1.273	0.990	-0.355	-0.880	0.160
IV oxytocin	Mechanical methods – foley catheter	0.268	1044	-1.717	-5.325	0.861	-0.221	-0.420	-0.028
IV oxytocin	Mechanical methods – laminaria including dilapan	0.758	1043.1	-0.274	-1.440	0.908	-0.085	-0.400	0.231
IV oxytocin	Mechanical methods – Double balloon or Cook's catheter	0.729	1044.1	-0.453	-1.661	0.736	-0.231	-0.525	0.066
IV oxytocin	Extra-amniotic PGE2 or PGF2	0.054	1041.4	-2.229	-5.312	-0.036	-0.034	-0.485	0.421
IV oxytocin	Vaginal PGE2 (tablet)	0.52	1043.7	-0.360	-1.259	0.523	-0.061	-0.289	0.170
IV oxytocin	Buccal/sublingual misoprostol	0.566	1043.3	-0.129	-1.239	0.987	-0.455	-0.701	-0.212
IV oxytocin	Vaginal PGE2 (gel)	0.728	1042.7	-0.373	-1.028	0.278	-0.250	-0.443	-0.055

IV oxytocin	Vaginal PGE2 (pessary – slow release)	0.615	1044	-0.405	-0.973	0.150	-0.249	-0.473	-0.024
IV oxytocin	PGF2 gel	0.817	1043.7	-0.553	-1.879	0.704	-0.383	-0.978	0.219
IV oxytocin	Intracervical PGE2	0.741	1042	-0.248	-0.669	0.169	-0.169	-0.365	0.025
IV oxytocin	Vaginal PGE2 pessary (normal release)	0.909	1041.5	-0.247	-0.923	0.406	-0.206	-0.471	0.058
IV oxytocin	Vaginal misoprostol (Dose less than 50 mcg)	0.426	1041.8	-0.601	-1.049	-0.158	-0.407	-0.598	-0.213
Amniotomy	IV oxytocin plus amniotomy	0.64	1042.7	-0.285	-0.973	0.399	-0.552	-1.514	0.371
Amniotomy	Mechanical methods – foley catheter	0.18	1044.5	-2.099	-5.811	0.259	-0.414	-1.041	0.188
Amniotomy	Mechanical methods – laminaria including dilapan	0.882	1043.2	-0.465	-2.601	1.563	-0.311	-0.963	0.336
Amniotomy	Vaginal PGE2 (gel)	0.56	1043.2	-0.200	-1.602	1.169	-0.643	-1.284	-0.017
IV oxytocin plus amniotomy	Mechanical methods – foley catheter	0.224	1042.7	-1.073	-2.844	0.442	-0.106	-0.423	0.211
IV oxytocin plus amniotomy	Oral prostaglandins	0.099	1039.8	0.473	-0.362	1.344	-0.393	-1.032	0.225
IV oxytocin plus amniotomy	Vaginal PGE2 (tablet)	0.781	1043.6	0.121	-0.774	1.018	-0.015	-0.359	0.330
IV oxytocin plus amniotomy	Buccal/sublingual misoprostol	0.963	1043.7	-0.392	-2.209	1.378	-0.350	-0.705	-0.008
IV oxytocin plus amniotomy	Vaginal PGE2 (gel)	0.119	1044.9	0.202	-0.357	0.767	-0.315	-0.664	0.025
IV oxytocin plus amniotomy	Intracervical PGE2	0.096	1041	1.802	-0.416	4.824	-0.136	-0.445	0.167
IV oxytocin plus amniotomy	Vaginal PGE2 pessary (normal release)	0.698	1041.7	-0.376	-1.746	0.997	-0.100	-0.455	0.254
Nitric oxide	Placebo	0.057	1045.5	0.065	-0.214	0.344	0.462	0.167	0.762
Nitric oxide	Mechanical methods – foley catheter	0.217	1042.8	-0.899	-2.712	0.699	0.133	-0.101	0.368
Nitric oxide	Mechanical methods – laminaria including dilapan	0.233	1037.5	0.946	-0.229	2.201	0.211	-0.116	0.543
Nitric oxide	Vaginal PGE2 (tablet)	0.913	1042.7	0.219	-0.599	1.038	0.269	0.002	0.542
Nitric oxide	Vaginal PGE2 (gel)	0.455	1044.4	0.250	-0.244	0.749	0.041	-0.197	0.280
Nitric oxide	Intracervical PGE2	0.287	1042.8	0.536	-0.188	1.270	0.124	-0.101	0.347

Mifepristone	Placebo	0.329	1043.4	0.388	-0.019	0.794	0.793	0.092	1.510
Mifepristone	Vaginal PGE2 (gel)	0.055	1042.4	-1.305	-3.363	0.404	0.410	0.017	0.802
Placebo	Oestrogens	0.338	1041.6	-0.035	-0.732	0.663	-0.483	-1.091	0.111
Placebo	Corticosteroids	0.118	1042.2	-0.179	-0.957	0.613	-2.003	-5.473	0.102
Placebo	Mechanical methods – laminaria including dilapan	0.697	1043.4	0.225	-0.947	1.401	-0.009	-0.323	0.297
Placebo	Extra-amniotic PGE2 or PGF2	0.245	1042.3	-0.986	-2.730	0.589	0.023	-0.438	0.488
Placebo	Oral prostaglandins	0.53	1043.4	-0.916	-4.738	1.758	-0.022	-0.508	0.476
Placebo	Vaginal PGE2 (tablet)	0.485	1040.5	0.620	-1.150	2.408	0.002	-0.224	0.227
Placebo	Vaginal PGE2 (gel)	0.576	1042.1	-0.054	-0.478	0.371	-0.190	-0.387	0.011
Placebo	Vaginal PGE2 (pessary – slow release)	0.332	1043	-0.572	-1.423	0.251	-0.148	-0.366	0.071
Placebo	PGF2 gel	0.496	1043.8	-0.506	-1.271	0.261	-0.137	-0.884	0.607
Placebo	Intracervical PGE2	0.595	1038.4	-0.152	-0.439	0.125	-0.060	-0.266	0.155
Placebo	Vaginal PGE2 pessary (normal release)	0.725	1041.9	-0.214	-0.791	0.349	-0.099	-0.363	0.154
Placebo	Vaginal misoprostol (Dose less than 50 mcg)	0.827	1043.6	-0.299	-0.770	0.173	-0.356	-0.553	-0.162
Oestrogens	Mechanical methods – laminaria including dilapan	0.065	1040.9	0.986	0.007	2.027	-0.095	-0.667	0.489
Oestrogens	Vaginal PGE2 (gel)	0.103	1044.2	0.536	-0.237	1.332	-0.255	-0.818	0.308
Mechanical methods – foley catheter	Mechanical methods – laminaria including dilapan	0.679	1043.9	0.032	-0.586	0.662	0.181	-0.138	0.496
Mechanical methods – foley catheter	Mechanical methods – Double balloon or Cook's catheter	0.136	1039.9	-0.176	-0.506	0.146	0.211	-0.177	0.599
Mechanical methods – foley catheter	Extra-amniotic PGE2 or PGF2	0.416	1041.8	-0.189	-0.964	0.584	0.204	-0.305	0.718
Mechanical methods – foley catheter	Vaginal PGE2 (tablet)	0.847	1042.4	0.199	-0.333	0.732	0.142	-0.071	0.358
Mechanical methods – foley catheter	Vaginal PGE2 (gel)	0.872	1037.1	-0.004	-0.300	0.295	-0.033	-0.218	0.151

Mechanical methods – foley catheter	Vaginal PGE2 (pessary – slow release)	0.669	1044.1	0.035	-0.361	0.428	-0.061	-0.265	0.143
Mechanical methods – foley catheter	PGF2 gel	0.443	1043.6	0.311	-1.054	1.671	-0.261	-0.869	0.335
Mechanical methods – foley catheter	Intracervical PGE2	0.138	1043.3	0.281	-0.067	0.633	-0.010	-0.177	0.159
Mechanical methods – foley catheter	Vaginal PGE2 pessary (normal release)	0.735	1040.2	-0.051	-0.579	0.478	0.047	-0.212	0.306
Mechanical methods – foley catheter	Vaginal misoprostol (Dose less than 50 mcg)	0.344	1036.8	-0.301	-0.543	-0.065	-0.158	-0.342	0.026
Mechanical methods – laminaria including dilapan	Vaginal PGE2 (tablet)	0.728	1042.6	0.164	-0.748	1.078	-0.004	-0.329	0.309
Mechanical methods – laminaria including dilapan	Vaginal PGE2 (gel)	0.356	1040.6	0.088	-0.501	0.673	-0.225	-0.545	0.093
Mechanical methods – laminaria including dilapan	Intracervical PGE2	0.205	1045.4	-0.355	-0.852	0.127	0.017	-0.297	0.339
Mechanical methods – laminaria including dilapan	Vaginal misoprostol (Dose less than 50 mcg)	0.262	1035.5	0.458	-0.912	1.930	-0.356	-0.643	-0.070
Mechanical methods – Double balloon or Cook's catheter	Vaginal PGE2 (tablet)	0.156	1042.6	-0.167	-0.706	0.379	0.282	-0.034	0.601
Mechanical methods – Double balloon or Cook's catheter	Vaginal PGE2 (gel)	0.53	1041.4	-0.243	-1.002	0.524	0.021	-0.263	0.310
Mechanical methods – Double balloon or Cook's catheter	Vaginal PGE2 (pessary – slow release)	0.687	1043.6	0.081	-0.508	0.666	-0.056	-0.364	0.253
Mechanical methods – Double balloon or Cook's catheter	Intracervical PGE2	0.181	1041.7	-0.774	-2.095	0.467	0.109	-0.159	0.378
Mechanical methods – Double balloon or Cook's catheter	Vaginal PGE2 pessary (normal release)	0.106	1040.4	-1.003	-2.418	0.286	0.100	-0.224	0.426

Extra-amniotic PGE2 or PGF2	Oral prostaglandins	0.099	1041.2	1.907	-0.411	5.139	-0.146	-0.800	0.496
Extra-amniotic PGE2 or PGF2	Vaginal PGE2 (tablet)	0.745	1044.1	0.156	-0.802	1.143	-0.022	-0.527	0.483
Extra-amniotic PGE2 or PGF2	Intracervical PGE2	0.474	1043.1	0.871	-1.643	4.308	-0.073	-0.498	0.368
Extra-amniotic PGE2 or PGF2	Vaginal PGE2 pessary (normal release)	0.872	1042.6	-0.072	-1.076	0.939	0.019	-0.515	0.556
Oral prostaglandins	Vaginal PGE2 (tablet)	0.601	1044.8	-0.408	-2.370	1.462	0.107	-0.409	0.620
Oral prostaglandins	Intracervical PGE2	0.289	1043.5	0.665	-0.723	2.096	-0.143	-0.632	0.355
Vaginal PGE2 (tablet)	Vaginal PGE2 (gel)	0.951	1041.9	-0.166	-0.701	0.368	-0.185	-0.395	0.027
Vaginal PGE2 (tablet)	Vaginal PGE2 (pessary – slow release)	0.209	1043.8	0.177	-0.437	0.783	-0.247	-0.485	-0.013
Vaginal PGE2 (tablet)	Intracervical PGE2	0.113	1042.4	-0.443	-0.899	0.012	-0.038	-0.246	0.168
Vaginal PGE2 (tablet)	Vaginal PGE2 pessary (normal release)	0.898	1042.9	-0.081	-0.876	0.705	-0.135	-0.410	0.139
Buccal/sublingual misoprostol	Vaginal PGE2 (gel)	0.91	1044	0.119	-0.983	1.230	0.183	-0.038	0.411
Buccal/sublingual misoprostol	Intracervical PGE2	0.099	1043.8	0.957	0.088	1.843	0.207	-0.009	0.426
Buccal/sublingual misoprostol	Vaginal misoprostol (Dose less than 50 mcg)	0.497	1043.5	-0.088	-0.404	0.231	0.051	-0.204	0.302
Vaginal PGE2 (gel)	Vaginal PGE2 (pessary – slow release)	0.807	1043.5	-0.057	-0.457	0.341	-0.001	-0.201	0.199
Vaginal PGE2 (gel)	PGF2 gel	0.759	1044	0.010	-1.025	1.078	-0.180	-0.825	0.451
Vaginal PGE2 (gel)	Intracervical PGE2	0.921	1042.2	0.058	-0.303	0.418	0.078	-0.080	0.235
Vaginal PGE2 (gel)	Vaginal PGE2 pessary (normal release)	0.446	1042.4	0.381	-0.501	1.265	0.026	-0.209	0.258
Vaginal PGE2 (gel)	Vaginal misoprostol (Dose less than 50 mcg)	0.142	1036.8	0.018	-0.284	0.322	-0.237	-0.400	-0.076
Vaginal PGE2 (pessary – slow release)	Intracervical PGE2	0.305	1043.2	0.248	-0.107	0.609	0.036	-0.162	0.230
Vaginal PGE2 (pessary – slow release)	Vaginal misoprostol (Dose less than 50 mcg)	0.91	1042.3	-0.147	-0.522	0.217	-0.171	-0.369	0.025

Intracervical PGE2	Vaginal PGE2 pessary (normal release)	0.977	1041.1	-0.019	-0.500	0.453	-0.011	-0.260	0.237
Intracervical PGE2	Vaginal misoprostol (Dose less than 50 mcg)	0.568	1042.2	-0.317	-0.567	-0.066	-0.231	-0.390	-0.075
Vaginal PGE2 pessary (normal release)	Vaginal misoprostol (Dose less than 50 mcg)	0.358	1043	0.216	-0.762	1.210	-0.256	-0.488	-0.020

Direct and indirect estimates of the treatment difference log-odds ratio (LOR) between pairs of interventions from node-splitting models of the outcome C-section, unfavourable cervix subgroup. Treatment comparisons where the difference between indirect and direct estimates indicates inconsistency (p value below 0.05) are presented at the top of the table, highlighted in yellow.

Intervention 1	Intervention 2	p-value	Residual deviance[2]	Direct			Indirect		
				Median	2.5% CrI	97.5% CrI	Median	2.5% CrI	97.5% CrI
Consistency model		-	783.9	-	-	-	-	-	-
Oral misoprostol tablet (dose less than 50 mcg)	Titrated (low dose) oral misoprostol solution	0.038	780.1	0.586	-0.114	1.297	-0.302	-0.766	0.154
Oral misoprostol tablet (dose less than 50 mcg)	Vaginal misoprostol (dose less than 50 mcg)	0.027	785.1	-0.913	-1.835	-0.003	0.189	-0.179	0.563
Nitric oxide	Placebo	0.019	788.2	0.055	-0.203	0.316	0.519	0.228	0.814
Nitric oxide	Vaginal misoprostol (dose less than 50 mcg)	0.008	779.7	0.982	0.123	1.907	-0.201	-0.427	0.022
Oestrogens	Mechanical methods – laminaria including dilapan	0.045	782.8	0.989	0.021	1.996	-0.192	-0.852	0.457
Oestrogens	Vaginal PGE2 (gel)	0.041	781.3	0.969	-0.015	1.981	-0.240	-0.847	0.364
Oestrogens	Intracervical PGE2	0.01	782.1	-0.512	-1.300	0.298	0.881	0.175	1.602
Placebo	Hyaluronidase	0.001	787.5	-1.505	-2.343	-0.691	0.568	-0.257	1.399
Hyaluronidase	Mechanical methods – foley catheter	0	786.1	-0.701	-1.527	0.110	1.387	0.548	2.275
No treatment	IV oxytocin	0.733	782.8	0.001	-0.813	0.846	0.153	-0.184	0.486
No treatment	Nitric oxide	0.917	784.3	-0.272	-1.014	0.476	-0.231	-0.561	0.093
No treatment	Placebo	0.888	782.7	0.037	-0.574	0.640	-0.011	-0.319	0.302
No treatment	Mechanical methods – foley catheter	0.6	782.6	0.217	-1.196	1.642	-0.165	-0.444	0.119

No treatment	Mechanical methods – laminaria including dilapan	0.71	782.7	-0.187	-0.803	0.430	-0.047	-0.457	0.362
No treatment	Oral prostaglandins	0.642	782.9	-1.100	-2.562	0.356	-0.693	-1.629	0.215
No treatment	Vaginal PGE2 (gel)	0.304	784.7	-0.623	-1.600	0.310	-0.114	-0.398	0.169
No treatment	Intracervical PGE2	0.842	781.4	-0.059	-0.394	0.277	-0.108	-0.495	0.254
No treatment	Vaginal PGE2 pessary (normal release)	0.749	782.6	0.048	-1.121	1.222	-0.151	-0.511	0.206
Vaginal misoprostol (dose 50 mcg or more)	Oral misoprostol tablet (dose 50mcg or more)	0.316	782	-0.009	-0.245	0.224	-0.176	-0.399	0.050
Vaginal misoprostol (dose 50 mcg or more)	IV oxytocin	0.35	783.5	0.261	-0.099	0.626	0.469	0.219	0.714
Vaginal misoprostol (dose 50 mcg or more)	Nitric oxide	0.925	783.3	0.053	-0.356	0.463	0.030	-0.220	0.279
Vaginal misoprostol (dose 50 mcg or more)	Placebo	0.797	784.6	0.469	-0.856	1.772	0.294	0.101	0.486
Vaginal misoprostol (dose 50 mcg or more)	Mechanical methods – foley catheter	0.811	783.4	0.039	-0.499	0.583	0.108	-0.059	0.277
Vaginal misoprostol (dose 50 mcg or more)	Buccal/sublingual misoprostol	0.714	784.3	-0.239	-0.593	0.112	-0.156	-0.435	0.124
Vaginal misoprostol (dose 50 mcg or more)	Vaginal PGE2 (tablet)	0.982	783.5	0.254	-0.103	0.611	0.258	0.008	0.509
Vaginal misoprostol (dose 50 mcg or more)	Vaginal PGE2 (gel)	0.589	781.2	0.038	-0.247	0.322	0.129	-0.050	0.312
Vaginal misoprostol (dose 50 mcg or more)	Vaginal PGE2 (pessary – slow release)	0.416	782.1	0.264	-0.169	0.710	0.062	-0.142	0.266
Vaginal misoprostol (dose 50 mcg or more)	Intracervical PGE2	0.789	782.2	0.139	-0.125	0.405	0.180	0.014	0.349
Vaginal misoprostol (dose 50 mcg or more)	Vaginal PGE2 pessary (normal release)	0.789	782.3	0.230	-0.495	0.951	0.124	-0.156	0.403
Vaginal misoprostol (dose 50 mcg or more)	Vaginal misoprostol (dose less than 50 mcg)	0.924	780	-0.095	-0.359	0.171	-0.081	-0.244	0.079
Oral misoprostol tablet (dose less than 50 mcg)	Oral misoprostol tablet (dose 50mcg or more)	0.873	785	-0.091	-1.503	1.396	0.035	-0.345	0.414

Oral misoprostol tablet (dose less than 50 mcg)	Mechanical methods – foley catheter	0.508	783.3	0.375	-0.197	0.959	0.134	-0.299	0.565
Oral misoprostol tablet (dose less than 50 mcg)	Vaginal PGE2 (gel)	0.714	785	0.071	-0.800	0.945	0.247	-0.136	0.634
Oral misoprostol tablet (dose less than 50 mcg)	Intracervical PGE2	0.436	783.8	-0.103	-1.162	0.916	0.332	-0.041	0.706
Oral misoprostol tablet (dose 50mcg or more)	Titrated (low dose) oral misoprostol solution	0.294	783.7	0.508	-0.586	1.650	-0.094	-0.390	0.208
Oral misoprostol tablet (dose 50mcg or more)	IV oxytocin	0.358	784.6	-0.463	-2.858	1.557	0.507	0.266	0.746
Oral misoprostol tablet (dose 50mcg or more)	Placebo	0.187	784.2	0.998	0.068	2.010	0.350	0.125	0.575
Oral misoprostol tablet (dose 50mcg or more)	Mechanical methods – foley catheter	0.717	779.3	0.120	-0.339	0.570	0.212	0.007	0.418
Oral misoprostol tablet (dose 50mcg or more)	Buccal/sublingual misoprostol	0.349	783.5	-0.308	-0.821	0.200	-0.036	-0.302	0.231
Oral misoprostol tablet (dose 50mcg or more)	Vaginal PGE2 (gel)	0.35	780	-0.072	-0.677	0.527	0.225	0.024	0.425
Oral misoprostol tablet (dose 50mcg or more)	Intracervical PGE2	0.834	782.3	0.212	-0.257	0.675	0.269	0.073	0.461
Oral misoprostol tablet (dose 50mcg or more)	Vaginal misoprostol (dose less than 50 mcg)	0.066	780.8	0.217	-0.060	0.502	-0.105	-0.309	0.098
Titrated (low dose) oral misoprostol solution	Sustained release misoprostol insert	0.76	783.9	0.392	-0.486	1.306	0.237	-0.245	0.722
Titrated (low dose) oral misoprostol solution	IV oxytocin	0.308	784.2	0.893	0.158	1.637	0.481	0.150	0.809
Titrated (low dose) oral misoprostol solution	Vaginal PGE2 (gel)	0.587	780.7	0.153	-0.295	0.609	0.305	-0.017	0.639
Titrated (low dose) oral misoprostol solution	Vaginal PGE2 (pessary – slow release)	0.201	784.7	0.855	-0.121	1.895	0.188	-0.102	0.484
Titrated (low dose) oral misoprostol solution	Vaginal PGE2 pessary (normal release)	0.99	784.1	0.290	-0.426	1.016	0.283	-0.079	0.650

Titrated (low dose) oral misoprostol solution	Vaginal misoprostol (dose less than 50 mcg)	0.514	780.2	0.200	-0.261	0.673	0.012	-0.315	0.334
Sustained release misoprostol insert	Vaginal PGE2 (pessary – slow release)	0.757	783.6	-0.010	-0.392	0.377	-0.170	-1.134	0.781
IV oxytocin	Mifepristone	0.406	784.2	-0.888	-2.002	0.218	-0.387	-0.829	0.061
IV oxytocin	Oestrogens	0.52	783.2	-0.134	-1.245	0.981	-0.547	-1.155	0.065
IV oxytocin	Mechanical methods – laminaria including dilapan	0.799	785	-0.391	-1.928	1.029	-0.200	-0.540	0.146
IV oxytocin	Mechanical methods – Double balloon or Cook's catheter	0.716	784.2	-0.451	-1.632	0.703	-0.231	-0.553	0.087
IV oxytocin	Extra-amniotic PGE2 or PGF2	0.135	782.6	-2.224	-5.672	-0.058	-0.445	-1.058	0.160
IV oxytocin	Oral prostaglandins	0.167	782.2	-0.253	-1.340	0.923	-1.315	-2.419	-0.289
IV oxytocin	Vaginal PGE2 (tablet)	0.597	782.6	-0.365	-1.237	0.500	-0.120	-0.388	0.155
IV oxytocin	Vaginal PGE2 (gel)	0.97	784.1	-0.287	-1.081	0.494	-0.304	-0.534	-0.077
IV oxytocin	Vaginal PGE2 (pessary – slow release)	0.683	784.3	-0.407	-0.959	0.144	-0.280	-0.538	-0.020
IV oxytocin	Intracervical PGE2	0.439	782.2	-0.392	-0.830	0.049	-0.195	-0.427	0.036
IV oxytocin	Vaginal PGE2 pessary (normal release)	0.632	782.9	-0.106	-0.822	0.614	-0.296	-0.612	0.016
IV oxytocin	Vaginal misoprostol (dose less than 50 mcg)	0.296	785	-0.222	-0.766	0.321	-0.531	-0.758	-0.306
Nitric oxide	Mechanical methods – foley catheter	0.22	782.5	-0.908	-2.708	0.631	0.086	-0.144	0.319
Nitric oxide	Mechanical methods – laminaria including dilapan	0.155	778.4	0.949	-0.168	2.206	0.086	-0.259	0.441
Nitric oxide	Vaginal PGE2 (tablet)	0.994	784.1	0.227	-0.576	1.026	0.229	-0.045	0.510
Nitric oxide	Vaginal PGE2 (gel)	0.398	784.5	0.249	-0.224	0.714	0.021	-0.215	0.265
Nitric oxide	Intracervical PGE2	0.237	784.9	0.543	-0.171	1.261	0.095	-0.123	0.315
Mifepristone	Placebo	0.764	782.9	0.386	-0.008	0.786	0.228	-0.670	1.128
Mifepristone	Vaginal PGE2 (gel)	0.085	784.2	-1.293	-3.398	0.413	0.251	-0.156	0.659
Oestrogens	Placebo	0.293	783	0.103	-0.701	0.915	0.657	0.001	1.318

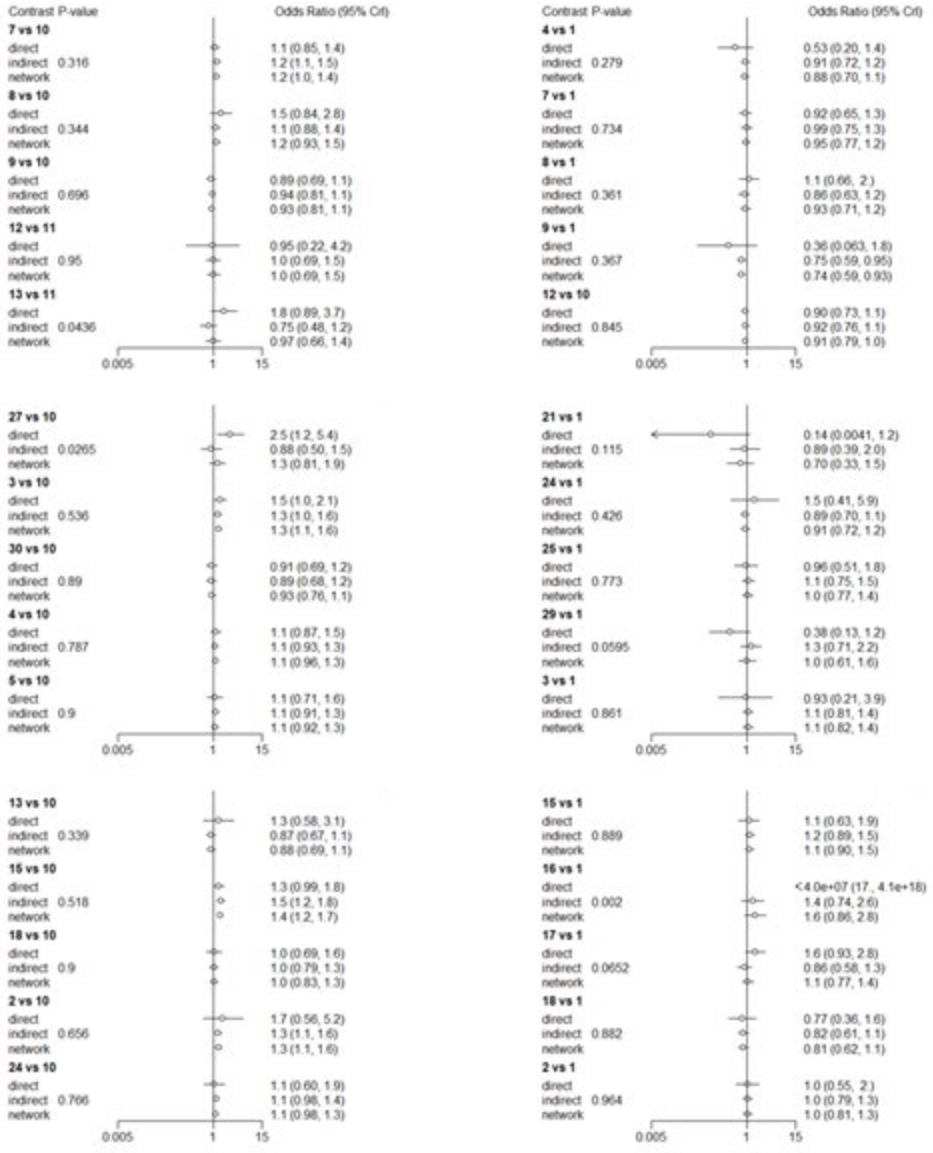
Placebo	Mechanical methods – laminaria including dilapan	0.542	784.1	0.232	-0.916	1.403	-0.140	-0.474	0.194
Placebo	Extra-amniotic PGE2 or PGF2	0.569	784.7	-0.945	-2.770	0.664	-0.445	-1.046	0.147
Placebo	Vaginal PGE2 (tablet)	0.413	781.6	-19.563	-46.505	10.939	-0.034	-0.270	0.208
Placebo	Vaginal PGE2 (gel)	0.87	785.7	-0.157	-0.582	0.280	-0.199	-0.410	0.011
Placebo	Vaginal PGE2 (pessary – slow release)	0.348	784.1	-0.577	-1.414	0.247	-0.169	-0.401	0.062
Placebo	PGF2 gel	0.707	783.4	-0.461	-2.809	1.619	-0.034	-0.927	0.875
Placebo	Intracervical PGE2	0.861	778.3	-0.154	-0.433	0.125	-0.121	-0.339	0.111
Placebo	Vaginal PGE2 pessary (normal release)	0.689	782.6	0.000	-0.834	0.863	-0.182	-0.484	0.118
Placebo	Vaginal misoprostol (dose less than 50 mcg)	0.951	782.7	-0.368	-0.866	0.133	-0.385	-0.592	-0.175
Mechanical methods – foley catheter	Mechanical methods – laminaria including dilapan	0.5	785.1	-0.090	-0.698	0.525	0.147	-0.188	0.479
Mechanical methods – foley catheter	Mechanical methods – Double balloon or Cook's catheter	0.373	781.2	-0.055	-0.398	0.281	0.175	-0.211	0.565
Mechanical methods – foley catheter	Extra-amniotic PGE2 or PGF2	0.71	785	-0.182	-0.960	0.601	-0.391	-1.176	0.353
Mechanical methods – foley catheter	Vaginal PGE2 (tablet)	0.865	784.4	0.198	-0.318	0.704	0.146	-0.086	0.387
Mechanical methods – foley catheter	Vaginal PGE2 (gel)	0.981	777.7	0.009	-0.302	0.320	0.006	-0.188	0.199
Mechanical methods – foley catheter	Vaginal PGE2 (pessary – slow release)	0.744	783.6	0.044	-0.338	0.414	-0.027	-0.237	0.181
Mechanical methods – foley catheter	PGF2 gel	0.676	784.5	0.316	-1.013	1.675	-0.045	-1.070	0.962
Mechanical methods – foley catheter	Intracervical PGE2	0.159	783.6	0.277	-0.061	0.618	0.008	-0.166	0.179
Mechanical methods – foley catheter	Vaginal PGE2 pessary (normal release)	0.678	781.5	-0.057	-0.563	0.442	0.066	-0.235	0.365

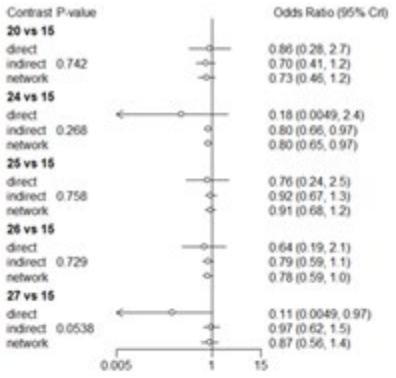
Mechanical methods – foley catheter	Vaginal misoprostol (dose less than 50 mcg)	0.278	778.8	-0.294	-0.528	-0.064	-0.127	-0.317	0.063
Mechanical methods – laminaria including dilapan	Vaginal PGE2 (tablet)	0.838	785.3	0.167	-0.737	1.044	0.066	-0.289	0.413
Mechanical methods – laminaria including dilapan	Vaginal PGE2 (gel)	0.549	781.6	0.086	-0.488	0.647	-0.115	-0.464	0.227
Mechanical methods – laminaria including dilapan	Intracervical PGE2	0.482	783.6	-0.248	-0.971	0.484	0.036	-0.291	0.358
Mechanical methods – laminaria including dilapan	Vaginal misoprostol (dose less than 50 mcg)	0.333	777.9	0.411	-0.965	1.847	-0.270	-0.576	0.032
Mechanical methods – Double balloon or Cook's catheter	Vaginal PGE2 (tablet)	0.425	783.7	-0.090	-0.664	0.478	0.174	-0.159	0.509
Mechanical methods – Double balloon or Cook's catheter	Vaginal PGE2 (gel)	0.555	783.2	-0.239	-0.956	0.483	-0.011	-0.301	0.288
Mechanical methods – Double balloon or Cook's catheter	Vaginal PGE2 (pessary – slow release)	0.605	784.5	0.072	-0.493	0.636	-0.097	-0.413	0.218
Mechanical methods – Double balloon or Cook's catheter	Intracervical PGE2	0.194	781.7	-0.763	-2.046	0.454	0.067	-0.208	0.347
Mechanical methods – Double balloon or Cook's catheter	Vaginal PGE2 pessary (normal release)	0.12	782.2	-0.999	-2.344	0.308	0.063	-0.285	0.408
Extra-amniotic PGE2 or PGF2	Oral prostaglandins	0.055	782.7	1.939	-0.439	5.519	-0.614	-1.592	0.361
Extra-amniotic PGE2 or PGF2	Vaginal PGE2 (tablet)	0.564	782.1	0.134	-0.830	1.093	0.479	-0.206	1.194
Extra-amniotic PGE2 or PGF2	Intracervical PGE2	0.624	786	1.043	-1.676	4.556	0.329	-0.228	0.896
Oral prostaglandins	Vaginal PGE2 (tablet)	0.188	785.2	-0.424	-2.374	1.409	0.903	0.099	1.769
Oral prostaglandins	Vaginal PGE2 (gel)	0.146	783.7	1.566	-0.031	3.238	0.229	-0.582	1.035
Oral prostaglandins	Intracervical PGE2	0.889	785.6	0.660	-0.742	2.091	0.536	-0.277	1.370
Buccal/sublingual misoprostol	Intracervical PGE2	0.136	784.2	0.968	0.133	1.827	0.305	0.066	0.548

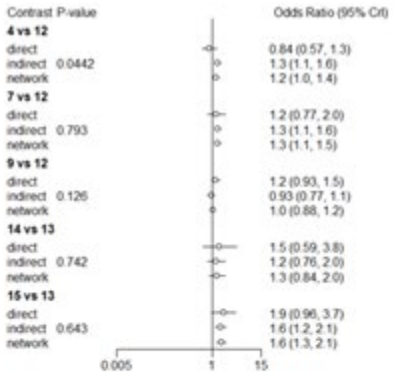
Buccal/sublingual misoprostol	Vaginal misoprostol (dose less than 50 mcg)	0.074	785.5	-0.092	-0.383	0.207	0.286	-0.008	0.582
Vaginal PGE2 (tablet)	Vaginal PGE2 (gel)	0.971	784.4	-0.166	-0.674	0.337	-0.156	-0.391	0.083
Vaginal PGE2 (tablet)	Vaginal PGE2 (pessary – slow release)	0.25	783.9	0.376	-0.578	1.344	-0.199	-0.446	0.049
Vaginal PGE2 (tablet)	Intracervical PGE2	0.073	784	-0.449	-0.897	-0.013	0.009	-0.227	0.238
Vaginal PGE2 (tablet)	Vaginal PGE2 pessary (normal release)	0.863	785.8	0.013	-1.540	1.577	-0.122	-0.424	0.183
Vaginal PGE2 (gel)	Vaginal PGE2 (pessary – slow release)	0.338	783.4	-0.213	-0.676	0.243	0.034	-0.173	0.241
Vaginal PGE2 (gel)	PGF2 gel	0.676	783.5	-0.011	-1.094	1.019	0.345	-1.018	1.689
Vaginal PGE2 (gel)	Intracervical PGE2	0.742	783.4	0.009	-0.372	0.397	0.078	-0.092	0.244
Vaginal PGE2 (gel)	Vaginal PGE2 pessary (normal release)	0.431	783.8	0.366	-0.487	1.245	0.004	-0.268	0.282
Vaginal PGE2 (gel)	Vaginal misoprostol (dose less than 50 mcg)	0.417	780.9	-0.056	-0.407	0.294	-0.218	-0.392	-0.045
Vaginal PGE2 (pessary – slow release)	Intracervical PGE2	0.386	783.9	0.229	-0.170	0.622	0.031	-0.174	0.235
Vaginal PGE2 (pessary – slow release)	Vaginal misoprostol (dose less than 50 mcg)	0.758	783.4	-0.133	-0.487	0.209	-0.197	-0.404	0.013
Intracervical PGE2	Vaginal PGE2 pessary (normal release)	0.995	780.7	-0.010	-0.473	0.464	-0.008	-0.316	0.292
Intracervical PGE2	Vaginal misoprostol (dose less than 50 mcg)	0.577	782	-0.318	-0.566	-0.068	-0.231	-0.400	-0.065
Vaginal PGE2 pessary (normal release)	Vaginal misoprostol (dose less than 50 mcg)	0.347	784.1	0.216	-0.735	1.221	-0.259	-0.526	0.004

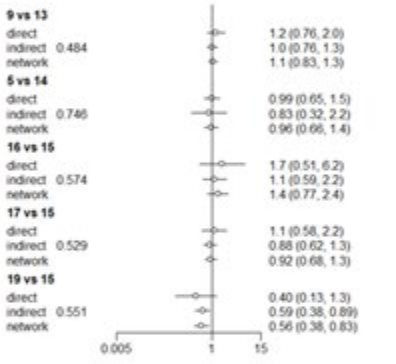
[2] *Posterior mean residual deviance – relative to 758 data points.*

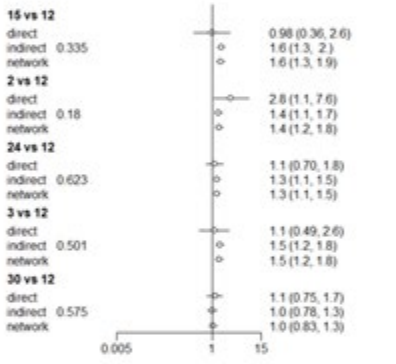
Direct, indirect, and network estimates of relative treatment effects on the odds-ratio scale based on node-splitting results (outcome: C-section, full dataset). Treatment codes: 1 - No treatment, 2 – Placebo, 3 - Vaginal PGE2 (tablet), 4 - Vaginal PGE2 (gel), 5 - Vaginal PGE2 (pessary – slow release), 6 - PGF2 gel, 7 - Intracervical PGE2, 8 - Vaginal PGE2 pessary (normal release), 9 - Vaginal misoprostol (Dose less than 50 mcg), 10 - Vaginal misoprostol (Dose 50 mcg or more), 11 - Oral misoprostol tablet (Dose less than 50 mcg), 12 - Oral misoprostol tablet (dose 50mcg or more), 13 - Titrated (low dose) oral misoprostol solution, 14 - Sustained release misoprostol insert, 15 - IV oxytocin, 16 – Amniotomy, 17 - IV oxytocin plus amniotomy, 18 - Nitric oxide, 19 – Mifepristone, 20 – Oestrogens, 21 – Corticosteroids, 22 – Relaxin, 23 – Hyaluronidase, 24 - Mechanical methods (Foley catheter), 25 - Mechanical methods (laminaria including dilapan), 26 - Mechanical methods (Double balloon or Cook's catheter), 27 - Extra-amniotic PGE2 or PGF2, 28 - IV prostaglandin, 29 - Oral prostaglandins, 30 - Buccal/sublingual misoprostol. Confidence intervals have been bounded at 0.005 and 15 to simplify presentation.

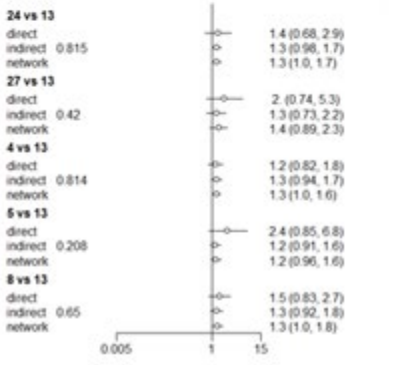


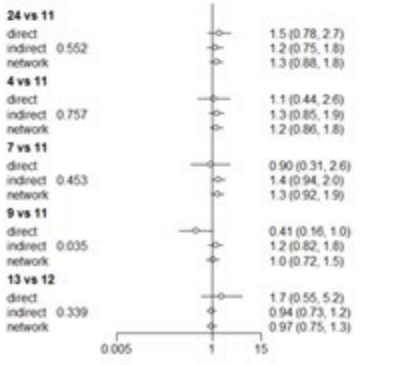

Contrast P-value
Odds Ratio (95% CrI)
20 vs 15
direct
indirect 0.742
network
0.86 (0.28, 2.7)
0.70 (0.41, 1.2)
0.73 (0.46, 1.2)
24 vs 15
direct
indirect 0.268
network
0.18 (0.0049, 2.4)
0.80 (0.66, 0.97)
0.80 (0.65, 0.97)
25 vs 15
direct
indirect 0.758
network
0.76 (0.24, 2.5)
0.92 (0.67, 1.3)
0.91 (0.68, 1.2)
26 vs 15
direct
indirect 0.729
network
0.64 (0.19, 2.1)
0.79 (0.59, 1.1)
0.78 (0.59, 1.0)
27 vs 15
direct
indirect 0.0538
network
0.11 (0.0049, 0.97)
0.97 (0.62, 1.5)
0.87 (0.56, 1.4)
0.005
1
15

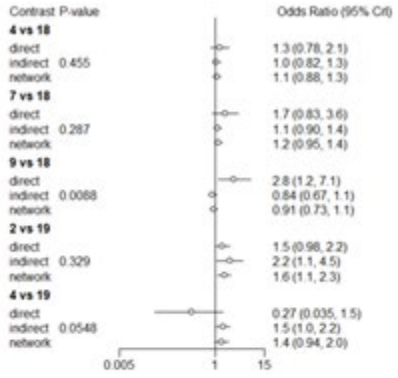

Contrast P-value
Odds Ratio (95% CrI)
4 vs 12
direct
indirect 0.0442
network
0.84 (0.57, 1.3)
1.3 (1.1, 1.6)
1.2 (1.0, 1.4)
7 vs 12
direct
indirect 0.793
network
1.2 (0.77, 2.0)
1.3 (1.1, 1.6)
1.3 (1.1, 1.5)
9 vs 12
direct
indirect 0.126
network
1.2 (0.93, 1.5)
0.93 (0.77, 1.1)
1.0 (0.88, 1.2)
14 vs 13
direct
indirect 0.742
network
1.5 (0.59, 3.8)
1.2 (0.76, 2.0)
1.3 (0.84, 2.0)
15 vs 13
direct
indirect 0.643
network
1.9 (0.96, 3.7)
1.6 (1.2, 2.1)
1.6 (1.3, 2.1)
0.005
1
15

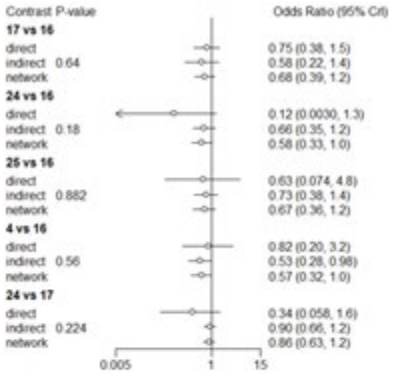

9 vs 13
direct
indirect 0.484
network
1.2 (0.76, 2.0)
1.0 (0.76, 1.3)
1.1 (0.83, 1.3)
5 vs 14
direct
indirect 0.746
network
0.99 (0.65, 1.5)
0.83 (0.32, 2.2)
0.96 (0.66, 1.4)
16 vs 15
direct
indirect 0.574
network
1.7 (0.51, 6.2)
1.1 (0.59, 2.2)
1.4 (0.77, 2.4)
17 vs 15
direct
indirect 0.529
network
1.1 (0.58, 2.2)
0.88 (0.62, 1.3)
0.92 (0.68, 1.3)
19 vs 15
direct
indirect 0.551
network
0.40 (0.13, 1.3)
0.59 (0.38, 0.89)
0.56 (0.38, 0.83)
0.005
1
15

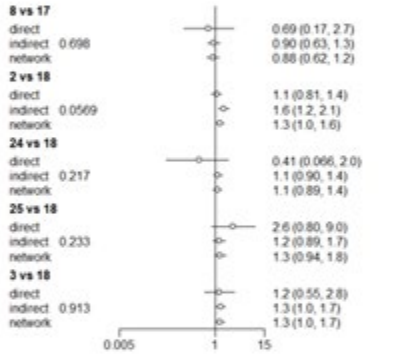

15 vs 12
direct
indirect 0.335
network
0.98 (0.36, 2.6)
1.6 (1.3, 2.)
1.6 (1.3, 1.9)
2 vs 12
direct
indirect 0.18
network
2.8 (1.1, 7.6)
1.4 (1.1, 1.7)
1.4 (1.2, 1.8)
24 vs 12
direct
indirect 0.623
network
1.1 (0.70, 1.8)
1.3 (1.1, 1.5)
1.3 (1.1, 1.5)
3 vs 12
direct
indirect 0.501
network
1.1 (0.49, 2.6)
1.5 (1.2, 1.8)
1.5 (1.2, 1.8)
30 vs 12
direct
indirect 0.575
network
1.1 (0.75, 1.7)
1.0 (0.78, 1.3)
1.0 (0.83, 1.3)
0.005
1
15

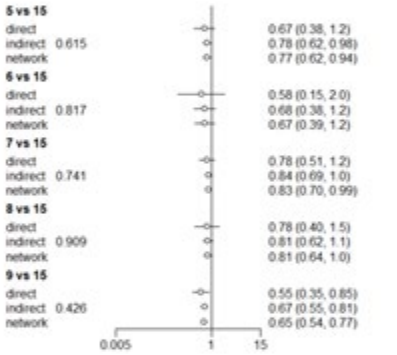

24 vs 13
direct
indirect 0.815
network
1.4 (0.68, 2.9)
1.3 (0.98, 1.7)
1.3 (1.0, 1.7)
27 vs 13
direct
indirect 0.42
network
2. (0.74, 5.3)
1.3 (0.73, 2.2)
1.4 (0.89, 2.3)
4 vs 13
direct
indirect 0.814
network
1.2 (0.82, 1.8)
1.3 (0.94, 1.7)
1.3 (1.0, 1.6)
5 vs 13
direct
indirect 0.208
network
2.4 (0.85, 6.8)
1.2 (0.91, 1.6)
1.2 (0.96, 1.6)
8 vs 13
direct
indirect 0.65
network
1.5 (0.83, 2.7)
1.3 (0.92, 1.8)
1.3 (1.0, 1.8)
0.005
1
15

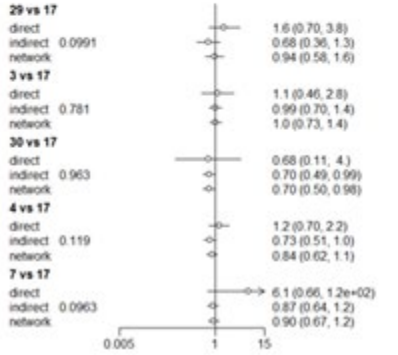

24 vs 11
direct
indirect 0.552
network
1.5 (0.78, 2.7)
1.2 (0.75, 1.8)
1.3 (0.88, 1.8)
4 vs 11
direct
indirect 0.757
network
1.1 (0.44, 2.6)
1.3 (0.85, 1.9)
1.2 (0.86, 1.8)
7 vs 11
direct
indirect 0.453
network
0.90 (0.31, 2.6)
1.4 (0.94, 2.0)
1.3 (0.92, 1.9)
9 vs 11
direct
indirect 0.035
network
0.41 (0.16, 1.0)
1.2 (0.82, 1.8)
1.0 (0.72, 1.5)
13 vs 12
direct
indirect 0.339
network
1.7 (0.55, 5.2)
0.94 (0.73, 1.2)
0.97 (0.75, 1.3)
0.005
1
15

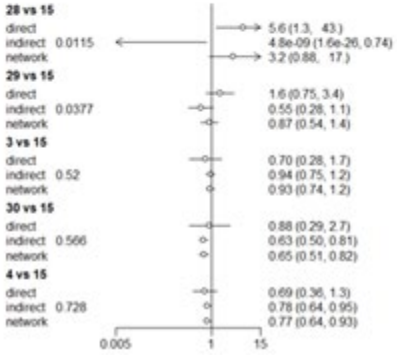

Contrast P-value
Odds Ratio (95% CrI)
4 vs 18
direct
1.3 (0.78, 2.1)
indirect 0.455
1.0 (0.82, 1.3)
network
1.1 (0.88, 1.3)
7 vs 18
direct
1.7 (0.83, 3.6)
indirect 0.287
1.1 (0.90, 1.4)
network
1.2 (0.95, 1.4)
9 vs 18
direct
2.8 (1.2, 7.1)
indirect 0.0068
0.84 (0.67, 1.1)
network
0.91 (0.73, 1.1)
2 vs 19
direct
1.5 (0.98, 2.2)
indirect 0.329
2.2 (1.1, 4.5)
network
1.6 (1.1, 2.3)
4 vs 19
direct
0.27 (0.035, 1.5)
indirect 0.0548
1.5 (1.0, 2.2)
network
1.4 (0.94, 2.0)
0.005
1
15

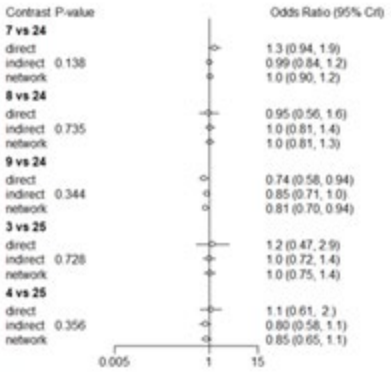

Contrast P-value
Odds Ratio (95% CrI)
17 vs 16
direct
0.75 (0.38, 1.5)
indirect 0.64
0.58 (0.22, 1.4)
network
0.68 (0.39, 1.2)
24 vs 16
direct
0.12 (0.0030, 1.3)
indirect 0.18
0.66 (0.35, 1.2)
network
0.58 (0.33, 1.0)
25 vs 16
direct
0.63 (0.074, 4.8)
indirect 0.882
0.73 (0.38, 1.4)
network
0.67 (0.36, 1.2)
4 vs 16
direct
0.82 (0.20, 3.2)
indirect 0.56
0.53 (0.28, 0.98)
network
0.57 (0.32, 1.0)
24 vs 17
direct
0.34 (0.058, 1.6)
indirect 0.224
0.90 (0.66, 1.2)
network
0.86 (0.63, 1.2)
0.005
1
15

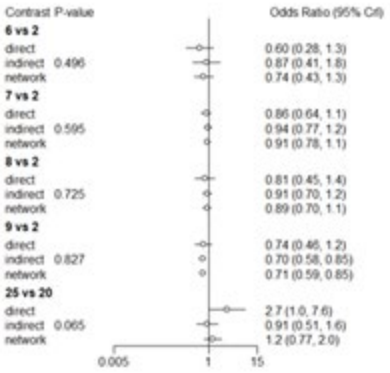

8 vs 17
direct
0.69 (0.17, 2.7)
indirect 0.698
0.90 (0.63, 1.3)
network
0.88 (0.62, 1.2)
2 vs 18
direct
1.1 (0.81, 1.4)
indirect 0.0569
1.6 (1.2, 2.1)
network
1.3 (1.0, 1.6)
24 vs 18
direct
0.41 (0.066, 2.0)
indirect 0.217
1.1 (0.90, 1.4)
network
1.1 (0.89, 1.4)
25 vs 18
direct
2.6 (0.80, 9.0)
indirect 0.233
1.2 (0.89, 1.7)
network
1.3 (0.94, 1.8)
3 vs 18
direct
1.2 (0.55, 2.8)
indirect 0.913
1.3 (1.0, 1.7)
network
1.3 (1.0, 1.7)
0.005
1
15

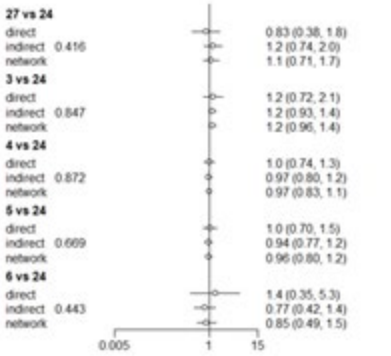

5 vs 15
direct
0.67 (0.38, 1.2)
indirect 0.615
0.78 (0.62, 0.98)
network
0.77 (0.62, 0.94)
6 vs 15
direct
0.58 (0.15, 2.0)
indirect 0.817
0.68 (0.38, 1.2)
network
0.67 (0.39, 1.2)
7 vs 15
direct
0.78 (0.51, 1.2)
indirect 0.741
0.84 (0.69, 1.0)
network
0.83 (0.70, 0.99)
8 vs 15
direct
0.78 (0.40, 1.5)
indirect 0.909
0.81 (0.62, 1.1)
network
0.81 (0.64, 1.0)
9 vs 15
direct
0.55 (0.35, 0.85)
indirect 0.426
0.67 (0.55, 0.81)
network
0.65 (0.54, 0.77)
0.005
1
15

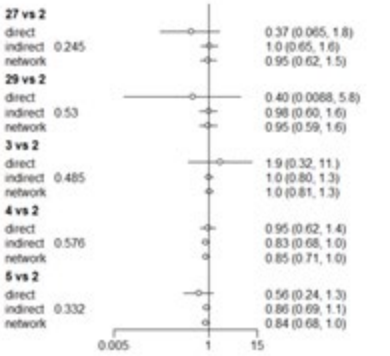

29 vs 17
direct
1.6 (0.70, 3.8)
indirect 0.0991
0.68 (0.36, 1.3)
network
0.94 (0.58, 1.6)
3 vs 17
direct
1.1 (0.46, 2.8)
indirect 0.781
0.99 (0.70, 1.4)
network
1.0 (0.73, 1.4)
30 vs 17
direct
0.68 (0.11, 4.)
indirect 0.963
0.70 (0.49, 0.99)
network
0.70 (0.50, 0.98)
4 vs 17
direct
1.2 (0.70, 2.2)
indirect 0.119
0.73 (0.51, 1.0)
network
0.84 (0.62, 1.1)
7 vs 17
direct
6.1 (0.66, 1.2e+02)
indirect 0.0963
0.87 (0.64, 1.2)
network
0.90 (0.67, 1.2)
0.005
1
15

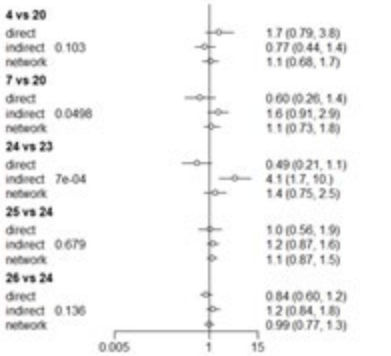

28 vs 15
direct
5.6 (1.3, 43.)
indirect 0.0115
4.8e-09 (1.6e-26, 0.74)
network
3.2 (0.88, 17.)
29 vs 15
direct
1.6 (0.75, 3.4)
indirect 0.0377
0.55 (0.28, 1.1)
network
0.87 (0.54, 1.4)
3 vs 15
direct
0.70 (0.28, 1.7)
indirect 0.52
0.94 (0.75, 1.2)
network
0.93 (0.74, 1.2)
30 vs 15
direct
0.88 (0.29, 2.7)
indirect 0.566
0.63 (0.50, 0.81)
network
0.65 (0.51, 0.82)
4 vs 15
direct
0.69 (0.36, 1.3)
indirect 0.728
0.78 (0.64, 0.95)
network
0.77 (0.64, 0.93)
0.005
1
15

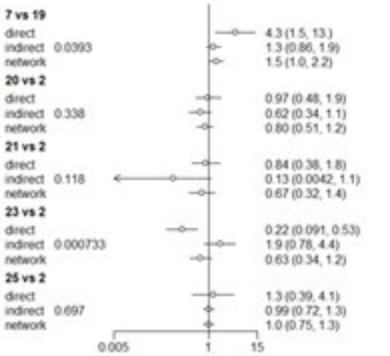

Contrast P-value
Odds Ratio (95% CrI)
7 vs 24
direct
indirect 0.138
network
1.3 (0.94, 1.9)
0.99 (0.84, 1.2)
1.0 (0.90, 1.2)
8 vs 24
direct
indirect 0.735
network
0.95 (0.56, 1.6)
1.0 (0.81, 1.4)
1.0 (0.81, 1.3)
9 vs 24
direct
indirect 0.344
network
0.74 (0.58, 0.94)
0.85 (0.71, 1.0)
0.81 (0.70, 0.94)
3 vs 25
direct
indirect 0.728
network
1.2 (0.47, 2.9)
1.0 (0.72, 1.4)
1.0 (0.75, 1.4)
4 vs 25
direct
indirect 0.356
network
1.1 (0.61, 2.)
0.80 (0.58, 1.1)
0.85 (0.65, 1.1)
0.005
1
15

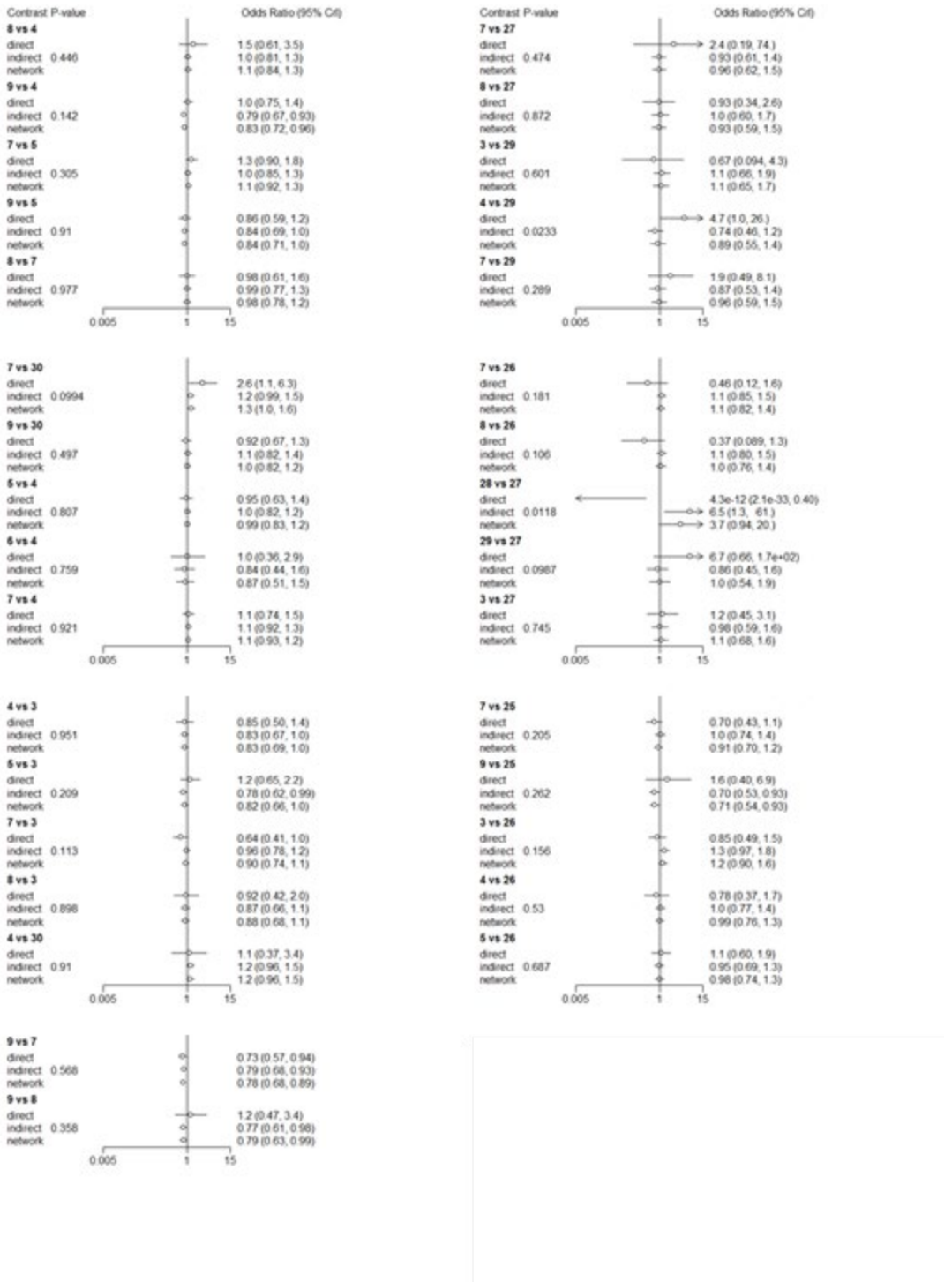

Contrast P-value
Odds Ratio (95% CrI)
6 vs 2
direct
indirect 0.496
network
0.60 (0.28, 1.3)
0.87 (0.41, 1.8)
0.74 (0.43, 1.3)
7 vs 2
direct
indirect 0.595
network
0.86 (0.64, 1.1)
0.94 (0.77, 1.2)
0.91 (0.78, 1.1)
8 vs 2
direct
indirect 0.725
network
0.81 (0.45, 1.4)
0.91 (0.70, 1.2)
0.89 (0.70, 1.1)
9 vs 2
direct
indirect 0.827
network
0.74 (0.46, 1.2)
0.70 (0.58, 0.85)
0.71 (0.59, 0.85)
25 vs 20
direct
indirect 0.065
network
2.7 (1.0, 7.6)
0.91 (0.51, 1.6)
1.2 (0.77, 2.0)
0.005
1
15


27 vs 24
direct
indirect 0.416
network
0.83 (0.38, 1.8)
1.2 (0.74, 2.0)
1.1 (0.71, 1.7)
3 vs 24
direct
indirect 0.847
network
1.2 (0.72, 2.1)
1.2 (0.93, 1.4)
1.2 (0.96, 1.4)
4 vs 24
direct
indirect 0.872
network
1.0 (0.74, 1.3)
0.97 (0.80, 1.2)
0.97 (0.83, 1.1)
5 vs 24
direct
indirect 0.669
network
1.0 (0.70, 1.5)
0.94 (0.77, 1.2)
0.96 (0.80, 1.2)
6 vs 24
direct
indirect 0.443
network
1.4 (0.35, 5.3)
0.77 (0.42, 1.4)
0.85 (0.49, 1.5)
0.005
1
15


27 vs 2
direct
indirect 0.245
network
0.37 (0.065, 1.8)
1.0 (0.65, 1.6)
0.95 (0.62, 1.5)
29 vs 2
direct
indirect 0.53
network
0.40 (0.0088, 5.8)
0.98 (0.60, 1.6)
0.95 (0.59, 1.6)
3 vs 2
direct
indirect 0.485
network
1.9 (0.32, 11.)
1.0 (0.80, 1.3)
1.0 (0.81, 1.3)
4 vs 2
direct
indirect 0.576
network
0.95 (0.62, 1.4)
0.83 (0.68, 1.0)
0.85 (0.71, 1.0)
5 vs 2
direct
indirect 0.332
network
0.56 (0.24, 1.3)
0.86 (0.69, 1.1)
0.84 (0.68, 1.0)
0.005
1
15

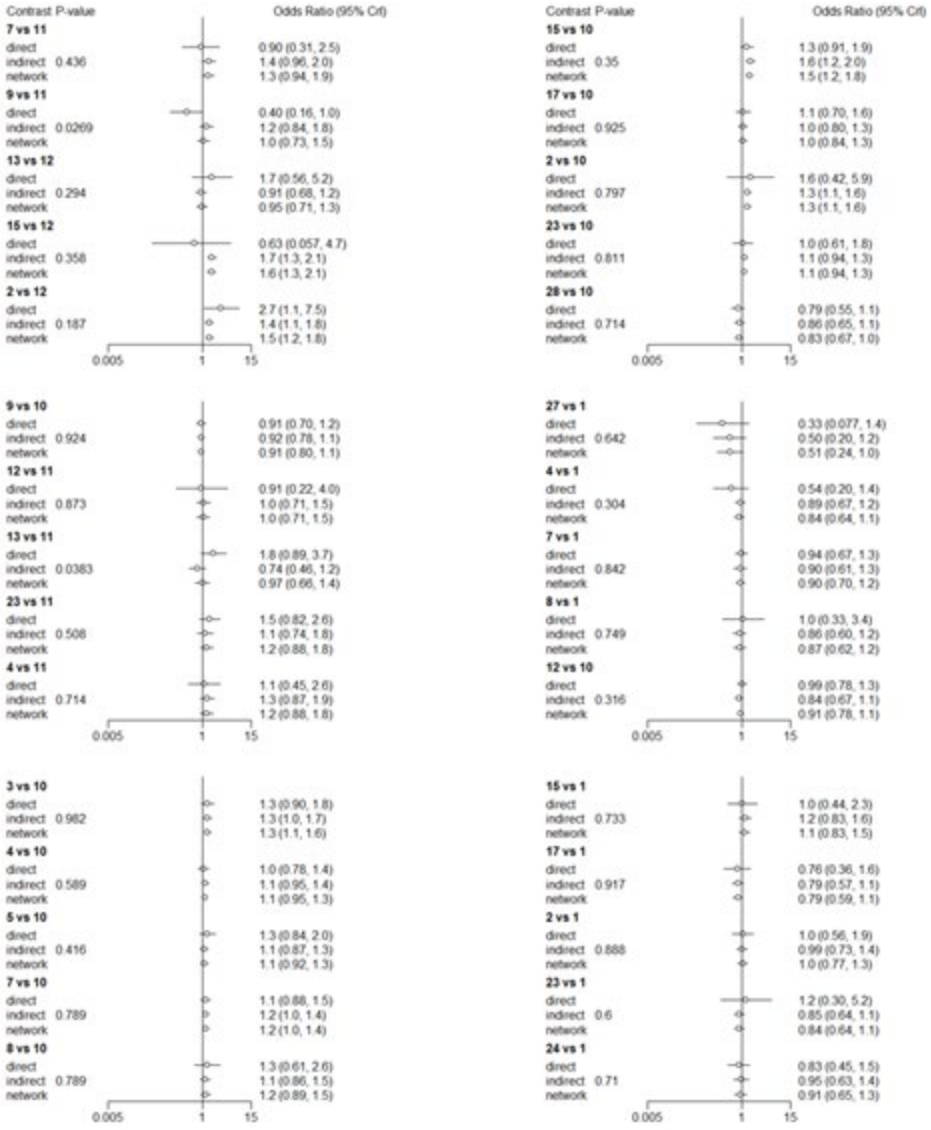

4 vs 20
direct
indirect 0.103
network
1.7 (0.79, 3.8)
0.77 (0.44, 1.4)
1.1 (0.68, 1.7)
7 vs 20
direct
indirect 0.0498
network
0.60 (0.26, 1.4)
1.6 (0.91, 2.9)
1.1 (0.73, 1.8)
24 vs 23
direct
indirect 7e-04
network
0.49 (0.21, 1.1)
4.1 (1.7, 10.)
1.4 (0.75, 2.5)
25 vs 24
direct
indirect 0.679
network
1.0 (0.56, 1.9)
1.2 (0.87, 1.6)
1.1 (0.87, 1.5)
26 vs 24
direct
indirect 0.136
network
0.84 (0.60, 1.2)
1.2 (0.84, 1.8)
0.99 (0.77, 1.3)
0.005
1
15

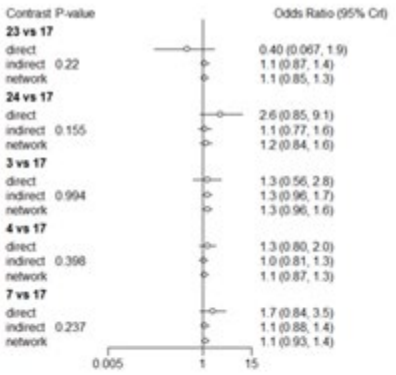

7 vs 19
direct
indirect 0.0393
network
4.3 (1.5, 13.)
1.3 (0.86, 1.9)
1.5 (1.0, 2.2)
20 vs 2
direct
indirect 0.338
network
0.97 (0.48, 1.9)
0.62 (0.34, 1.1)
0.80 (0.51, 1.2)
21 vs 2
direct
indirect 0.118
network
0.84 (0.38, 1.8)
0.13 (0.0042, 1.1)
0.67 (0.32, 1.4)
23 vs 2
direct
indirect 0.000733
network
0.22 (0.091, 0.53)
1.9 (0.78, 4.4)
0.63 (0.34, 1.2)
25 vs 2
direct
indirect 0.697
network
1.3 (0.39, 4.1)
0.99 (0.72, 1.3)
1.0 (0.75, 1.3)
0.005
1
15

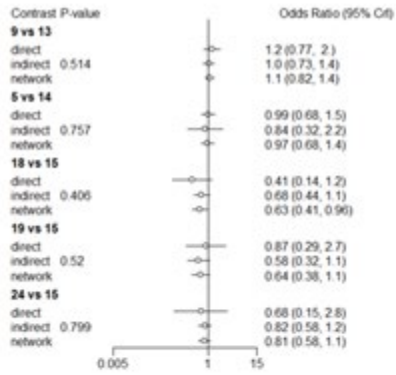


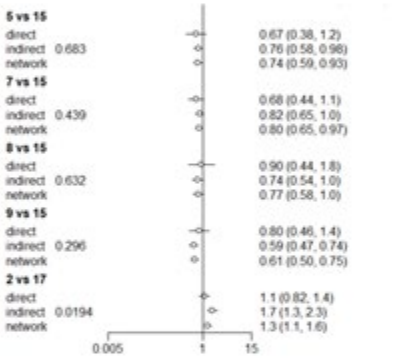
Direct, indirect, and network estimates of relative treatment effects on the odds-ratio scale based on node-splitting results (outcome: C-section, unfavourable cervix dataset). Treatment codes: 1 - No treatment, 2 – Placebo, 3 - Vaginal PGE2 (tablet), 4 - Vaginal PGE2 (gel), 5 - Vaginal PGE2 (pessary – slow release), 6 - PGF2 gel, 7 - Intracervical PGE2, 8 - Vaginal PGE2 pessary (normal release), 9 - Vaginal misoprostol (Dose less than 50 mcg), 10 - Vaginal misoprostol (Dose 50 mcg or more), 11 - Oral misoprostol tablet (Dose less than 50 mcg), 12 - Oral misoprostol tablet (dose 50mcg or more), 13 - Titrated (low dose) oral misoprostol solution, 14 - Sustained release misoprostol insert, 15 - IV oxytocin, 16 – IV

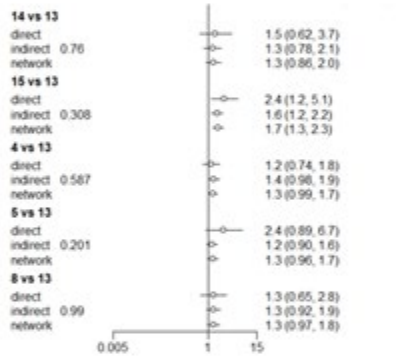
oxytocin plus amniotomy, 17 - Nitric oxide, 18 – Mifepristone, 19 – Oestrogens, 20 – Corticosteroids, 21 – Relaxin, 22 – Hyaluronidase, 23 - Mechanical methods (Foley catheter), 24 - Mechanical methods (laminaria including dilapan), 25 - Mechanical methods (Double balloon or Cook's catheter), 26 - Extra-amniotic PGE2 or PGF2, 27 - Oral prostaglandins, 28 - Buccal/sublingual misoprostol. Confidence intervals have been bounded at 0.005 and 15 to simplify presentation.

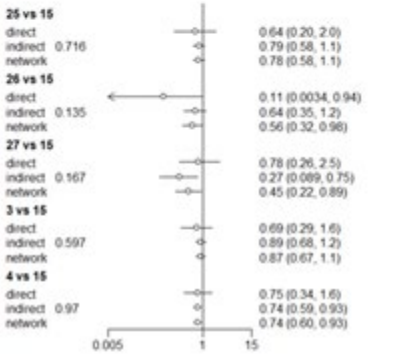


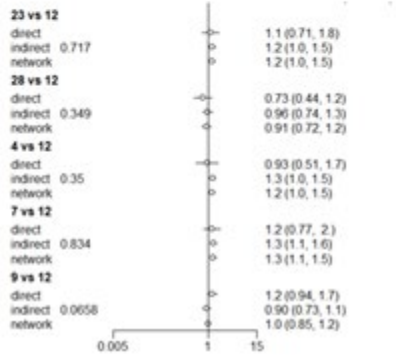

Contrast P-value
Odds Ratio (95% CrI)
23 vs 17
direct
indirect 0.22
network
0.40 (0.067, 1.9)
1.1 (0.87, 1.4)
1.1 (0.85, 1.3)
24 vs 17
direct
indirect 0.155
network
2.6 (0.85, 9.1)
1.1 (0.77, 1.6)
1.2 (0.84, 1.6)
3 vs 17
direct
indirect 0.994
network
1.3 (0.56, 2.8)
1.3 (0.96, 1.7)
1.3 (0.96, 1.6)
4 vs 17
direct
indirect 0.398
network
1.3 (0.80, 2.0)
1.0 (0.81, 1.3)
1.1 (0.87, 1.3)
7 vs 17
direct
indirect 0.237
network
1.7 (0.84, 3.5)
1.1 (0.88, 1.4)
1.1 (0.93, 1.4)
0.005
1
15

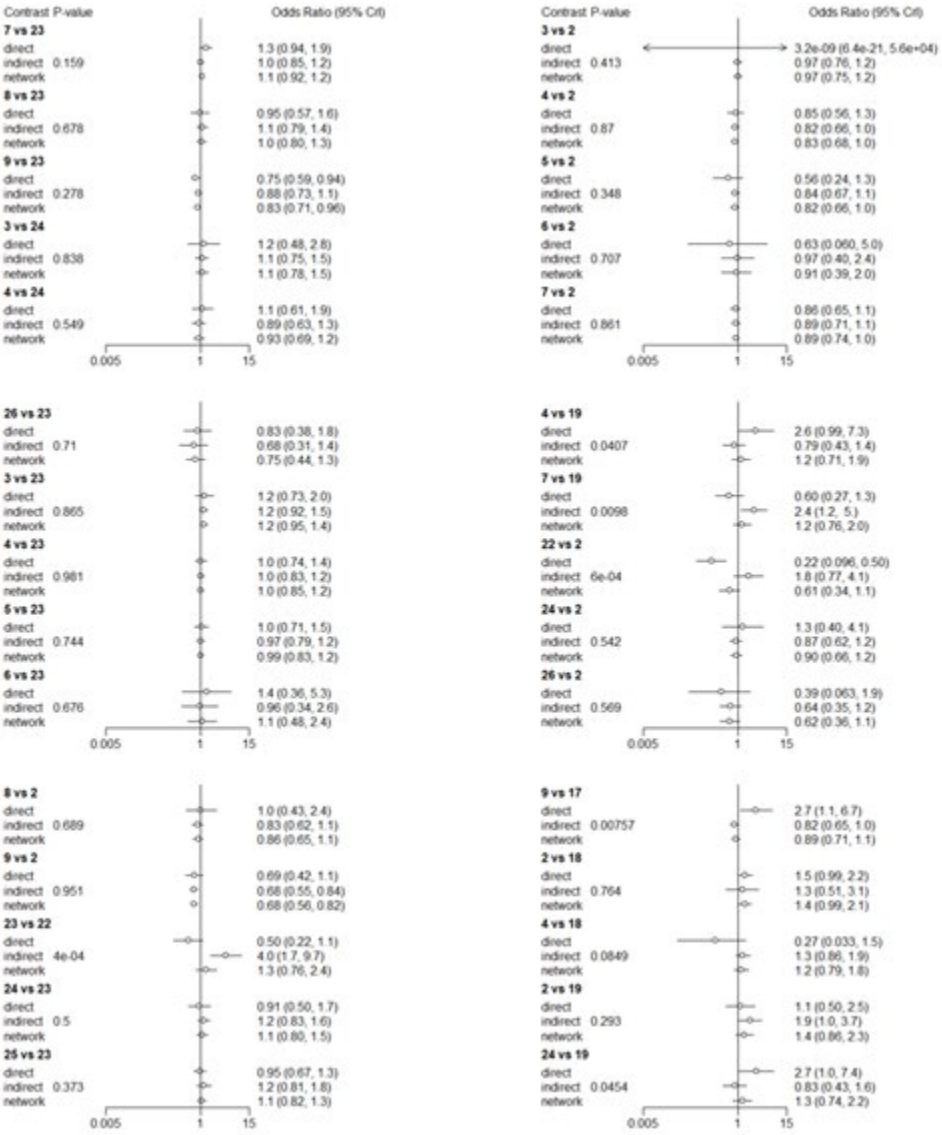

Contrast P-value
Odds Ratio (95% CrI)
9 vs 13
direct
indirect 0.514
network
1.2 (0.77, 2.)
1.0 (0.73, 1.4)
1.1 (0.82, 1.4)
5 vs 14
direct
indirect 0.757
network
0.99 (0.68, 1.5)
0.84 (0.32, 2.2)
0.97 (0.68, 1.4)
18 vs 15
direct
indirect 0.406
network
0.41 (0.14, 1.2)
0.68 (0.44, 1.1)
0.63 (0.41, 0.96)
19 vs 15
direct
indirect 0.52
network
0.87 (0.29, 2.7)
0.58 (0.32, 1.1)
0.64 (0.38, 1.1)
24 vs 15
direct
indirect 0.799
network
0.68 (0.15, 2.8)
0.82 (0.58, 1.2)
0.81 (0.58, 1.1)
0.005
1
15

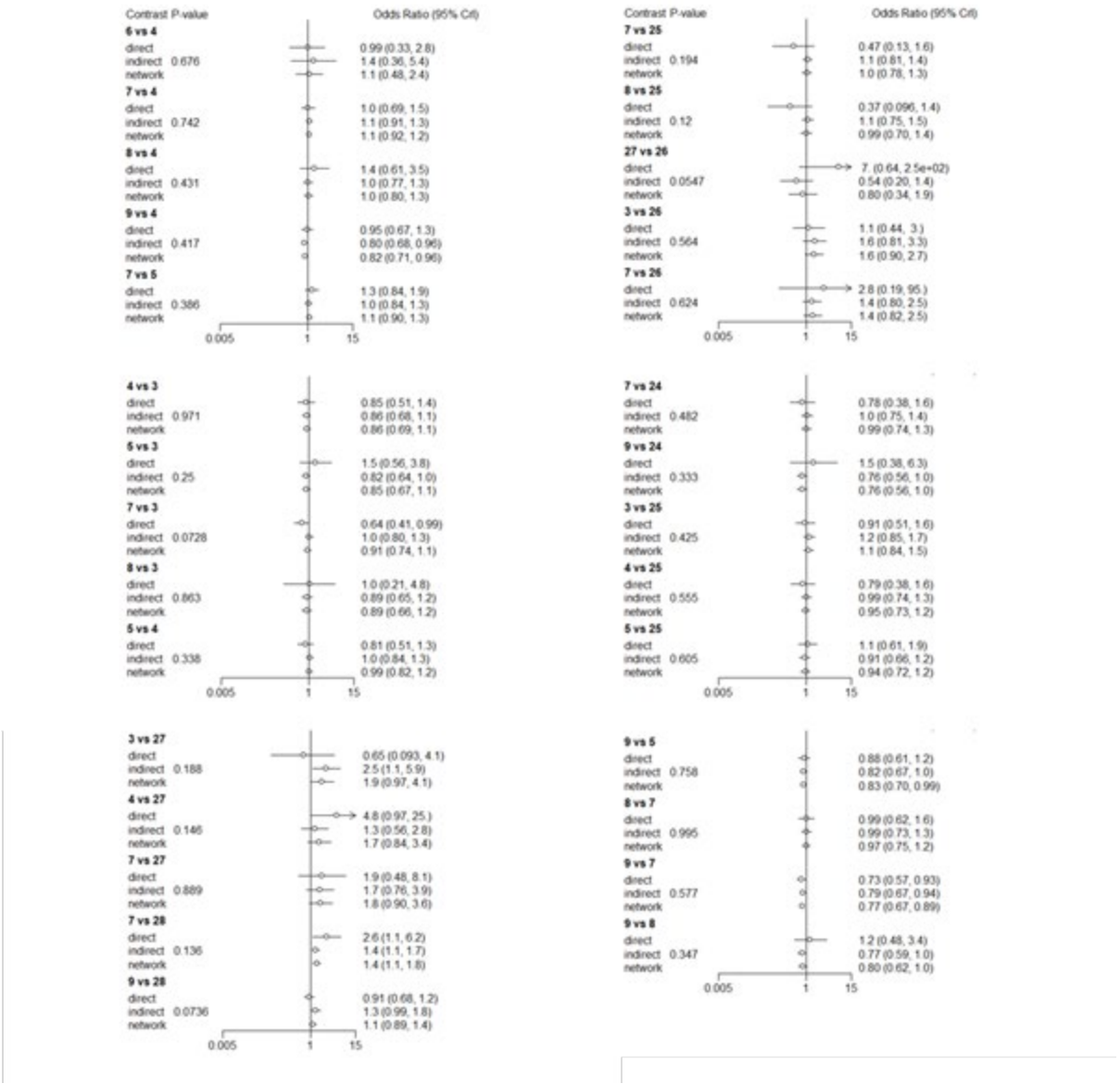

5 vs 15
direct
indirect 0.683
network
0.67 (0.38, 1.2)
0.76 (0.58, 0.98)
0.74 (0.59, 0.93)
7 vs 15
direct
indirect 0.439
network
0.68 (0.44, 1.1)
0.82 (0.65, 1.0)
0.80 (0.65, 0.97)
8 vs 15
direct
indirect 0.632
network
0.90 (0.44, 1.8)
0.74 (0.54, 1.0)
0.77 (0.58, 1.0)
9 vs 15
direct
indirect 0.296
network
0.80 (0.46, 1.4)
0.59 (0.47, 0.74)
0.61 (0.50, 0.75)
2 vs 17
direct
indirect 0.0194
network
1.1 (0.82, 1.4)
1.7 (1.3, 2.3)
1.3 (1.1, 1.6)
0.005
1
15


14 vs 13
direct
indirect 0.76
network
1.5 (0.62, 3.7)
1.3 (0.78, 2.1)
1.3 (0.86, 2.0)
15 vs 13
direct
indirect 0.308
network
2.4 (1.2, 5.1)
1.6 (1.2, 2.2)
1.7 (1.3, 2.3)
4 vs 13
direct
indirect 0.587
network
1.2 (0.74, 1.8)
1.4 (0.98, 1.9)
1.3 (0.99, 1.7)
5 vs 13
direct
indirect 0.201
network
2.4 (0.89, 6.7)
1.2 (0.90, 1.6)
1.3 (0.96, 1.7)
8 vs 13
direct
indirect 0.99
network
1.3 (0.65, 2.8)
1.3 (0.92, 1.9)
1.3 (0.97, 1.8)
0.005
1
15


25 vs 15
direct
indirect 0.716
network
0.64 (0.20, 2.0)
0.79 (0.58, 1.1)
0.78 (0.58, 1.1)
26 vs 15
direct
indirect 0.135
network
0.11 (0.0034, 0.94)
0.64 (0.35, 1.2)
0.56 (0.32, 0.98)
27 vs 15
direct
indirect 0.167
network
0.78 (0.26, 2.5)
0.27 (0.089, 0.75)
0.45 (0.22, 0.89)
3 vs 15
direct
indirect 0.597
network
0.69 (0.29, 1.6)
0.89 (0.68, 1.2)
0.87 (0.67, 1.1)
4 vs 15
direct
indirect 0.97
network
0.75 (0.34, 1.6)
0.74 (0.59, 0.93)
0.74 (0.60, 0.93)
0.005
1
15


23 vs 12
direct
indirect 0.717
network
1.1 (0.71, 1.8)
1.2 (1.0, 1.5)
1.2 (1.0, 1.5)
28 vs 12
direct
indirect 0.349
network
0.73 (0.44, 1.2)
0.96 (0.74, 1.3)
0.91 (0.72, 1.2)
4 vs 12
direct
indirect 0.35
network
0.93 (0.51, 1.7)
1.3 (1.0, 1.5)
1.2 (1.0, 1.5)
7 vs 12
direct
indirect 0.834
network
1.2 (0.77, 2.)
1.3 (1.1, 1.6)
1.3 (1.1, 1.5)
9 vs 12
direct
indirect 0.0658
network
1.2 (0.94, 1.7)
0.90 (0.73, 1.1)
1.0 (0.85, 1.2)
0.005
1
15


Contrast P-value
Odds Ratio (95% CrI)
7 vs 23
direct
indirect 0.159
network
1.3 (0.94, 1.9)
1.0 (0.85, 1.2)
1.1 (0.92, 1.2)
8 vs 23
direct
indirect 0.678
network
0.95 (0.57, 1.6)
1.1 (0.79, 1.4)
1.0 (0.80, 1.3)
9 vs 23
direct
indirect 0.278
network
0.75 (0.59, 0.94)
0.88 (0.73, 1.1)
0.83 (0.71, 0.96)
3 vs 24
direct
indirect 0.838
network
1.2 (0.48, 2.8)
1.1 (0.75, 1.5)
1.1 (0.78, 1.5)
4 vs 24
direct
indirect 0.549
network
1.1 (0.61, 1.9)
0.89 (0.63, 1.3)
0.93 (0.69, 1.2)
0.005
1
15
Contrast P-value
Odds Ratio (95% CrI)
3 vs 2
direct
indirect 0.413
network
3.2e-09 (6.4e-21, 5.6e+04)
0.97 (0.76, 1.2)
0.97 (0.75, 1.2)
4 vs 2
direct
indirect 0.87
network
0.85 (0.56, 1.3)
0.82 (0.66, 1.0)
0.83 (0.68, 1.0)
5 vs 2
direct
indirect 0.348
network
0.56 (0.24, 1.3)
0.84 (0.67, 1.1)
0.82 (0.66, 1.0)
6 vs 2
direct
indirect 0.707
network
0.63 (0.060, 5.0)
0.97 (0.40, 2.4)
0.91 (0.39, 2.0)
7 vs 2
direct
indirect 0.861
network
0.86 (0.65, 1.1)
0.89 (0.71, 1.1)
0.89 (0.74, 1.0)
0.005
1
15
26 vs 23
direct
indirect 0.71
network
0.83 (0.38, 1.8)
0.68 (0.31, 1.4)
0.75 (0.44, 1.3)
3 vs 23
direct
indirect 0.865
network
1.2 (0.73, 2.0)
1.2 (0.92, 1.5)
1.2 (0.95, 1.4)
4 vs 23
direct
indirect 0.981
network
1.0 (0.74, 1.4)
1.0 (0.83, 1.2)
1.0 (0.85, 1.2)
5 vs 23
direct
indirect 0.744
network
1.0 (0.71, 1.5)
0.97 (0.79, 1.2)
0.99 (0.83, 1.2)
6 vs 23
direct
indirect 0.676
network
1.4 (0.36, 5.3)
0.96 (0.34, 2.6)
1.1 (0.48, 2.4)
0.005
1
15
4 vs 19
direct
indirect 0.0407
network
2.6 (0.99, 7.3)
0.79 (0.43, 1.4)
1.2 (0.71, 1.9)
7 vs 19
direct
indirect 0.0098
network
0.60 (0.27, 1.3)
2.4 (1.2, 5.)
1.2 (0.76, 2.0)
22 vs 2
direct
indirect 6e-04
network
0.22 (0.096, 0.50)
1.8 (0.77, 4.1)
0.61 (0.34, 1.1)
24 vs 2
direct
indirect 0.542
network
1.3 (0.40, 4.1)
0.87 (0.62, 1.2)
0.90 (0.66, 1.2)
26 vs 2
direct
indirect 0.569
network
0.39 (0.063, 1.9)
0.64 (0.35, 1.2)
0.62 (0.36, 1.1)
0.005
1
15
8 vs 2
direct
indirect 0.689
network
1.0 (0.43, 2.4)
0.83 (0.62, 1.1)
0.86 (0.65, 1.1)
9 vs 2
direct
indirect 0.951
network
0.69 (0.42, 1.1)
0.68 (0.55, 0.84)
0.68 (0.56, 0.82)
23 vs 22
direct
indirect 4e-04
network
0.50 (0.22, 1.1)
4.0 (1.7, 9.7)
1.3 (0.76, 2.4)
24 vs 23
direct
indirect 0.5
network
0.91 (0.50, 1.7)
1.2 (0.83, 1.6)
1.1 (0.80, 1.5)
25 vs 23
direct
indirect 0.373
network
0.95 (0.67, 1.3)
1.2 (0.81, 1.8)
1.1 (0.82, 1.3)
0.005
1
15
9 vs 17
direct
indirect 0.00757
network
2.7 (1.1, 6.7)
0.82 (0.65, 1.0)
0.89 (0.71, 1.1)
2 vs 18
direct
indirect 0.764
network
1.5 (0.99, 2.2)
1.3 (0.51, 3.1)
1.4 (0.99, 2.1)
4 vs 18
direct
indirect 0.0849
network
0.27 (0.033, 1.5)
1.3 (0.86, 1.9)
1.2 (0.79, 1.8)
2 vs 19
direct
indirect 0.293
network
1.1 (0.50, 2.5)
1.9 (1.0, 3.7)
1.4 (0.86, 2.3)
24 vs 19
direct
indirect 0.0454
network
2.7 (1.0, 7.4)
0.83 (0.43, 1.6)
1.3 (0.74, 2.2)
0.005
1
15



Instrumental birth

Analysis of the full dataset included 243 trials of 28 treatments (500 arms) whilst analysis of the unfavourable cervix dataset included 171 trials of 27 treatments (354 arms). Fitting of fixed-effect (FE) and random-effect (RE) models, which estimate a parameter for between-study standard deviation (SD), supported use of the RE model (Table 1). There was estimated to be relatively low between-study SD; however, use of the RE model structure resulted in a reduction in mean residual deviance.

Random-effects models required an informative prior to aid convergence, with the standard, Un(0,5) uninformative prior on between-study standard deviation (SD) (as specified in TSD2) was replaced with an informative prior for between-study SD drawn from Turner et al. 2015 for obstetric non-pharmacological vs pharmacological interventions. Results were based on 80,000 iterations following a burn-in of 40,000 iterations, which was sufficient to achieve convergence according to the Brooks Gelman-Rubin statistic. Convergence was satisfactory for the fixed effect model assuming inconsistency after 20,000 iterations, and the consistency and inconsistency models were compared using results based on samples from a further

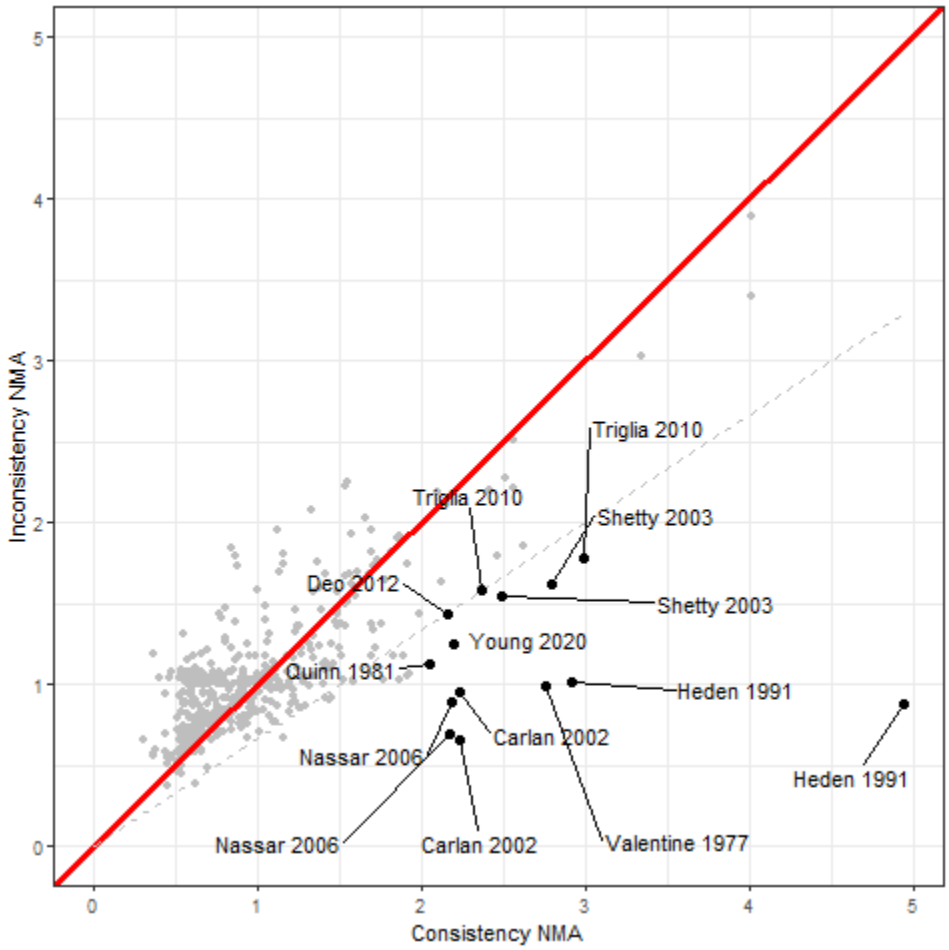
240,000 iterations on two chains. WinBUGS code for the inconsistency model is provided below.

Network meta-analysis (NMA) models of the outcome instrumental delivery, comparison of fixed- (FE) and random-effect (RE) models. Residual deviance is the model's posterior mean residual deviance, to be compared to number of data points, lower values preferred. DIC is the Deviance information criteria – lower values preferred.

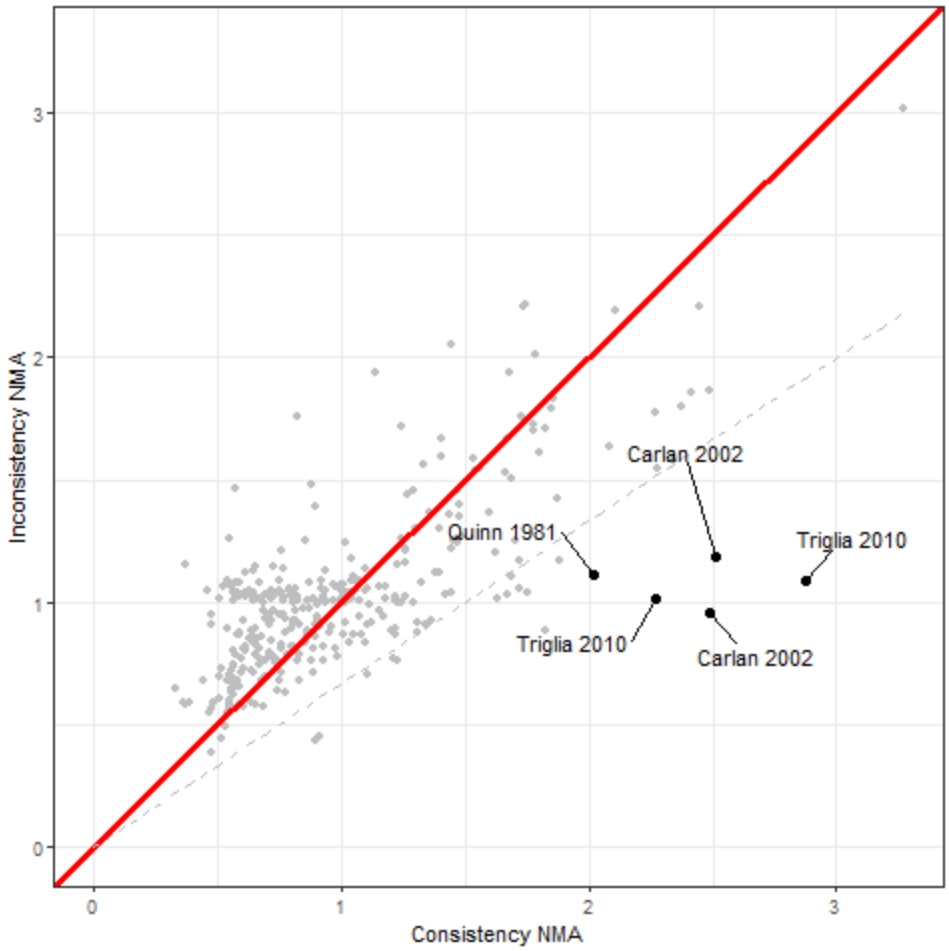
Dataset	Model	Between-study SD (mean)			Mean residual deviance	Data points (arms)	DIC
		Mean	2.5% CrI	97.5% CrI			
Full	Consistency NMA (FE)	-	-	-	504.0	500	2526.75
	Consistency NMA (RE)	0.12	0.04	0.22	493.3	500	2528.99
	Inconsistency NMA (RE)	0.17	0.05	0.31	510.4	500	2624.22
Subgroup (unfav. cervix)	Consistency NMA (FE)	-	-	-	354.7	354	1774.60
	Consistency NMA (RE)	0.13	0.04	0.25	346.8	354	1776.53
	Inconsistency NMA (RE)	0.17	0.05	0.34	359.1	354	1844.35

Consistency and inconsistency random-effects NMA models were fitted to the full and subgroup datasets. In both cases there was no global evidence of inconsistency based on the DIC or the posterior mean residual deviance. The estimate of between-study SD was higher and more uncertain within the inconsistency model, which is likely due to lower estimating power when the consistency assumption is relaxed.

To explore this further we plotted the contribution of each study arm to the total residual deviance for the inconsistency model vs the consistency model in a dev-dev plot.A simple rule was used to identify study arms with relatively high deviance in the consistency model: points with relatively high deviance were those with mean deviance in the consistency NMA model greater than 2, and where the residual deviance in the consistency NMA was at least 1.5 times that estimated under the inconsistency model.



Dev-dev plots of each study arm's deviance in the consistency and inconsistency NMA models of instrumental delivery, full dataset. Studies were relatively poorly predicted by the consistency NMA are shown as labelled black points. Red line indicates line of equivalence.



Dev-dev plots of each study arm's deviance in the consistency and inconsistency NMA models of instrumental delivery, unfavourable cervix subgroup dataset. Studies that were relatively poorly predicted by the consistency NMA are shown as labelled black points. Red line indicates line of equivalence.

Three studies within both full and unfavourable cervix groups were flagged as having relatively high residual deviance within the consistency NMA model:

- Carlan 2002 was a two-armed trial comparing vaginal misoprostol (dose 50 mcg or more) and buccal/sublingual misoprostol (codes 10 and 30 in full dataset).
- Quinn 1981 was a two-armed trial comparing Foley catheter and extra-amniotic PGE2 or PGF2 (codes 24 and 27 in full dataset).
- Triglia 2010 was a two-armed trial comparing vaginal PGE2 (gel) and vaginal PGE2 (pessary – slow release) (codes 4 and 5 in full dataset).

Six studies were flagged in the full dataset only:

- Deo 2012 was a was a three-armed trial of vaginal PGE2 (gel), vaginal misoprostol (dose less than 50 mcg) and Foley catheter (codes 4, 9, 24).
- Valentine 1977 was a three-armed trial comparing no treatment, IV oxytocin and oral prostaglandin (treatment codes 1, 15, 29).
- Heden 1991 was a two-armed trial comparing no treatment and nitric oxide (codes 1 and 17).

- Nassar 2006 was a two-armed trial comparing vaginal misoprostol (dose 50 mcg or more) and buccal/sublingual misoprostol (codes 10 and 30).
- Shetty 2003 was a two-armed trial comparing vaginal misoprostol (dose less than 50 mcg) and oral misoprostol tablet (dose 50mcg or more) (codes 9 and 12).
- Young 2020 was a three-armed trial comparing vaginal PGE2 gel, vaginal misoprostol (dose less than 50 mcg) and oral misoprostol tablet (dose 50mcg or more) (codes 4, 9 and 12).

Inconsistency between direct and indirect evidence ($p < 0.05$) was indicated in 4 out of 109 comparisons in the full dataset (Table 2) and 1 out of 83 comparisons in the unfavourable cervix subgroup (Table 3). Multiple testing would suggest that 5/109 and 4/83 comparisons might be expected to have p values below 0.05.

These results indicate potential inconsistency in the treatment comparisons estimated between IV oxytocin plus amniotomy and no treatment, between treatment with vaginal misoprostol (dose 50 mcg or more) and buccal/sublingual misoprostol and between titrated low-dose oral misoprostol and Foley catheter.

Whilst node-splitting models highlighted 10 treatment comparisons where the treatment difference drawn from the direct evidence was poorly estimated because of being drawn from single studies, in each case the network treatment effect estimate was well estimated.

Table 2. Direct and indirect estimates of treatment difference (LOR), outcome instrumental delivery, full dataset. Where direct and indirect estimates are inconsistent (p<0.05), treatment comparisons are highlighted in yellow. Residual deviance is the model's posterior mean residual deviance, to be compared to number of data points (500), lower values preferred.

Intervention 1	Intervention 2	p-value	Residual deviance	Direct			Indirect		
				Median	2.5% CrI	97.5% CrI	Median	2.5% CrI	97.5% CrI
Consistency model		-	495.5	-	-	-	-	-	-
No treatment	IV oxytocin plus amniotomy	0.003	488.7	-1.749	-2.861	-0.697	-0.050	-0.493	0.452
No treatment	Oral prostaglandins	0.037	493.7	0.498	-0.766	2.048	-0.979	-1.677	-0.382
Vaginal misoprostol (Dose 50 mcg or more)	Buccal/sublingual misoprostol	0.006	491.2	-0.971	-1.764	-0.155	0.366	-0.045	0.784
Titrated (low dose) oral misoprostol solution	Mechanical methods – foley catheter	0.044	494.3	-1.221	-2.396	-0.219	-0.167	-0.493	0.247
No treatment	IV oxytocin	0.186	498.1	0.458	-0.697	1.248	-0.471	-0.946	-0.065
No treatment	Nitric oxide	0.534	498.9	0.036	-1.745	1.860	-0.442	-0.921	0.007
No treatment	Mechanical methods – laminaria including dilapan	0.411	498.8	0.450	-1.623	2.794	-0.546	-1.116	0.020
No treatment	Intracervical PGE2	0.695	499	-0.811	-2.353	1.196	-0.450	-0.856	-0.109
No treatment	Vaginal PGE2 pessary (normal release)	0.722	497.9	-0.313	-0.869	0.222	-0.130	-0.677	0.382
No treatment	Vaginal misoprostol (Dose less than 50 mcg)	0.129	494	0.168	-0.856	1.087	-0.698	-1.149	-0.248
Vaginal misoprostol (Dose 50 mcg or more)	Oral misoprostol tablet (dose 50mcg or more)	0.258	497.2	-0.109	-0.336	0.206	0.117	-0.136	0.362
Vaginal misoprostol (Dose 50 mcg or more)	Titrated (low dose) oral misoprostol solution	0.998	497.5	-0.094	-1.824	1.703	-0.110	-0.417	0.215
Vaginal misoprostol (Dose 50 mcg or more)	IV oxytocin	0.358	497.8	0.248	-0.180	0.679	0.010	-0.272	0.330
Vaginal misoprostol (Dose 50 mcg or more)	Nitric oxide	0.832	498.3	0.400	-3.426	4.764	-0.005	-0.336	0.330
Vaginal misoprostol (Dose 50 mcg or more)	Placebo	0.779	500.6	-0.121	-0.944	0.868	0.016	-0.266	0.373

Vaginal misoprostol (Dose 50 mcg or more)	Mechanical methods – foley catheter	0.814	497.6	-0.129	-1.987	1.124	-0.303	-0.515	-0.095
Vaginal misoprostol (Dose 50 mcg or more)	Vaginal PGE2 (tablet)	0.856	498.5	-0.057	-0.418	0.329	-0.011	-0.276	0.278
Vaginal misoprostol (Dose 50 mcg or more)	Vaginal PGE2 (gel)	0.159	497.6	0.102	-0.200	0.420	-0.147	-0.349	0.031
Vaginal misoprostol (Dose 50 mcg or more)	Vaginal PGE2 (pessary – slow release)	0.935	498.3	-0.260	-0.982	0.462	-0.315	-0.590	-0.024
Vaginal misoprostol (Dose 50 mcg or more)	Intracervical PGE2	0.711	497.5	-0.136	-0.548	0.262	-0.045	-0.270	0.191
Vaginal misoprostol (Dose 50 mcg or more)	Vaginal PGE2 pessary (normal release)	0.831	500.8	0.225	-0.590	1.068	0.133	-0.148	0.398
Vaginal misoprostol (Dose 50 mcg or more)	Vaginal misoprostol (Dose less than 50 mcg)	0.428	495.8	-0.049	-0.412	0.303	-0.220	-0.457	-0.001
Oral misoprostol tablet (Dose less than 50 mcg)	Titrated (low dose) oral misoprostol solution	0.074	494.5	-1.034	-2.843	0.535	0.448	-0.276	1.185
Oral misoprostol tablet (Dose less than 50 mcg)	Mechanical methods – foley catheter	0.579	498.2	0.451	-1.062	2.400	-0.022	-0.771	0.649
Oral misoprostol tablet (Dose less than 50 mcg)	Vaginal PGE2 (gel)	0.33	497	0.417	-0.281	1.133	-0.215	-1.493	0.918
Oral misoprostol tablet (dose 50mcg or more)	IV oxytocin	0.432	495.5	-0.470	-1.971	1.048	0.119	-0.159	0.398
Oral misoprostol tablet (dose 50mcg or more)	Mechanical methods – foley catheter	0.366	496.2	-0.401	-0.762	-0.048	-0.205	-0.455	0.024
Oral misoprostol tablet (dose 50mcg or more)	Buccal/sublingual misoprostol	0.131	495	0.319	-0.206	0.865	-0.243	-0.760	0.298
Oral misoprostol tablet (dose 50mcg or more)	Vaginal PGE2 (tablet)	0.617	497.6	-0.184	-0.815	0.467	0.007	-0.253	0.259
Oral misoprostol tablet (dose 50mcg or more)	Vaginal PGE2 (gel)	0.493	494.8	-0.227	-0.722	0.261	-0.035	-0.258	0.177
Oral misoprostol tablet (dose 50mcg or more)	Intracervical PGE2	0.666	498.2	0.055	-0.556	0.615	-0.087	-0.297	0.154

Oral misoprostol tablet (dose 50mcg or more)	Vaginal misoprostol (Dose less than 50 mcg)	0.38	494.7	-0.310	-0.669	0.186	-0.093	-0.316	0.159
Titrated (low dose) oral misoprostol solution	IV oxytocin	0.822	498.8	0.050	-1.296	1.210	0.233	-0.160	0.598
Titrated (low dose) oral misoprostol solution	Vaginal PGE2 (gel)	0.425	493.9	-0.011	-0.325	0.353	0.264	-0.253	0.695
Titrated (low dose) oral misoprostol solution	Vaginal PGE2 (pessary – slow release)	0.337	496.1	1.135	-1.405	3.924	-0.222	-0.621	0.129
Titrated (low dose) oral misoprostol solution	Vaginal PGE2 pessary (normal release)	0.625	497.1	0.399	-0.290	1.038	0.202	-0.247	0.612
Titrated (low dose) oral misoprostol solution	Vaginal misoprostol (Dose less than 50 mcg)	0.592	498.4	-0.600	-2.431	1.063	-0.075	-0.374	0.262
IV oxytocin	Amniotomy	0.952	497.8	-0.249	-1.286	0.809	-0.230	-0.768	0.321
IV oxytocin	IV oxytocin plus amniotomy	0.586	498.2	0.165	-0.727	1.068	-0.119	-0.491	0.198
IV oxytocin	Oestrogens	0.595	498.1	-0.050	-2.350	1.975	-0.632	-1.537	0.245
IV oxytocin	Extra-amniotic PGE2 or PGF2	0.211	497.6	0.857	-1.095	2.923	-0.420	-0.917	0.190
IV oxytocin	IV prostaglandin	0.882	499.8	0.807	-0.286	2.147	0.540	-2.623	3.327
IV oxytocin	Oral prostaglandins	0.754	494.1	-0.580	-1.301	0.052	-0.425	-1.163	0.318
IV oxytocin	Vaginal PGE2 (tablet)	0.633	497.9	0.355	-1.197	2.190	-0.140	-0.436	0.160
IV oxytocin	Vaginal PGE2 (gel)	0.891	498.4	-0.134	-0.791	0.641	-0.209	-0.450	0.062
IV oxytocin	Vaginal PGE2 (pessary – slow release)	0.263	496.7	0.469	-0.937	2.845	-0.440	-0.781	-0.117
IV oxytocin	Intracervical PGE2	0.96	497.5	-0.178	-0.730	0.467	-0.168	-0.432	0.176
IV oxytocin	Vaginal PGE2 pessary (normal release)	0.52	500.4	0.193	-0.372	0.764	-0.075	-0.365	0.361
IV oxytocin	Vaginal misoprostol (Dose less than 50 mcg)	0.645	497.7	-0.635	-2.075	0.759	-0.236	-0.587	0.039
Amniotomy	IV oxytocin plus amniotomy	0.758	497.6	0.073	-0.448	0.653	0.204	-0.436	0.925
Amniotomy	Vaginal PGE2 (gel)	0.889	498.7	0.126	-0.585	0.856	0.077	-0.500	0.582
IV oxytocin plus amniotomy	Mechanical methods – foley catheter	0.461	496.6	0.034	-1.200	1.584	-0.344	-0.660	0.005
IV oxytocin plus amniotomy	Oral prostaglandins	0.476	497.2	-0.586	-1.378	0.211	-0.228	-0.823	0.369

IV oxytocin plus amniotomy	Buccal/sublingual misoprostol	0.613	498.2	0.323	-1.131	1.750	0.003	-0.480	0.441
IV oxytocin plus amniotomy	Vaginal PGE2 (tablet)	0.483	496.7	0.141	-0.421	0.746	-0.139	-0.500	0.250
IV oxytocin plus amniotomy	Vaginal PGE2 (gel)	0.104	498.2	-0.435	-0.963	0.083	0.114	-0.243	0.457
IV oxytocin plus amniotomy	Intracervical PGE2	0.221	497.3	-0.802	-1.935	0.433	0.018	-0.343	0.316
IV oxytocin plus amniotomy	Vaginal PGE2 pessary (normal release)	0.355	494.8	-0.478	-1.957	0.999	0.165	-0.174	0.507
Nitric oxide	Placebo	0.885	495.9	0.067	-0.195	0.328	0.027	-0.531	0.623
Nitric oxide	Vaginal PGE2 (gel)	0.857	495.8	-0.035	-0.529	0.474	-0.104	-0.511	0.344
Nitric oxide	Intracervical PGE2	0.971	498.9	-0.022	-3.039	3.749	-0.060	-0.401	0.267
Mifepristone	Placebo	0.329	495.9	-0.460	-0.913	-0.053	0.633	-1.328	2.802
Mifepristone	Vaginal PGE2 (gel)	0.273	495.3	0.618	-2.261	2.905	-0.588	-1.203	-0.061
Placebo	Oestrogens	0.944	496.9	-0.197	-1.163	0.739	-0.291	-2.866	1.414
Placebo	Extra-amniotic PGE2 or PGF2	0.47	497.4	0.377	-1.257	1.962	-0.258	-0.875	0.369
Placebo	Vaginal PGE2 (gel)	0.341	496.9	-0.687	-1.993	0.453	-0.104	-0.394	0.202
Placebo	Vaginal PGE2 (pessary – slow release)	0.436	496.7	-0.055	-0.915	0.781	-0.412	-0.811	-0.017
Placebo	PGF2 gel	0.71	498	-0.659	-1.102	-0.230	-0.336	-1.943	1.234
Placebo	Intracervical PGE2	0.576	495.4	0.043	-0.502	0.552	-0.140	-0.507	0.257
Placebo	Vaginal PGE2 pessary (normal release)	0.483	498.6	-0.058	-0.584	0.469	0.183	-0.211	0.595
Placebo	Vaginal misoprostol (Dose less than 50 mcg)	0.363	497.6	-0.816	-2.328	0.441	-0.130	-0.433	0.179
Mechanical methods – foley catheter	Mechanical methods – laminaria including dilapan	0.489	496.2	0.620	-0.469	1.767	0.147	-0.381	0.617
Mechanical methods – foley catheter	Mechanical methods – Double balloon or Cook's catheter	0.358	496.9	-0.032	-0.392	0.311	0.257	-0.218	0.738
Mechanical methods – foley catheter	Extra-amniotic PGE2 or PGF2	0.168	498.1	-0.596	-1.556	0.359	0.352	-0.310	0.987
Mechanical methods – foley catheter	Vaginal PGE2 (tablet)	0.559	500.1	0.094	-0.505	0.818	0.314	0.048	0.595

Mechanical methods – foley catheter	Vaginal PGE2 (gel)	0.843	494	0.187	-0.084	0.482	0.227	-0.026	0.486
Mechanical methods – foley catheter	Vaginal PGE2 (pessary – slow release)	0.113	495.3	0.376	-0.192	1.069	-0.128	-0.441	0.178
Mechanical methods – foley catheter	PGF2 gel	0.635	498.8	0.001	-1.500	2.828	-0.366	-0.884	0.145
Mechanical methods – foley catheter	Intracervical PGE2	0.744	496.9	0.126	-0.515	0.732	0.238	0.031	0.468
Mechanical methods – foley catheter	Vaginal PGE2 pessary (normal release)	0.969	498.3	0.431	-0.392	1.367	0.455	0.147	0.741
Mechanical methods – foley catheter	Vaginal misoprostol (Dose less than 50 mcg)	0.775	498.4	0.189	-0.234	0.529	0.118	-0.128	0.358
Mechanical methods – laminaria including dilapan	Vaginal PGE2 (tablet)	0.766	497.5	-0.155	-1.604	1.331	0.054	-0.483	0.589
Mechanical methods – laminaria including dilapan	Vaginal PGE2 (gel)	0.066	498	0.441	-0.197	1.167	-0.337	-0.915	0.245
Mechanical methods – laminaria including dilapan	Intracervical PGE2	0.578	496.9	-0.210	-1.041	0.614	0.089	-0.473	0.594
Mechanical methods – Double balloon or Cook's catheter	Vaginal PGE2 (tablet)	0.256	497.6	0.011	-0.467	0.483	0.366	-0.025	0.716
Mechanical methods – Double balloon or Cook's catheter	Vaginal PGE2 (gel)	0.875	495.6	0.198	-0.470	0.880	0.135	-0.187	0.457
Mechanical methods – Double balloon or Cook's catheter	Vaginal PGE2 (pessary – slow release)	0.539	496.6	-0.370	-1.479	0.468	-0.031	-0.399	0.338
Mechanical methods – Double balloon or Cook's catheter	Intracervical PGE2	0.672	497	0.446	-1.016	2.208	0.153	-0.184	0.437
Mechanical methods – Double balloon or Cook's catheter	Vaginal PGE2 pessary (normal release)	0.143	496.3	1.325	-0.068	2.964	0.283	-0.081	0.656

Extra-amniotic PGE2 or PGF2	IV prostaglandin	0.901	497.8	1.106	-1.578	3.619	1.234	-0.221	2.564
Extra-amniotic PGE2 or PGF2	Oral prostaglandins	0.533	495.4	-0.808	-2.346	1.075	-0.180	-0.896	0.591
Extra-amniotic PGE2 or PGF2	Vaginal PGE2 (tablet)	0.464	497.1	-0.027	-0.765	0.715	0.370	-0.444	1.257
Oral prostaglandins	Vaginal PGE2 (tablet)	0.745	498.8	0.091	-1.937	2.118	0.334	-0.220	0.850
Oral prostaglandins	Vaginal PGE2 (gel)	0.706	496.7	-0.069	-1.909	2.400	0.305	-0.206	0.765
Oral prostaglandins	Intracervical PGE2	0.342	498.1	-0.256	-1.722	1.068	0.360	-0.158	0.864
Buccal/sublingual misoprostol	Vaginal PGE2 (gel)	0.834	496.4	-0.225	-1.747	1.113	-0.101	-0.474	0.298
Buccal/sublingual misoprostol	Intracervical PGE2	0.888	499	-0.180	-1.468	1.086	-0.088	-0.509	0.332
Buccal/sublingual misoprostol	Vaginal misoprostol (Dose less than 50 mcg)	0.307	497.5	-1.299	-3.638	1.417	-0.158	-0.525	0.252
Vaginal PGE2 (tablet)	Vaginal PGE2 (gel)	0.225	497.3	-0.333	-0.806	0.164	0.001	-0.239	0.230
Vaginal PGE2 (tablet)	Vaginal PGE2 (pessary – slow release)	0.967	497.7	-0.315	-0.984	0.390	-0.329	-0.652	0.038
Vaginal PGE2 (tablet)	Intracervical PGE2	0.686	500	-0.343	-2.751	1.809	-0.022	-0.232	0.263
Vaginal PGE2 (tablet)	Vaginal PGE2 pessary (normal release)	0.622	498.3	-0.140	-1.043	0.841	0.165	-0.219	0.462
Vaginal PGE2 (gel)	Vaginal PGE2 (pessary – slow release)	0.242	497.4	-0.618	-1.281	-0.056	-0.144	-0.606	0.136
Vaginal PGE2 (gel)	Intracervical PGE2	0.423	497.3	-0.128	-0.504	0.293	0.077	-0.149	0.295
Vaginal PGE2 (gel)	Vaginal misoprostol (Dose less than 50 mcg)	0.089	489.9	0.201	-0.158	0.554	-0.189	-0.439	0.052
Vaginal PGE2 (pessary – slow release)	Intracervical PGE2	0.934	498.5	0.277	-0.793	1.003	0.260	-0.051	0.578
Vaginal PGE2 (pessary – slow release)	Vaginal misoprostol (Dose less than 50 mcg)	0.359	495.9	0.420	-0.208	1.056	0.095	-0.246	0.410
Intracervical PGE2	Vaginal PGE2 pessary (normal release)	0.763	495.6	0.276	-0.268	0.836	0.182	-0.136	0.501
Intracervical PGE2	Vaginal misoprostol (Dose less than 50 mcg)	0.078	496	-0.357	-0.769	-0.037	-0.010	-0.245	0.230

Table 3. Direct and indirect estimates of treatment difference (LOR), outcome instrumental delivery, unfavourable cervix subgroup. Where direct and indirect estimates are inconsistent (p<0.05), treatment comparisons are highlighted in yellow. Residual deviance is the model's posterior mean residual deviance, to be compared to number of data points (354), lower values preferred.

Intervention 1	Intervention 2	p-value	Residual deviance	Direct			Indirect		
				Median	2.5% CrI	97.5% CrI	Median	2.5% CrI	97.5% CrI
Consistency Model	-	NA	349.9	-	-	-	-	-	-
Vaginal PGE2 (gel)	Vaginal PGE2 (pessary – slow release)	0.029	347	-1.912	-3.591	-0.370	-0.174	-0.520	0.179
No treatment	IV oxytocin	0.37	350.1	0.995	-0.680	2.760	0.136	-0.943	1.644
No treatment	Nitric oxide	0.869	351.8	0.174	-1.381	1.749	0.055	-1.155	1.202
No treatment	Mechanical methods – foley catheter	0.831	350.1	0.272	-1.833	2.461	-0.016	-0.991	0.979
No treatment	Oral prostaglandins	0.722	348.4	0.453	-0.970	1.954	0.122	-1.197	1.455
No treatment	Intracervical PGE2	0.247	348.3	-0.568	-2.306	1.003	0.411	-0.614	1.375
Vaginal misoprostol (Dose 50 mcg or more)	Oral misoprostol tablet (dose 50mcg or more)	0.265	349.8	-0.214	-0.484	0.056	0.065	-0.323	0.406
Vaginal misoprostol (Dose 50 mcg or more)	IV oxytocin	0.105	346.9	1.396	0.073	3.371	0.114	-0.285	0.485
Vaginal misoprostol (Dose 50 mcg or more)	Nitric oxide	0.917	351.5	0.171	-3.116	4.105	-0.041	-0.400	0.332
Vaginal misoprostol (Dose 50 mcg or more)	Placebo	0.861	349.7	-0.079	-1.291	1.100	0.020	-0.349	0.380
Vaginal misoprostol (Dose 50 mcg or more)	Hyaluronidase	0.898	350.2	-0.176	-1.394	0.981	-0.251	-0.483	-0.014
Vaginal misoprostol (Dose 50 mcg or more)	Buccal/sublingual misoprostol	0.07	347.1	-0.772	-1.956	0.269	0.287	-0.190	0.788
Vaginal misoprostol (Dose 50 mcg or more)	Vaginal PGE2 (tablet)	0.933	350.6	0.024	-0.388	0.427	0.005	-0.358	0.345
Vaginal misoprostol (Dose 50 mcg or more)	Vaginal PGE2 (gel)	0.238	349.3	0.110	-0.206	0.414	-0.144	-0.430	0.147
Vaginal misoprostol (Dose 50 mcg or more)	Intracervical PGE2	0.574	349.6	-0.187	-0.668	0.398	0.012	-0.282	0.277

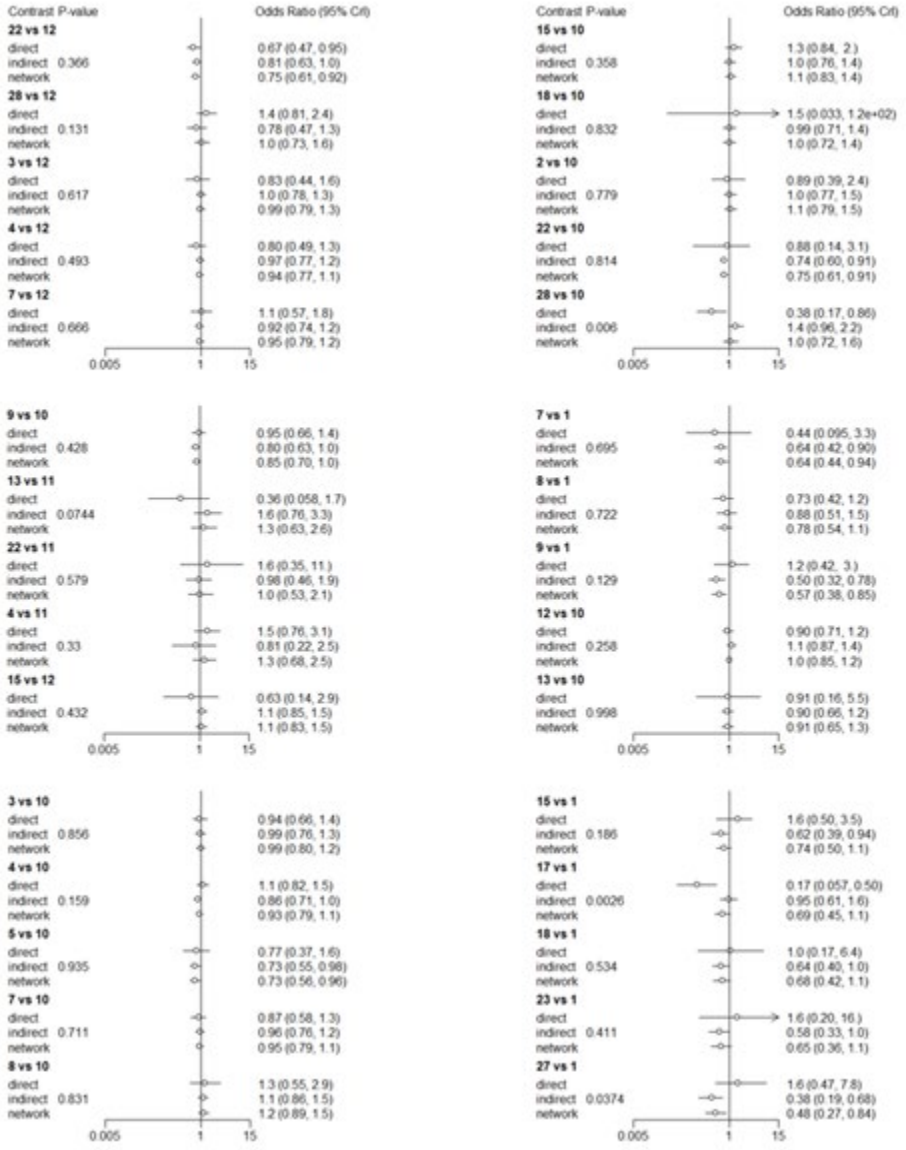
Vaginal misoprostol (Dose 50 mcg or more)	Vaginal PGE2 pessary (normal release)	0.818	350	0.268	-0.449	1.073	0.161	-0.204	0.517
Vaginal misoprostol (Dose 50 mcg or more)	Vaginal misoprostol (Dose less than 50 mcg)	0.424	348.9	-0.045	-0.434	0.381	-0.233	-0.506	0.035
Oral misoprostol tablet (Dose less than 50 mcg)	Titrated (low dose) oral misoprostol solution	0.093	348.7	-0.993	-3.227	0.491	0.410	-0.334	1.149
Oral misoprostol tablet (Dose less than 50 mcg)	Hyaluronidase	0.734	349.9	0.354	-1.584	2.377	-0.037	-0.680	0.615
Oral misoprostol tablet (Dose less than 50 mcg)	Vaginal PGE2 (gel)	0.367	349.8	0.417	-0.290	1.110	-0.249	-1.430	0.931
Oral misoprostol tablet (dose 50mcg or more)	Hyaluronidase	0.074	347.2	-0.409	-0.775	-0.039	0.009	-0.287	0.324
Oral misoprostol tablet (dose 50mcg or more)	Buccal/sublingual misoprostol	0.396	348.9	0.362	-0.185	0.898	-0.053	-0.800	0.695
Oral misoprostol tablet (dose 50mcg or more)	Intracervical PGE2	0.967	351	0.098	-0.459	0.633	0.092	-0.325	0.361
Oral misoprostol tablet (dose 50mcg or more)	Vaginal misoprostol (Dose less than 50 mcg)	0.877	350.1	-0.107	-0.711	0.483	-0.056	-0.348	0.250
Titrated (low dose) oral misoprostol solution	Vaginal PGE2 (gel)	0.266	348.8	-0.087	-0.555	0.384	0.362	-0.222	0.979
Titrated (low dose) oral misoprostol solution	Vaginal PGE2 (pessary – slow release)	0.419	350	0.894	-1.458	5.262	-0.227	-0.720	0.246
Titrated (low dose) oral misoprostol solution	Vaginal PGE2 pessary (normal release)	0.571	349.7	0.419	-0.245	1.067	0.183	-0.337	0.732
Titrated (low dose) oral misoprostol solution	Vaginal misoprostol (Dose less than 50 mcg)	0.673	351.3	-0.566	-2.850	1.926	-0.043	-0.480	0.388
IV oxytocin	Oestrogens	0.453	351.3	0.109	-2.050	1.908	-0.676	-1.540	0.277
IV oxytocin	Mechanical methods – Double balloon or Cook's catheter	0.16	350.2	1.058	-1.020	2.983	-0.495	-1.258	0.489
IV oxytocin	Oral prostaglandins	0.949	349	-0.127	-1.213	0.968	-0.025	-1.375	1.231
IV oxytocin	Vaginal PGE2 (tablet)	0.431	350	0.563	-1.398	2.524	-0.272	-0.675	0.155
IV oxytocin	Vaginal PGE2 (gel)	0.961	349.2	-0.178	-1.059	0.643	-0.194	-0.607	0.186

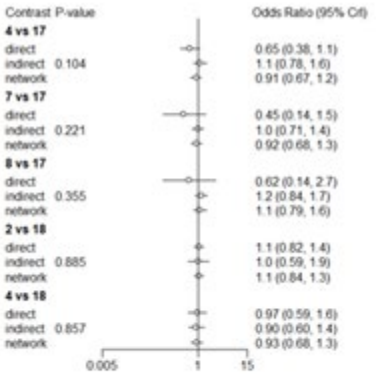
IV oxytocin	Vaginal PGE2 (pessary – slow release)	0.151	347.5	0.530	-0.933	2.030	-0.583	-1.069	-0.078
IV oxytocin	Intracervical PGE2	0.588	350.3	-0.032	-0.713	0.647	-0.290	-0.701	0.146
IV oxytocin	Vaginal PGE2 pessary (normal release)	0.79	349.6	-0.070	-0.680	0.526	0.028	-0.497	0.488
IV oxytocin	Vaginal misoprostol (Dose less than 50 mcg)	0.788	350.3	-0.535	-2.062	0.812	-0.349	-0.715	0.076
Nitric oxide	Placebo	0.733	350.3	0.082	-0.198	0.330	-0.023	-0.610	0.566
Nitric oxide	Vaginal PGE2 (gel)	0.832	350.4	-0.009	-0.495	0.450	0.059	-0.427	0.471
Nitric oxide	Intracervical PGE2	0.919	350	-0.168	-3.901	2.909	0.053	-0.336	0.416
Mifepristone	Placebo	0.265	349	-0.434	-0.913	-0.064	0.658	-1.147	2.657
Mifepristone	Vaginal PGE2 (gel)	0.305	349.6	0.525	-1.498	2.433	-0.542	-1.108	0.013
Oestrogens	Placebo	0.891	349.8	0.290	-0.706	1.225	0.126	-1.543	2.148
Placebo	Mechanical methods – Double balloon or Cook's catheter	0.582	350.6	0.228	-1.324	1.820	-0.248	-0.958	0.410
Placebo	Vaginal PGE2 (gel)	0.259	349.3	-0.816	-2.412	0.500	0.013	-0.320	0.331
Placebo	Vaginal PGE2 (pessary – slow release)	0.381	349.6	0.015	-0.857	0.950	-0.442	-0.900	0.064
Placebo	Intracervical PGE2	0.904	350.1	-0.074	-0.563	0.593	0.014	-0.472	0.358
Placebo	Vaginal PGE2 pessary (normal release)	0.193	348.4	-0.744	-2.162	0.563	0.233	-0.260	0.649
Placebo	Vaginal misoprostol (Dose less than 50 mcg)	0.439	349.7	-1.521	-4.654	2.854	-0.146	-0.512	0.217
Hyaluronidase	Mechanical methods – foley catheter	0.586	350.1	0.509	-0.557	1.770	0.113	-0.390	0.627
Hyaluronidase	Mechanical methods – laminaria including dilapan	0.433	350.1	-0.021	-0.377	0.285	0.220	-0.279	0.676
Hyaluronidase	Mechanical methods – Double balloon or Cook's catheter	0.172	348.2	-0.431	-1.459	0.552	0.387	-0.258	1.045
Hyaluronidase	Vaginal PGE2 (tablet)	0.726	349.6	0.109	-0.587	0.828	0.263	-0.045	0.538

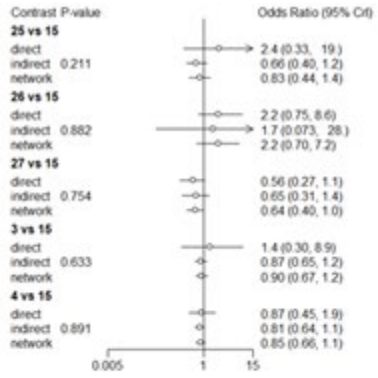
Hyaluronidase	Vaginal PGE2 (gel)	0.24	344	0.077	-0.239	0.384	0.344	0.072	0.618
Hyaluronidase	Vaginal PGE2 (pessary – slow release)	0.096	348.2	0.439	-0.200	1.009	-0.190	-0.691	0.238
Hyaluronidase	Intracervical PGE2	0.723	349.8	0.131	-0.503	0.761	0.253	-0.003	0.557
Hyaluronidase	Vaginal PGE2 pessary (normal release)	0.765	347.8	0.301	-0.425	1.068	0.421	0.066	0.780
Hyaluronidase	Vaginal misoprostol (Dose less than 50 mcg)	0.542	348.8	0.182	-0.204	0.547	0.032	-0.286	0.326
Mechanical methods – foley catheter	Vaginal PGE2 (tablet)	0.75	349.6	-0.177	-1.682	1.354	0.073	-0.437	0.620
Mechanical methods – foley catheter	Vaginal PGE2 (gel)	0.105	349.4	0.297	-0.214	1.163	-0.170	-0.777	0.267
Mechanical methods – foley catheter	Intracervical PGE2	0.569	349.7	-0.190	-1.015	0.721	0.117	-0.475	0.663
Mechanical methods – laminaria including dilapan	Vaginal PGE2 (tablet)	0.361	350.8	0.006	-0.505	0.498	0.323	-0.107	0.725
Mechanical methods – laminaria including dilapan	Vaginal PGE2 (gel)	0.791	349.4	0.197	-0.471	0.848	0.110	-0.217	0.483
Mechanical methods – laminaria including dilapan	Vaginal PGE2 (pessary – slow release)	0.532	350.5	-0.397	-1.418	0.531	-0.049	-0.433	0.421
Mechanical methods – laminaria including dilapan	Intracervical PGE2	0.628	347.7	0.522	-0.911	2.385	0.155	-0.188	0.515
Mechanical methods – laminaria including dilapan	Vaginal PGE2 pessary (normal release)	0.09	347.9	1.293	0.101	2.876	0.250	-0.161	0.676
Mechanical methods – Double balloon or Cook's catheter	Oral prostaglandins	0.46	350.8	-0.378	-2.335	1.338	0.333	-0.781	1.516
Mechanical methods – Double balloon or Cook's catheter	Vaginal PGE2 (tablet)	0.511	348.5	0.015	-0.711	0.729	0.374	-0.482	1.214
Oral prostaglandins	Vaginal PGE2 (tablet)	0.806	351.8	0.056	-1.736	2.164	-0.181	-1.231	0.733
Oral prostaglandins	Vaginal PGE2 (gel)	0.994	351.5	-0.095	-2.748	2.153	-0.096	-0.993	0.716
Oral prostaglandins	Intracervical PGE2	0.59	349.8	-0.397	-1.793	1.054	0.037	-0.843	0.846

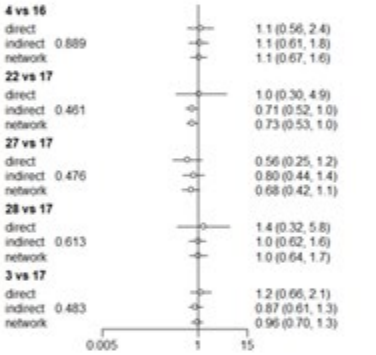
Buccal/sublingual misoprostol	Intracervical PGE2	0.946	351	-0.184	-1.386	0.903	-0.141	-0.635	0.335
Buccal/sublingual misoprostol	Vaginal misoprostol (Dose less than 50 mcg)	0.368	347.9	-1.000	-2.952	0.663	-0.214	-0.717	0.278
Vaginal PGE2 (tablet)	Vaginal PGE2 (gel)	0.105	348.7	-0.357	-0.849	0.127	0.121	-0.178	0.440
Vaginal PGE2 (tablet)	Vaginal PGE2 (pessary – slow release)	0.295	347.2	0.443	-1.040	1.900	-0.340	-0.766	0.070
Vaginal PGE2 (tablet)	Intracervical PGE2	0.903	349.5	-0.131	-3.036	2.146	-0.002	-0.302	0.302
Vaginal PGE2 (tablet)	Vaginal PGE2 pessary (normal release)	0.539	349.7	-0.130	-1.164	0.918	0.200	-0.168	0.617
Vaginal PGE2 (gel)	Intracervical PGE2	0.23	348.3	-0.293	-0.878	0.274	0.083	-0.177	0.329
Vaginal PGE2 (gel)	Vaginal misoprostol (Dose less than 50 mcg)	0.272	346.7	0.137	-0.385	0.745	-0.195	-0.461	0.093
Vaginal PGE2 (pessary – slow release)	Intracervical PGE2	0.112	347.1	1.310	-0.069	2.611	0.187	-0.182	0.565
Vaginal PGE2 (pessary – slow release)	Vaginal misoprostol (Dose less than 50 mcg)	0.356	350.8	0.423	-0.245	1.048	0.029	-0.384	0.480
Intracervical PGE2	Vaginal PGE2 pessary (normal release)	0.676	347.3	0.261	-0.283	0.811	0.120	-0.256	0.517
Intracervical PGE2	Vaginal misoprostol (Dose less than 50 mcg)	0.176	348.4	-0.369	-0.763	0.040	0.004	-0.352	0.309

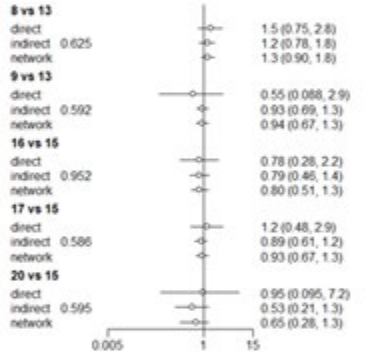
Forest plots for the outcome instrumental delivery, full dataset, showing direct, indirect and network estimates of treatment difference (contrast), odds ratio scale. Treatment codes: 1 - No treatment, 2 – Placebo, 3 - Vaginal PGE2 (tablet), 4 - Vaginal PGE2 (gel), 5 - Vaginal PGE2 (pessary – slow release), 6 - PGF2 gel, 7 - Intracervical PGE2, 8 - Vaginal PGE2 pessary (normal release), 9 - Vaginal misoprostol (dose less than 50 mcg), 10 - Vaginal misoprostol (dose 50 mcg or more), 11 - Oral misoprostol tablet (dose less than 50 mcg), 12 - Oral misoprostol tablet (dose 50mcg or more), 13 - Titrated (low dose) oral misoprostol solution, 14 - Sustained release misoprostol insert, 15 - IV oxytocin, 16 – Amniotomy, 17 - IV oxytocin plus amniotomy, 18 - Nitric oxide, 19 – Mifepristone, 20- Oestrogens, 21 – Relaxin, 22 - Mechanical methods – Foley catheter, 23 - Mechanical methods – laminaria including dilapan, 24 - Mechanical methods – Double balloon or Cook's catheter, 25 - Extra-amniotic PGE2 or PGF2, 26 - IV prostaglandin, 27 - Oral prostaglandins, 28 - Buccal/sublingual misoprostol.

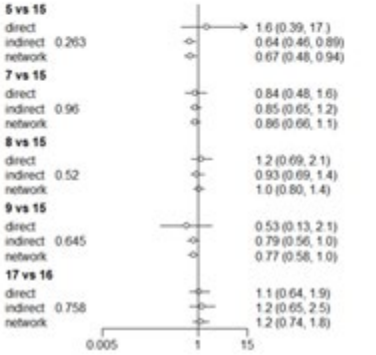


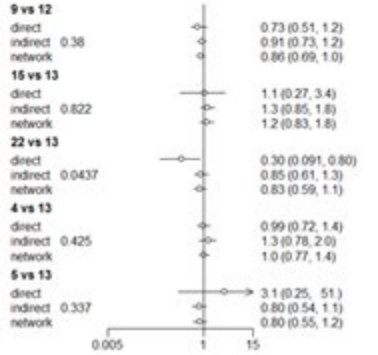

Contrast P-value
Odds Ratio (95% CrI)
4 vs 17
direct
indirect 0.104
network
0.65 (0.38, 1.1)
1.1 (0.78, 1.6)
0.91 (0.67, 1.2)
7 vs 17
direct
indirect 0.221
network
0.45 (0.14, 1.5)
1.0 (0.71, 1.4)
0.92 (0.68, 1.3)
8 vs 17
direct
indirect 0.355
network
0.62 (0.14, 2.7)
1.2 (0.84, 1.7)
1.1 (0.79, 1.6)
2 vs 18
direct
indirect 0.885
network
1.1 (0.82, 1.4)
1.0 (0.59, 1.9)
1.1 (0.84, 1.3)
4 vs 18
direct
indirect 0.857
network
0.97 (0.59, 1.6)
0.90 (0.60, 1.4)
0.93 (0.68, 1.3)
0.005
1
15

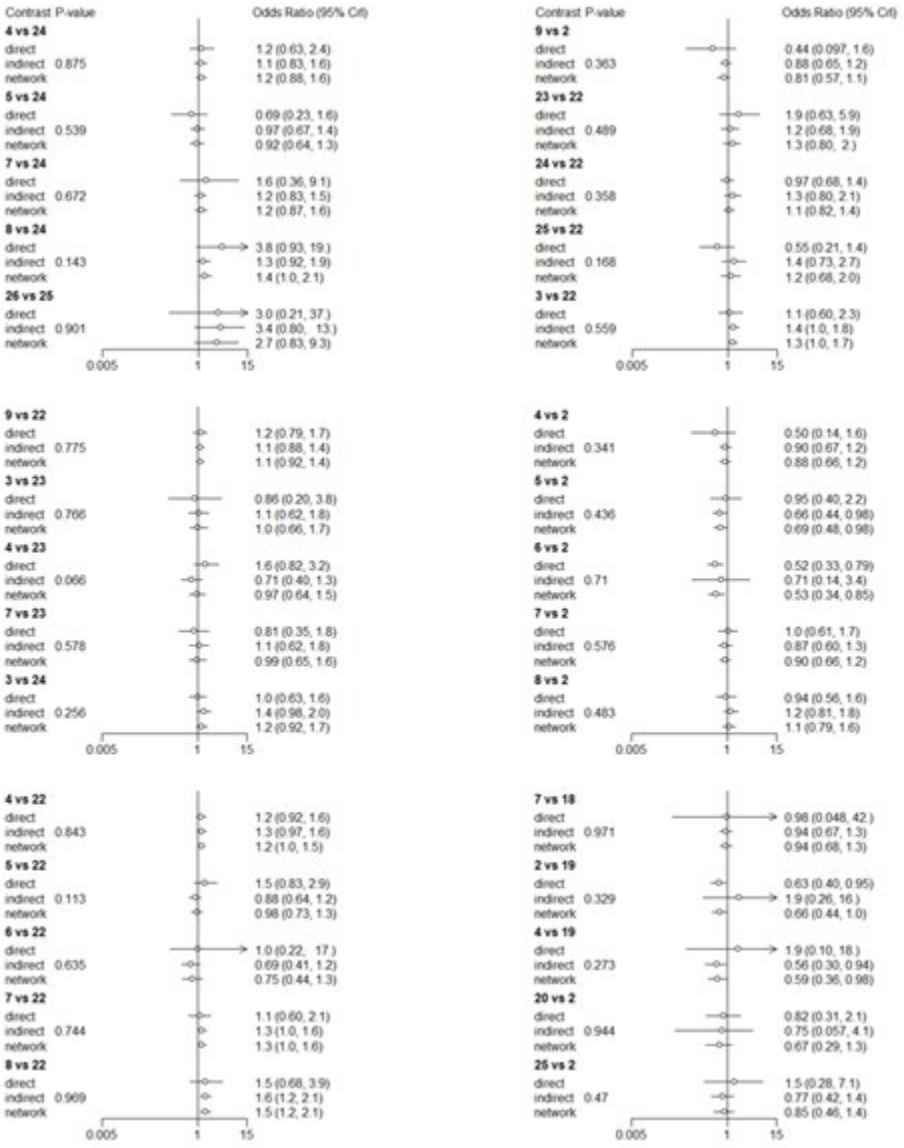

Contrast P-value
Odds Ratio (95% CrI)
25 vs 15
direct
indirect 0.211
network
2.4 (0.33, 19.)
0.66 (0.40, 1.2)
0.83 (0.44, 1.4)
26 vs 15
direct
indirect 0.882
network
2.2 (0.75, 8.6)
1.7 (0.073, 28.)
2.2 (0.70, 7.2)
27 vs 15
direct
indirect 0.754
network
0.56 (0.27, 1.1)
0.65 (0.31, 1.4)
0.64 (0.40, 1.0)
3 vs 15
direct
indirect 0.633
network
1.4 (0.30, 8.9)
0.87 (0.65, 1.2)
0.90 (0.67, 1.2)
4 vs 15
direct
indirect 0.891
network
0.87 (0.45, 1.9)
0.81 (0.64, 1.1)
0.85 (0.66, 1.1)
0.005
1
15

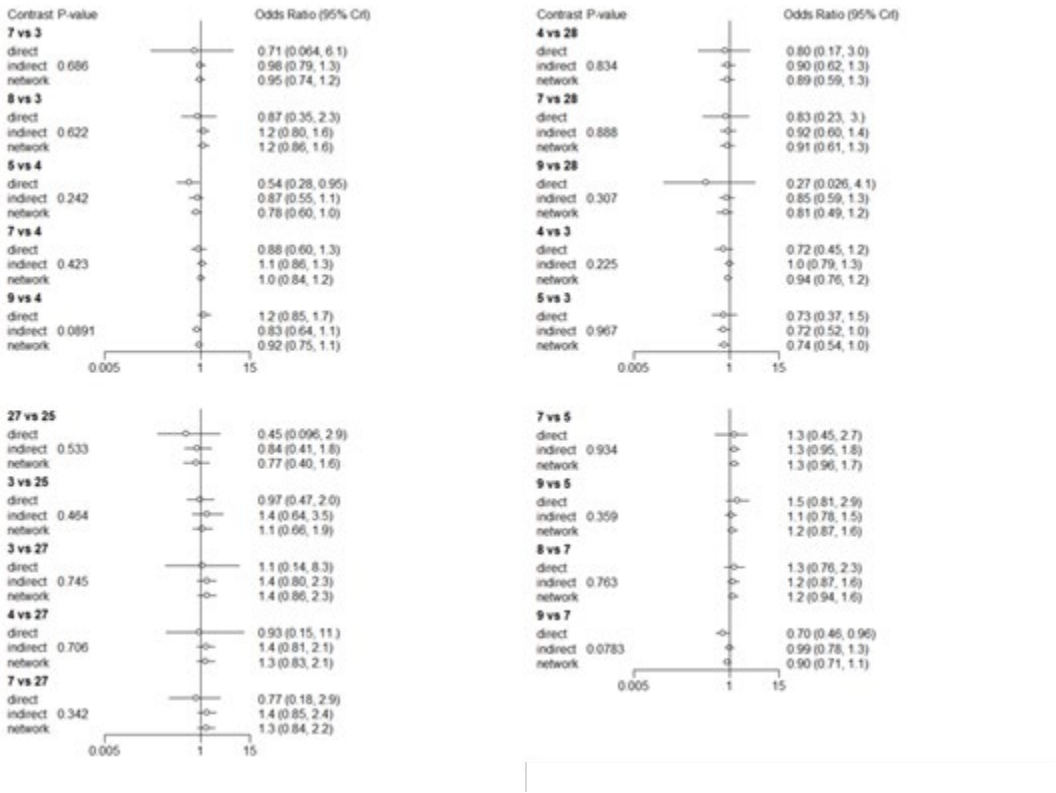

4 vs 16
direct
indirect 0.889
network
1.1 (0.56, 2.4)
1.1 (0.61, 1.8)
1.1 (0.67, 1.6)
22 vs 17
direct
indirect 0.461
network
1.0 (0.30, 4.9)
0.71 (0.52, 1.0)
0.73 (0.53, 1.0)
27 vs 17
direct
indirect 0.476
network
0.56 (0.25, 1.2)
0.80 (0.44, 1.4)
0.68 (0.42, 1.1)
28 vs 17
direct
indirect 0.613
network
1.4 (0.32, 5.8)
1.0 (0.62, 1.6)
1.0 (0.64, 1.7)
3 vs 17
direct
indirect 0.483
network
1.2 (0.66, 2.1)
0.87 (0.61, 1.3)
0.96 (0.70, 1.3)
0.005
1
15


8 vs 13
direct
indirect 0.625
network
1.5 (0.75, 2.8)
1.2 (0.78, 1.8)
1.3 (0.90, 1.8)
9 vs 13
direct
indirect 0.592
network
0.55 (0.088, 2.9)
0.93 (0.69, 1.3)
0.94 (0.67, 1.3)
16 vs 15
direct
indirect 0.952
network
0.78 (0.28, 2.2)
0.79 (0.46, 1.4)
0.80 (0.51, 1.3)
17 vs 15
direct
indirect 0.586
network
1.2 (0.48, 2.9)
0.89 (0.61, 1.2)
0.93 (0.67, 1.3)
20 vs 15
direct
indirect 0.595
network
0.95 (0.095, 7.2)
0.53 (0.21, 1.3)
0.65 (0.28, 1.3)
0.005
1
15

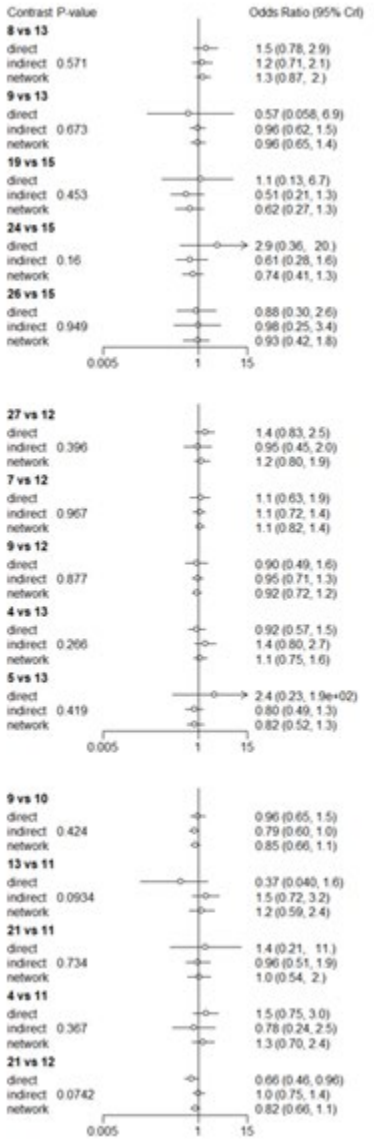

5 vs 15
direct
indirect 0.263
network
1.6 (0.39, 17.)
0.64 (0.46, 0.89)
0.67 (0.48, 0.94)
7 vs 15
direct
indirect 0.96
network
0.84 (0.48, 1.6)
0.85 (0.65, 1.2)
0.86 (0.66, 1.1)
8 vs 15
direct
indirect 0.52
network
1.2 (0.69, 2.1)
0.93 (0.69, 1.4)
1.0 (0.80, 1.4)
9 vs 15
direct
indirect 0.645
network
0.53 (0.13, 2.1)
0.79 (0.56, 1.0)
0.77 (0.58, 1.0)
17 vs 16
direct
indirect 0.758
network
1.1 (0.64, 1.9)
1.2 (0.65, 2.5)
1.2 (0.74, 1.8)
0.005
1
15

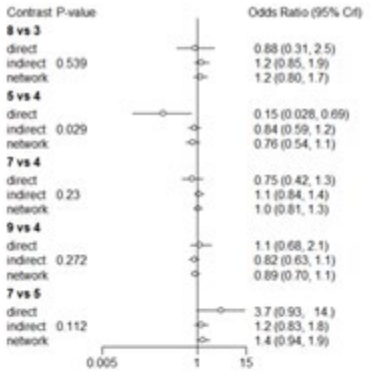

9 vs 12
direct
indirect 0.38
network
0.73 (0.51, 1.2)
0.91 (0.73, 1.2)
0.86 (0.69, 1.0)
15 vs 13
direct
indirect 0.822
network
1.1 (0.27, 3.4)
1.3 (0.85, 1.8)
1.2 (0.83, 1.8)
22 vs 13
direct
indirect 0.0437
network
0.30 (0.091, 0.80)
0.85 (0.61, 1.3)
0.83 (0.59, 1.1)
4 vs 13
direct
indirect 0.425
network
0.99 (0.72, 1.4)
1.3 (0.78, 2.0)
1.0 (0.77, 1.4)
5 vs 13
direct
indirect 0.337
network
3.1 (0.25, 51.)
0.80 (0.54, 1.1)
0.80 (0.55, 1.2)
0.005
1
15

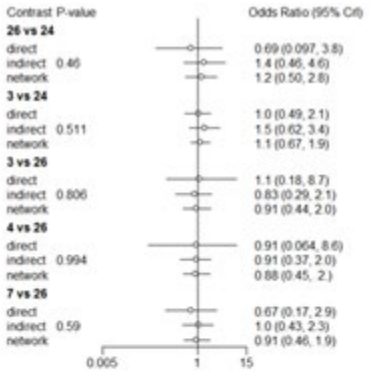

Contrast P-value
Odds Ratio (95% CrI)
4 vs 24
direct
indirect 0.875
network
1.2 (0.63, 2.4)
1.1 (0.83, 1.6)
1.2 (0.88, 1.6)
5 vs 24
direct
indirect 0.539
network
0.69 (0.23, 1.6)
0.97 (0.67, 1.4)
0.92 (0.64, 1.3)
7 vs 24
direct
indirect 0.672
network
1.6 (0.36, 9.1)
1.2 (0.83, 1.5)
1.2 (0.87, 1.6)
8 vs 24
direct
indirect 0.143
network
3.8 (0.93, 19.)
1.3 (0.92, 1.9)
1.4 (1.0, 2.1)
26 vs 25
direct
indirect 0.901
network
3.0 (0.21, 37.)
3.4 (0.80, 13.)
2.7 (0.83, 9.3)
0.005
1
15
9 vs 2
direct
indirect 0.363
network
0.44 (0.097, 1.6)
0.88 (0.65, 1.2)
0.81 (0.57, 1.1)
23 vs 22
direct
indirect 0.489
network
1.9 (0.63, 5.9)
1.2 (0.68, 1.9)
1.3 (0.80, 2.)
24 vs 22
direct
indirect 0.358
network
0.97 (0.68, 1.4)
1.3 (0.80, 2.1)
1.1 (0.82, 1.4)
25 vs 22
direct
indirect 0.168
network
0.55 (0.21, 1.4)
1.4 (0.73, 2.7)
1.2 (0.68, 2.0)
3 vs 22
direct
indirect 0.559
network
1.1 (0.60, 2.3)
1.4 (1.0, 1.8)
1.3 (1.0, 1.7)
0.005
1
15
9 vs 22
direct
indirect 0.775
network
1.2 (0.79, 1.7)
1.1 (0.88, 1.4)
1.1 (0.92, 1.4)
3 vs 23
direct
indirect 0.766
network
0.86 (0.20, 3.8)
1.1 (0.62, 1.8)
1.0 (0.66, 1.7)
4 vs 23
direct
indirect 0.066
network
1.6 (0.82, 3.2)
0.71 (0.40, 1.3)
0.97 (0.64, 1.5)
7 vs 23
direct
indirect 0.578
network
0.81 (0.35, 1.8)
1.1 (0.62, 1.8)
0.99 (0.65, 1.6)
3 vs 24
direct
indirect 0.256
network
1.0 (0.63, 1.6)
1.4 (0.98, 2.0)
1.2 (0.92, 1.7)
0.005
1
15
4 vs 2
direct
indirect 0.341
network
0.50 (0.14, 1.6)
0.90 (0.67, 1.2)
0.88 (0.66, 1.2)
5 vs 2
direct
indirect 0.436
network
0.95 (0.40, 2.2)
0.66 (0.44, 0.98)
0.69 (0.48, 0.98)
6 vs 2
direct
indirect 0.71
network
0.52 (0.33, 0.79)
0.71 (0.14, 3.4)
0.53 (0.34, 0.85)
7 vs 2
direct
indirect 0.576
network
1.0 (0.61, 1.7)
0.87 (0.60, 1.3)
0.90 (0.66, 1.2)
8 vs 2
direct
indirect 0.483
network
0.94 (0.56, 1.6)
1.2 (0.81, 1.8)
1.1 (0.79, 1.6)
0.005
1
15
4 vs 22
direct
indirect 0.843
network
1.2 (0.92, 1.6)
1.3 (0.97, 1.6)
1.2 (1.0, 1.5)
5 vs 22
direct
indirect 0.113
network
1.5 (0.83, 2.9)
0.88 (0.64, 1.2)
0.98 (0.73, 1.3)
6 vs 22
direct
indirect 0.635
network
1.0 (0.22, 17.)
0.69 (0.41, 1.2)
0.75 (0.44, 1.3)
7 vs 22
direct
indirect 0.744
network
1.1 (0.60, 2.1)
1.3 (1.0, 1.6)
1.3 (1.0, 1.6)
8 vs 22
direct
indirect 0.969
network
1.5 (0.68, 3.9)
1.6 (1.2, 2.1)
1.5 (1.2, 2.1)
0.005
1
15
7 vs 18
direct
indirect 0.971
network
0.98 (0.048, 42.)
0.94 (0.67, 1.3)
0.94 (0.68, 1.3)
2 vs 19
direct
indirect 0.329
network
0.63 (0.40, 0.95)
1.9 (0.26, 16.)
0.66 (0.44, 1.0)
4 vs 19
direct
indirect 0.273
network
1.9 (0.10, 18.)
0.56 (0.30, 0.94)
0.59 (0.36, 0.98)
20 vs 2
direct
indirect 0.944
network
0.82 (0.31, 2.1)
0.75 (0.057, 4.1)
0.67 (0.29, 1.3)
25 vs 2
direct
indirect 0.47
network
1.5 (0.28, 7.1)
0.77 (0.42, 1.4)
0.85 (0.46, 1.4)
0.005
1
15

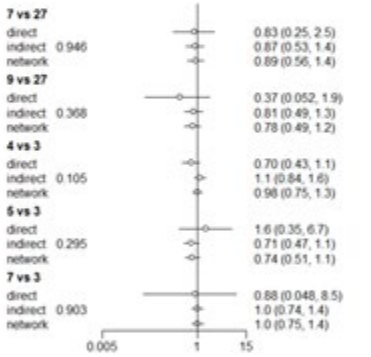


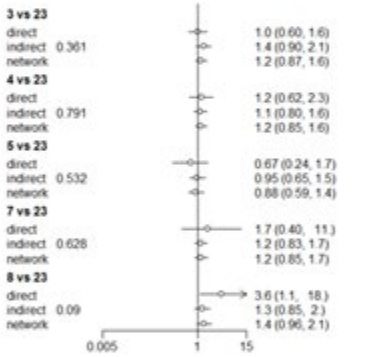
Forest plots for the outcome instrumental delivery, unfavourable cervix subgroup, showing direct, indirect and network estimates of treatment difference (contrast), odds ratio scale. Treatment codes: 1 - No treatment, 2 - Placebo, 3 - Vaginal PGE2 (tablet), 4 - Vaginal PGE2 (gel), 5 - Vaginal PGE2 (pessary – slow release), 6 - PGF2 gel, 7 - Intracervical PGE2, 8 - Vaginal PGE2 pessary (normal release), 9 - Vaginal misoprostol (dose less than 50 mcg), 10 - Vaginal misoprostol (dose 50 mcg or more), 11 - Oral misoprostol tablet (dose less than 50 mcg), 12 - Oral misoprostol tablet (dose 50mcg or more), 13 - Titrated (low dose) oral misoprostol solution, 14 - Sustained release misoprostol insert, 15 - IV oxytocin, 16 - IV oxytocin plus amniotomy, 17 - Nitric oxide, 18 - Mifepristone, 19 - Oestrogens, 20 - Relaxin, 21 - Mechanical methods – Foley catheter, 22 - Mechanical methods – laminaria including dilapan, 23 - Mechanical methods – Double balloon or Cook's catheter, 24 - Extra-amniotic PGE2 or PGF2, 25 - IV prostaglandin, 26 - Oral prostaglandins, 27 - Buccal/sublingual misoprostol

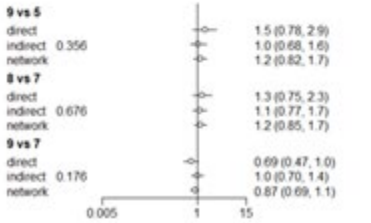

Contrast P-value
Odds Ratio (95% CrI)
8 vs 13
direct
indirect 0.571
network
1.5 (0.78, 2.9)
1.2 (0.71, 2.1)
1.3 (0.87, 2.)
9 vs 13
direct
indirect 0.673
network
0.57 (0.058, 6.9)
0.96 (0.62, 1.5)
0.96 (0.65, 1.4)
19 vs 15
direct
indirect 0.453
network
1.1 (0.13, 6.7)
0.51 (0.21, 1.3)
0.62 (0.27, 1.3)
24 vs 15
direct
indirect 0.16
network
2.9 (0.36, 20.)
0.61 (0.28, 1.6)
0.74 (0.41, 1.3)
26 vs 15
direct
indirect 0.949
network
0.88 (0.30, 2.6)
0.98 (0.25, 3.4)
0.93 (0.42, 1.8)
0.005
1
15
27 vs 12
direct
indirect 0.396
network
1.4 (0.83, 2.5)
0.95 (0.45, 2.0)
1.2 (0.80, 1.9)
7 vs 12
direct
indirect 0.967
network
1.1 (0.63, 1.9)
1.1 (0.72, 1.4)
1.1 (0.82, 1.4)
9 vs 12
direct
indirect 0.877
network
0.90 (0.49, 1.6)
0.95 (0.71, 1.3)
0.92 (0.72, 1.2)
4 vs 13
direct
indirect 0.266
network
0.92 (0.57, 1.5)
1.4 (0.80, 2.7)
1.1 (0.75, 1.6)
5 vs 13
direct
indirect 0.419
network
2.4 (0.23, 1.9e+02)
0.80 (0.49, 1.3)
0.82 (0.52, 1.3)
0.005
1
15
9 vs 10
direct
indirect 0.424
network
0.96 (0.65, 1.5)
0.79 (0.60, 1.0)
0.85 (0.66, 1.1)
13 vs 11
direct
indirect 0.0934
network
0.37 (0.040, 1.6)
1.5 (0.72, 3.2)
1.2 (0.59, 2.4)
21 vs 11
direct
indirect 0.734
network
1.4 (0.21, 11.)
0.96 (0.51, 1.9)
1.0 (0.54, 2.)
4 vs 11
direct
indirect 0.367
network
1.5 (0.75, 3.0)
0.78 (0.24, 2.5)
1.3 (0.70, 2.4)
21 vs 12
direct
indirect 0.0742
network
0.66 (0.46, 0.96)
1.0 (0.75, 1.4)
0.82 (0.66, 1.1)
0.005
1
15
Contrast P-value
Odds Ratio (95% CrI)
27 vs 10
direct
indirect 0.0701
network
0.46 (0.14, 1.3)
1.3 (0.83, 2.2)
1.1 (0.71, 1.7)
3 vs 10
direct
indirect 0.933
network
1.0 (0.68, 1.5)
1.0 (0.70, 1.4)
0.97 (0.74, 1.3)
4 vs 10
direct
indirect 0.238
network
1.1 (0.81, 1.5)
0.87 (0.65, 1.2)
0.95 (0.78, 1.2)
7 vs 10
direct
indirect 0.574
network
0.83 (0.51, 1.5)
1.0 (0.75, 1.3)
0.98 (0.77, 1.2)
8 vs 10
direct
indirect 0.818
network
1.3 (0.64, 2.9)
1.2 (0.82, 1.7)
1.1 (0.82, 1.6)
0.005
1
15
12 vs 10
direct
indirect 0.265
network
0.81 (0.62, 1.1)
1.1 (0.72, 1.5)
0.92 (0.75, 1.1)
15 vs 10
direct
indirect 0.105
network
4.0 (1.1, 29.)
1.1 (0.75, 1.6)
1.2 (0.78, 1.7)
17 vs 10
direct
indirect 0.917
network
1.2 (0.044, 61.)
0.96 (0.67, 1.4)
0.94 (0.64, 1.4)
2 vs 10
direct
indirect 0.861
network
0.92 (0.27, 3.0)
1.0 (0.71, 1.5)
0.99 (0.71, 1.4)
21 vs 10
direct
indirect 0.898
network
0.84 (0.25, 2.7)
0.78 (0.62, 0.99)
0.76 (0.62, 0.96)
0.005
1
15
15 vs 1
direct
indirect 0.37
network
2.7 (0.51, 16.)
1.1 (0.39, 5.2)
1.4 (0.53, 3.2)
17 vs 1
direct
indirect 0.869
network
1.2 (0.25, 5.7)
1.1 (0.32, 3.3)
1.1 (0.48, 2.5)
22 vs 1
direct
indirect 0.831
network
1.3 (0.16, 12.)
0.98 (0.37, 2.7)
1.1 (0.40, 2.6)
26 vs 1
direct
indirect 0.722
network
1.6 (0.38, 7.1)
1.1 (0.30, 4.3)
1.2 (0.45, 3.2)
7 vs 1
direct
indirect 0.247
network
0.57 (0.100, 2.7)
1.5 (0.54, 4.)
1.2 (0.49, 2.6)
0.005
1
15

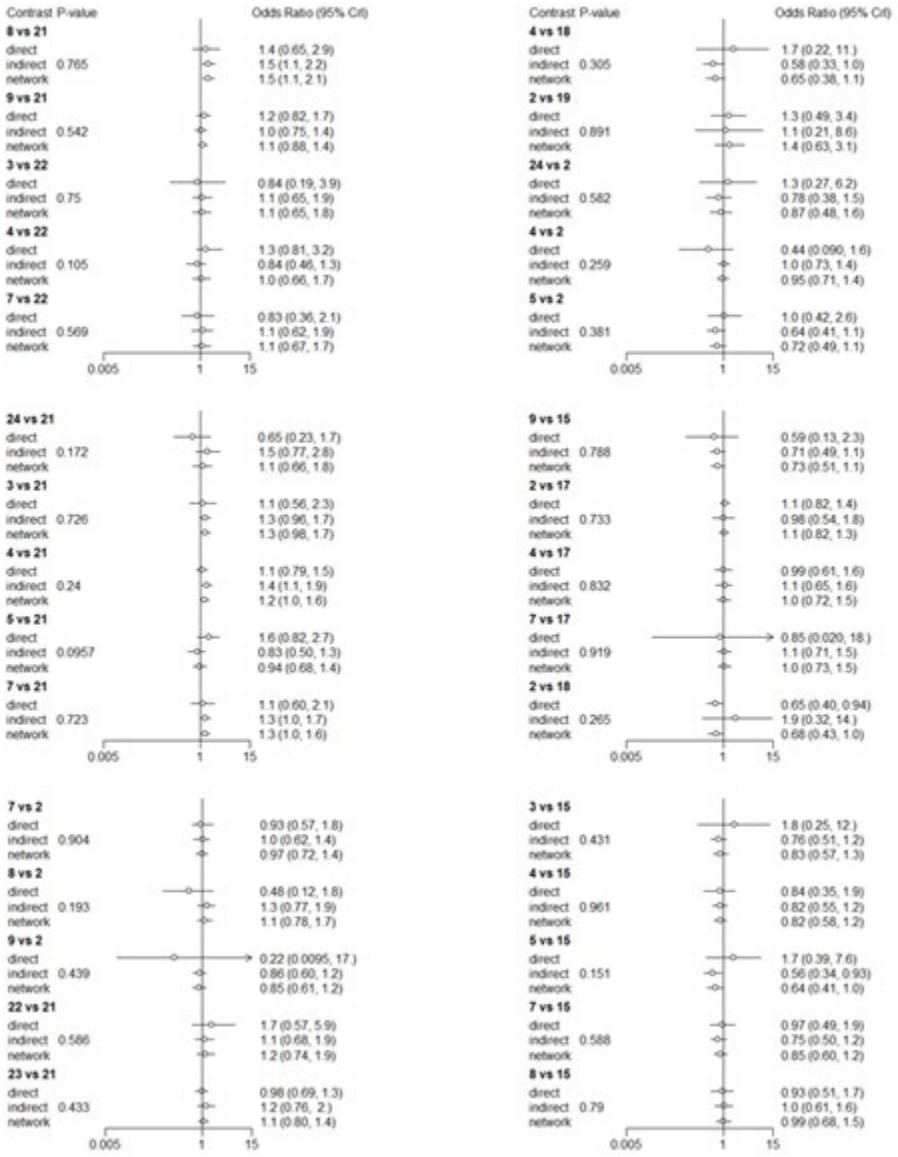

Contrast P-value
Odds Ratio (95% CrI)
8 vs 3
direct
indirect 0.539
network
0.88 (0.31, 2.5)
1.2 (0.85, 1.9)
1.2 (0.80, 1.7)
6 vs 4
direct
indirect 0.029
network
0.15 (0.028, 0.69)
0.84 (0.59, 1.2)
0.76 (0.54, 1.1)
7 vs 4
direct
indirect 0.23
network
0.75 (0.42, 1.3)
1.1 (0.84, 1.4)
1.0 (0.81, 1.3)
9 vs 4
direct
indirect 0.272
network
1.1 (0.68, 2.1)
0.82 (0.63, 1.1)
0.89 (0.70, 1.1)
7 vs 5
direct
indirect 0.112
network
3.7 (0.93, 14.)
1.2 (0.83, 1.8)
1.4 (0.94, 1.9)
0.005
1
15


Contrast P-value
Odds Ratio (95% CrI)
26 vs 24
direct
indirect 0.46
network
0.69 (0.097, 3.8)
1.4 (0.46, 4.6)
1.2 (0.50, 2.8)
3 vs 24
direct
indirect 0.511
network
1.0 (0.49, 2.1)
1.5 (0.62, 3.4)
1.1 (0.67, 1.9)
3 vs 26
direct
indirect 0.806
network
1.1 (0.18, 8.7)
0.83 (0.29, 2.1)
0.91 (0.44, 2.0)
4 vs 26
direct
indirect 0.994
network
0.91 (0.064, 8.6)
0.91 (0.37, 2.0)
0.88 (0.45, 2.)
7 vs 26
direct
indirect 0.59
network
0.67 (0.17, 2.9)
1.0 (0.43, 2.3)
0.91 (0.46, 1.9)
0.005
1
15


7 vs 27
direct
indirect 0.946
network
0.83 (0.25, 2.5)
0.87 (0.53, 1.4)
0.89 (0.56, 1.4)
9 vs 27
direct
indirect 0.368
network
0.37 (0.052, 1.9)
0.81 (0.49, 1.3)
0.78 (0.49, 1.2)
4 vs 3
direct
indirect 0.105
network
0.70 (0.43, 1.1)
1.1 (0.84, 1.6)
0.98 (0.75, 1.3)
6 vs 3
direct
indirect 0.295
network
1.6 (0.35, 6.7)
0.71 (0.47, 1.1)
0.74 (0.51, 1.1)
7 vs 3
direct
indirect 0.903
network
0.88 (0.048, 8.5)
1.0 (0.74, 1.4)
1.0 (0.75, 1.4)
0.005
1
15


3 vs 23
direct
indirect 0.361
network
1.0 (0.60, 1.6)
1.4 (0.90, 2.1)
1.2 (0.87, 1.6)
4 vs 23
direct
indirect 0.791
network
1.2 (0.62, 2.3)
1.1 (0.80, 1.6)
1.2 (0.85, 1.6)
5 vs 23
direct
indirect 0.532
network
0.67 (0.24, 1.7)
0.95 (0.65, 1.5)
0.88 (0.59, 1.4)
7 vs 23
direct
indirect 0.628
network
1.7 (0.40, 11.)
1.2 (0.83, 1.7)
1.2 (0.85, 1.7)
8 vs 23
direct
indirect 0.09
network
3.6 (1.1, 18.)
1.3 (0.85, 2.)
1.4 (0.96, 2.1)
0.005
1
15


9 vs 5
direct
indirect 0.356
network
1.5 (0.78, 2.9)
1.0 (0.68, 1.6)
1.2 (0.82, 1.7)
8 vs 7
direct
indirect 0.676
network
1.3 (0.75, 2.3)
1.1 (0.77, 1.7)
1.2 (0.85, 1.7)
9 vs 7
direct
indirect 0.176
network
0.69 (0.47, 1.0)
1.0 (0.70, 1.4)
0.87 (0.69, 1.1)
0.005
1
15


Contrast P-value
Odds Ratio (95% CrI)
8 vs 21
direct
indirect 0.765
network
1.4 (0.65, 2.9)
1.5 (1.1, 2.2)
1.5 (1.1, 2.1)
9 vs 21
direct
indirect 0.542
network
1.2 (0.82, 1.7)
1.0 (0.75, 1.4)
1.1 (0.88, 1.4)
3 vs 22
direct
indirect 0.75
network
0.84 (0.19, 3.9)
1.1 (0.65, 1.9)
1.1 (0.65, 1.8)
4 vs 22
direct
indirect 0.105
network
1.3 (0.81, 3.2)
0.84 (0.46, 1.3)
1.0 (0.66, 1.7)
7 vs 22
direct
indirect 0.569
network
0.83 (0.36, 2.1)
1.1 (0.62, 1.9)
1.1 (0.67, 1.7)
0.005
1
15
Contrast P-value
Odds Ratio (95% CrI)
4 vs 18
direct
indirect 0.305
network
1.7 (0.22, 11.)
0.58 (0.33, 1.0)
0.65 (0.38, 1.1)
2 vs 19
direct
indirect 0.891
network
1.3 (0.49, 3.4)
1.1 (0.21, 8.6)
1.4 (0.63, 3.1)
24 vs 2
direct
indirect 0.582
network
1.3 (0.27, 6.2)
0.78 (0.38, 1.5)
0.87 (0.48, 1.6)
4 vs 2
direct
indirect 0.259
network
0.44 (0.090, 1.6)
1.0 (0.73, 1.4)
0.95 (0.71, 1.4)
5 vs 2
direct
indirect 0.381
network
1.0 (0.42, 2.6)
0.64 (0.41, 1.1)
0.72 (0.49, 1.1)
0.005
1
15
24 vs 21
direct
indirect 0.172
network
0.65 (0.23, 1.7)
1.5 (0.77, 2.8)
1.1 (0.66, 1.8)
3 vs 21
direct
indirect 0.726
network
1.1 (0.56, 2.3)
1.3 (0.96, 1.7)
1.3 (0.98, 1.7)
4 vs 21
direct
indirect 0.24
network
1.1 (0.79, 1.5)
1.4 (1.1, 1.9)
1.2 (1.0, 1.6)
5 vs 21
direct
indirect 0.0957
network
1.6 (0.82, 2.7)
0.83 (0.50, 1.3)
0.94 (0.68, 1.4)
7 vs 21
direct
indirect 0.723
network
1.1 (0.60, 2.1)
1.3 (1.0, 1.7)
1.3 (1.0, 1.6)
0.005
1
15
9 vs 15
direct
indirect 0.788
network
0.59 (0.13, 2.3)
0.71 (0.49, 1.1)
0.73 (0.51, 1.1)
2 vs 17
direct
indirect 0.733
network
1.1 (0.82, 1.4)
0.98 (0.54, 1.8)
1.1 (0.82, 1.3)
4 vs 17
direct
indirect 0.832
network
0.99 (0.61, 1.6)
1.1 (0.65, 1.6)
1.0 (0.72, 1.5)
7 vs 17
direct
indirect 0.919
network
0.85 (0.020, 18.)
1.1 (0.71, 1.5)
1.0 (0.73, 1.5)
2 vs 18
direct
indirect 0.265
network
0.65 (0.40, 0.94)
1.9 (0.32, 14.)
0.68 (0.43, 1.0)
0.005
1
15
7 vs 2
direct
indirect 0.904
network
0.93 (0.57, 1.8)
1.0 (0.62, 1.4)
0.97 (0.72, 1.4)
8 vs 2
direct
indirect 0.193
network
0.48 (0.12, 1.8)
1.3 (0.77, 1.9)
1.1 (0.78, 1.7)
9 vs 2
direct
indirect 0.439
network
0.22 (0.0095, 17.)
0.86 (0.60, 1.2)
0.85 (0.61, 1.2)
22 vs 21
direct
indirect 0.586
network
1.7 (0.57, 5.9)
1.1 (0.68, 1.9)
1.2 (0.74, 1.9)
23 vs 21
direct
indirect 0.433
network
0.98 (0.69, 1.3)
1.2 (0.76, 2.)
1.1 (0.80, 1.4)
0.005
1
15
3 vs 15
direct
indirect 0.431
network
1.8 (0.25, 12.)
0.76 (0.51, 1.2)
0.83 (0.57, 1.3)
4 vs 15
direct
indirect 0.961
network
0.84 (0.35, 1.9)
0.82 (0.55, 1.2)
0.82 (0.58, 1.2)
5 vs 15
direct
indirect 0.151
network
1.7 (0.39, 7.6)
0.56 (0.34, 0.93)
0.64 (0.41, 1.0)
7 vs 15
direct
indirect 0.588
network
0.97 (0.49, 1.9)
0.75 (0.50, 1.2)
0.85 (0.60, 1.2)
8 vs 15
direct
indirect 0.79
network
0.93 (0.51, 1.7)
1.0 (0.61, 1.6)
0.99 (0.68, 1.5)
0.005
1
15

Epidural

Inconsistency checks were performed using the random effects model, as this had lower DIC than the fixed effects model. Convergence was satisfactory for the random effects model assuming inconsistency after 50,000 iterations, and the consistency and inconsistency models were compared using results based on samples from a further 50,000 iterations on four chains. WinBUGS code for the inconsistency model is provided below.

Analysis of the full dataset for the epidural outcome covered 85 trials (174 arms) with 25 treatments. Analysis of the unfavourable cervix subgroup dataset covered 60 trials (123 arms) of 21 treatments.

Comparing model fit for fixed and random-effect network meta-analysis (NMA) models indicates support for the random-effect model on the basis of improved fit shown by a sizeable decrease in the posterior mean residual deviance and a lower DIC (which accounts for model complexity) (Table 1). We therefore used the random effects model to assess the consistency assumption.

It was not possible to fit the inconsistency model using the standard, Un(0,5) uninformative prior on between-study standard deviation (SD) (as specified in TSD2 (1)). Instead we used an informative prior for between-study SD drawn from Turner et al. 2015 (2) for obstetric non-pharmacological vs pharmacological interventions (0). This was used for both inconsistency and consistency models to enable a fair comparison. Results were based on 60,000 iterations following a burn-in of 20,000 iterations, which was sufficient to achieve convergence according to the Brooks Gelman-Rubin statistic (3).

There is some evidence of inconsistency, with the posterior mean residual deviance approximately 3.6 lower in the inconsistency NMA than in the consistency NMA. The central estimate of between-study SD, though not the 95% credible interval, was lower in the inconsistency model, suggesting some of the heterogeneity is explained by inconsistency. When model complexity is taken into account however, the consistency model is preferred based on DIC.

Four studies were denoted potentially inconsistent in the full dataset; these were the same studies identified in the 2019 analysis (MacKenzie 1979, Sciscione 2001, Ferraiolo 2010 and Cromi 2011). Three of these four (Cromi 2011, MacKenzie 1979 and Ferraiolo 2010) were also flagged as inconsistent in the unfavourable cervix subgroup analysis.

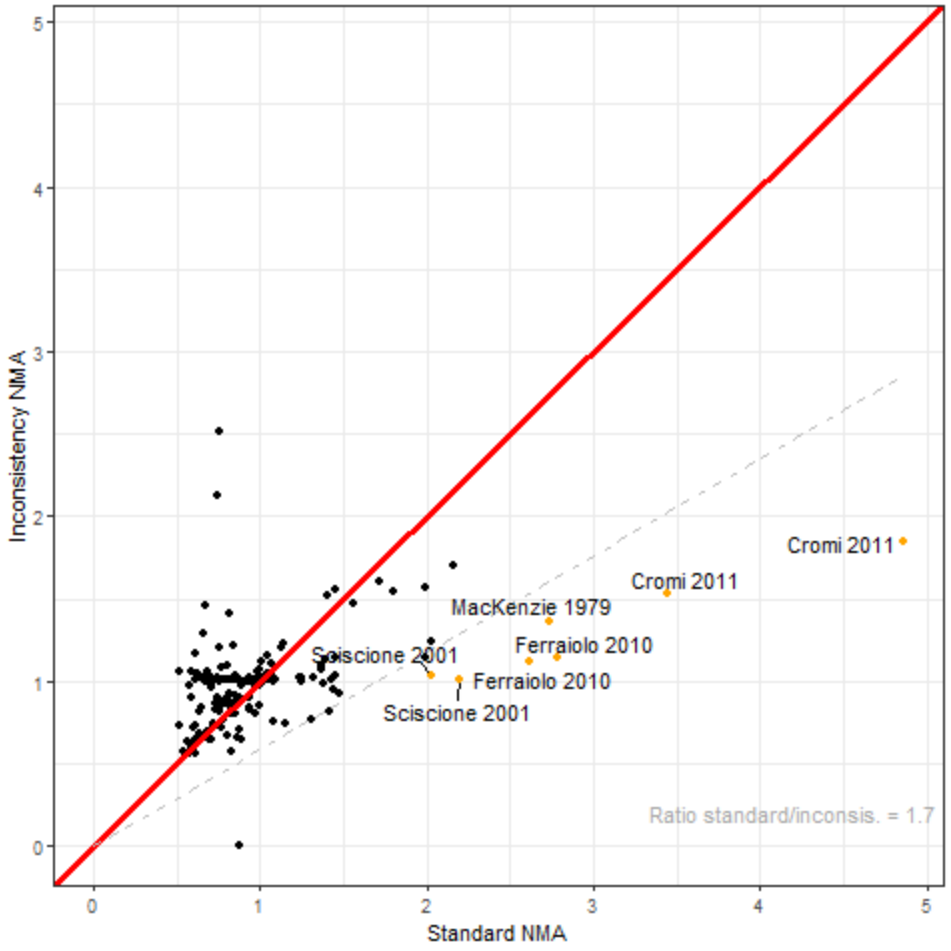
- Cromi 2011
  - Compares Vaginal PGE2 (pessary – slow release) and Foley catheter
  - Codes in full dataset model: 5 and 22
- Ferraiolo 2010
  - Compares Vaginal PGE2 (gel) and Vaginal PGE2 (pessary – slow release)
  - Codes in full dataset model: 4 and 5
- Sciscione 2001 (inconsistent in full dataset only)
  - Compares Vaginal misoprostol (dose 50 mcg or more) and Foley catheter
  - Codes in full dataset model: 10 and 22
- MacKenzie 1979
  - Compares Placebo, Vaginal PGE2 (gel) and PGF2 gel
  - o Codes in full dataset model: 1, 4 and 6

Table 54. Model fit statistics for NMA of Epidural outcome on full dataset.

Dataset	Model	Between-study SD (median, 95% CrI)	Residual Deviance [a]	DIC [b]
Full	Consistency model - FE	-	190.0	1062.60
	Consistency model – RE	0.176 (0.066, 0.301)	173.8	1059.64
	Inconsistency model – RE	0.119 (0.007, 0.303)	169.8	1076.92
Unfavourable cervix subgroup	Consistency model - FE	-	143.1	773.22
	Consistency model – RE	0.220 (0.084, 0.377)	125.9	768.13
	Inconsistency model – RE	0.202 (0.065, 0.393)	122.0	777.86

a Posterior mean residual deviance compared to 174 data points, lower values preferred

b Deviance information criteria (DIC) – lower values preferred



Dev-dev plot of each study arms' residual deviance under the standard and inconsistency models for the outcome epidural, full dataset. Points with relatively high deviance in the standard model compared with the inconsistency model shown in orange with labels.

Node-splitting compares the direct and indirect estimates for each comparison where both estimates are available. Direct and indirect evidence on most treatment comparisons agree. Evidence conflicted on comparisons between vaginal PGE2 slow-release pessary (treatment 5) and Foley catheter (treatment 22); titrated (low dose) oral misoprostol solution and vaginal misoprostol (dose less than 50 mcg); and vaginal PGE2 (gel) and vaginal PGE2 (pessary – slow release). Given multiple testing of 50 contrasts, we would expect p-values below 0.05 in at least two cases.

Forest plots of both the full and unfavourable cervix subgroups indicate that the inconsistency between direct and indirect estimates of the treatment difference between vaginal misoprostol (dose less than 50mcg) (intervention 9) and titrated (low dose) oral misoprostol solution (intervention 13) is likely to be due to the difficulty in estimating a direct effect. Only one included study (Souza et al. 2013) compared these treatments directly.

Direct and indirect treatment effect estimates (LOR) for Epidural node-split (full dataset).

Intervention 1	Intervention 2	p-value [b]	Residual deviance [a]	Direct			Indirect		
				Median	2.5% CrI	97.5 CrI	Median	2.5% CrI	97.5 CrI
Consistency model		NA	175						
Titrated (low dose) oral misoprostol solution	Vaginal misoprostol (dose less than 50 mcg)	0.018	173.6	-21.035	-62.248	-2.112	-0.207	-0.691	0.293
Mechanical methods – foley catheter	Vaginal PGE2 (pessary – slow release)	0.003	172.9	-0.830	-1.224	-0.415	0.033	-0.313	0.387
Vaginal PGE2 (gel)	Vaginal PGE2 (pessary – slow release)	0.006	174.4	0.377	-0.066	0.817	-0.438	-0.777	-0.084
No treatment	Mechanical methods – laminaria including dilapan	0.12	174.6	0.086	-0.507	0.685	-0.980	-2.221	0.236
No treatment	Vaginal PGE2 pessary (normal release)	0.123	174.6	0.089	-0.451	0.632	1.120	-0.086	2.381
Vaginal misoprostol (dose 50 mcg or more)	Oral misoprostol tablet (dose 50mcg or more)	0.853	174.7	0.175	-0.108	0.491	0.130	-0.282	0.530
Vaginal misoprostol (dose 50 mcg or more)	IV oxytocin	0.906	175.3	-0.024	-0.932	0.868	0.035	-0.493	0.568
Vaginal misoprostol (dose 50 mcg or more)	Nitric oxide	0.137	174	-0.374	-1.212	0.464	0.364	-0.149	0.890
Vaginal misoprostol	Mechanical methods – foley catheter	0.06	172.9	-0.885	-2.362	0.444	0.402	0.140	0.689

(dose 50 mcg or more)									
Vaginal misoprostol (dose 50 mcg or more)	Buccal/sublingual misoprostol	0.657	176	0.240	-0.238	0.720	0.073	-0.485	0.648
Vaginal misoprostol (dose 50 mcg or more)	Vaginal PGE2 (gel)	0.944	175.2	0.158	-0.193	0.523	0.144	-0.160	0.447
Vaginal misoprostol (dose 50 mcg or more)	Vaginal PGE2 (pessary – slow release)	0.608	176.1	0.355	-0.921	1.661	0.002	-0.345	0.375
Vaginal misoprostol (dose 50 mcg or more)	Intracervical PGE2	0.685	175.7	0.670	-0.228	1.603	0.459	-0.066	0.982
Vaginal misoprostol (dose 50 mcg or more)	Vaginal PGE2 pessary (normal release)	0.134	174	0.776	-0.104	1.718	-0.259	-1.265	0.773
Oral misoprostol tablet (dose less than 50 mcg)	Mechanical methods – foley catheter	0.869	174.7	0.361	-0.139	0.863	0.438	-0.382	1.267
Oral misoprostol tablet (dose less than 50 mcg)	Vaginal PGE2 (gel)	0.871	175.1	0.238	-0.546	1.008	0.159	-0.380	0.713
Oral misoprostol tablet (dose 50mcg or more)	Mechanical methods – foley catheter	0.831	173.5	0.160	-0.288	0.611	0.215	-0.158	0.566
Oral misoprostol tablet (dose 50mcg or more)	Vaginal PGE2 (gel)	0.36	172.3	0.217	-0.325	0.759	-0.062	-0.382	0.235
Oral misoprostol tablet (dose 50mcg or more)	Vaginal misoprostol (dose less than 50 mcg)	0.772	173.2	-0.055	-0.514	0.427	0.026	-0.323	0.409

Titrated (low dose) oral misoprostol solution	Sustained release misoprostol insert	0.802	175.3	-0.601	-1.515	0.283	-0.753	-1.510	0.049
Titrated (low dose) oral misoprostol solution	Vaginal PGE2 (gel)	0.963	175.4	-0.247	-0.727	0.240	-0.271	-1.357	0.766
Sustained release misoprostol insert	Vaginal PGE2 (pessary – slow release)	0.805	175.2	0.356	-0.181	0.887	0.215	-0.838	1.318
IV oxytocin	IV oxytocin plus amniotomy	0.627	175.5	0.269	-0.337	0.870	0.502	-0.230	1.227
IV oxytocin	Vaginal misoprostol (dose less than 50 mcg)	0.719	175.3	0.218	-0.355	0.787	0.065	-0.562	0.707
Amniotomy	IV oxytocin plus amniotomy	0.911	175.6	-0.454	-1.125	0.231	-0.515	-1.597	0.506
Amniotomy	Vaginal PGE2 (gel)	0.948	176.3	-0.715	-1.702	0.174	-0.682	-1.478	0.120
IV oxytocin plus amniotomy	Buccal/sublingual misoprostol	0.486	175.5	0.238	-1.134	1.683	-0.288	-0.843	0.286
IV oxytocin plus amniotomy	Vaginal PGE2 (gel)	0.435	174.8	-0.391	-1.010	0.225	-0.052	-0.658	0.535
Nitric oxide	Placebo	0.499	174.8	0.179	-0.406	0.765	0.502	-0.225	1.283
Nitric oxide	Vaginal PGE2 (gel)	0.515	175	-0.140	-0.697	0.435	0.127	-0.458	0.724
Placebo	Vaginal PGE2 (gel)	0.078	172.6	-0.831	-1.639	-0.074	0.016	-0.546	0.601
Placebo	Vaginal PGE2 (pessary – slow release)	0.163	174.5	0.260	-0.840	1.310	-0.607	-1.181	-0.040
Placebo	Vaginal misoprostol (dose less than 50 mcg)	0.806	175.9	-0.103	-1.722	1.530	-0.326	-0.835	0.207
Mechanical methods – foley catheter	Mechanical methods – laminaria including dilapan	0.518	175.1	-0.567	-1.269	0.113	-0.222	-1.040	0.618

Mechanical methods – foley catheter	Mechanical methods – Double balloon or Cook's catheter	0.656	174.1	0.290	-0.096	0.683	0.452	-0.161	1.075
Mechanical methods – foley catheter	Vaginal PGE2 (gel)	0.922	171.4	-0.195	-0.543	0.144	-0.216	-0.497	0.077
Mechanical methods – foley catheter	Intracervical PGE2	0.125	173.6	0.972	-0.168	2.212	0.004	-0.490	0.498
Mechanical methods – foley catheter	Vaginal misoprostol (dose less than 50 mcg)	0.781	173.6	-0.153	-0.509	0.239	-0.222	-0.586	0.147
Mechanical methods – laminaria including dilapan	Vaginal PGE2 (tablet)	0.858	177.9	0.395	-1.692	2.649	0.195	-0.476	0.871
Mechanical methods – laminaria including dilapan	Vaginal PGE2 (gel)	0.583	175.8	0.521	-0.685	1.763	0.135	-0.449	0.731
Mechanical methods – Double balloon or Cook's catheter	Vaginal PGE2 (tablet)	0.321	175.7	-0.108	-1.068	0.860	-0.669	-1.251	-0.074
Mechanical methods – Double balloon or Cook's catheter	Vaginal PGE2 (gel)	0.262	174.6	-0.111	-0.906	0.666	-0.611	-0.998	-0.225
Mechanical methods – Double balloon or Cook's catheter	Vaginal PGE2 (pessary – slow release)	0.19	173.7	-1.008	-1.690	-0.325	-0.462	-0.910	0.015
Buccal/sublingual misoprostol	Vaginal misoprostol (dose less than 50 mcg)	0.45	175.4	0.134	-0.366	0.634	-0.154	-0.693	0.390
Vaginal PGE2 (tablet)	Vaginal PGE2 (gel)	0.311	174.6	0.156	-0.389	0.703	-0.293	-1.008	0.416
Vaginal PGE2 (tablet)	Vaginal PGE2 (pessary – slow release)	0.302	175.3	0.785	-1.017	2.574	-0.204	-0.710	0.321
Vaginal PGE2 (tablet)	Intracervical PGE2	0.256	175.3	-0.323	-1.705	0.982	0.504	-0.144	1.143

Vaginal PGE2 (gel)	PGF2 gel	0.082	172.3	1.121	-0.371	2.664	-0.351	-1.063	0.362
Vaginal PGE2 (gel)	Intracervical PGE2	0.48	176.9	0.236	-0.318	0.772	0.527	-0.097	1.224
Vaginal PGE2 (gel)	Vaginal misoprostol (dose less than 50 mcg)	0.071	171.9	-0.130	-0.435	0.164	0.284	-0.069	0.646

a Posterior mean residual deviance compared to 174 total data points.

b p-values < 0.05 are indicative of evidence of inconsistency between the direct and indirect estimates. Comparisons where this is the case are highlighted in yellow.

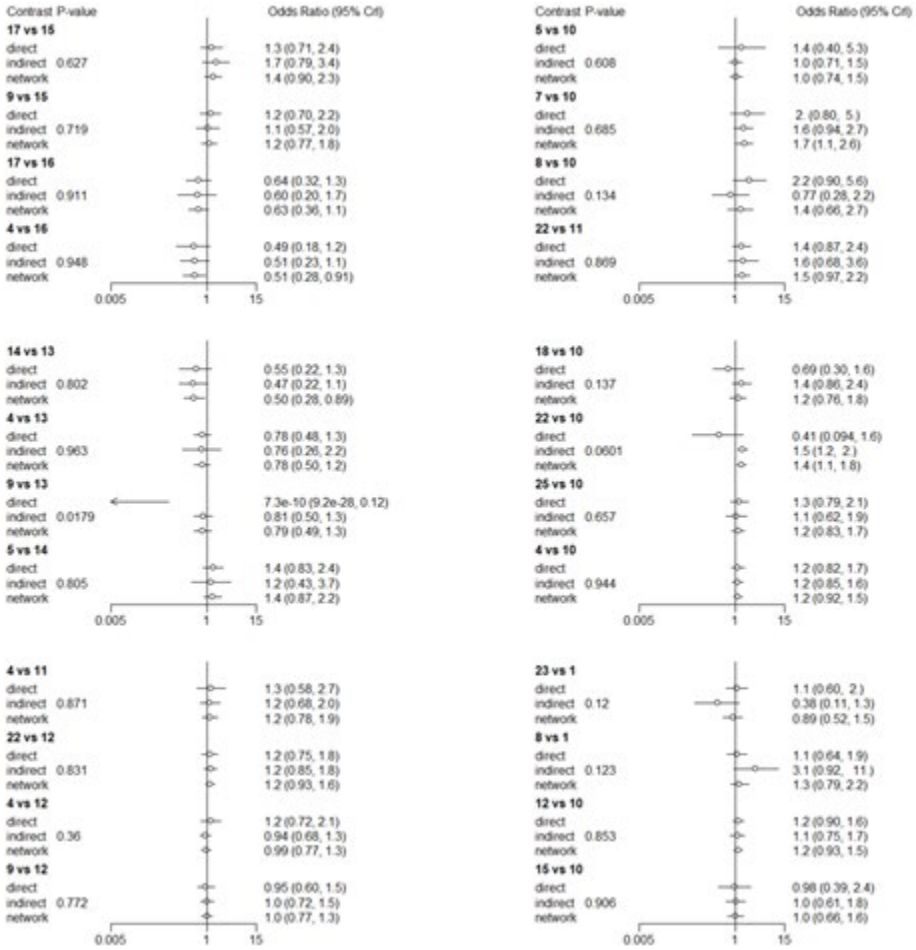
Direct and indirect treatment effect estimates (LOR) for Epidural node-split (unfavourable cervix dataset).

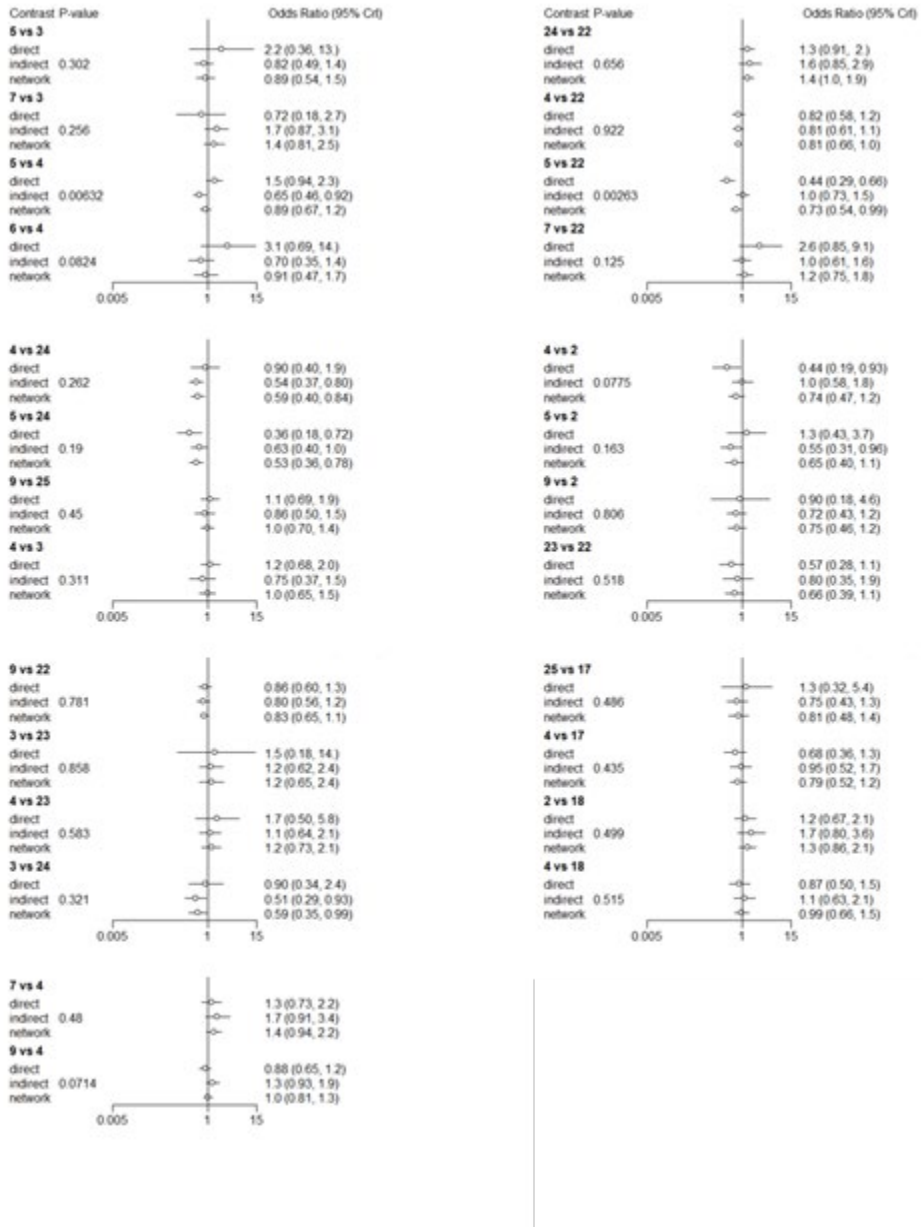
Intervention 1	Intervention 2	p-value [b]	Residual deviance [a]	Direct			Indirect		
				Median	2.5% CrI	97.5 CrI	Median	2.5% CrI	97.5 CrI
Consistency model		-	126.2	-	-	-	-	-	-
Titrated (low dose) oral misoprostol solution	Vaginal misoprostol (dose less than 50 mcg)	0.023	124.4	-24.058	-51.451	-1.396	-0.164	-0.748	0.446
Mechanical methods – Foley catheter	Vaginal PGE2 (pessary – slow release)	0.007	125.9	-0.813	-1.236	-0.359	0.046	-0.370	0.474
Vaginal PGE2 (gel)	Vaginal PGE2 (pessary – slow release)	0.005	126.2	0.549	-0.030	1.148	-0.454	-0.813	-0.069
Vaginal misoprostol (dose 50 mcg or more)	Oral misoprostol tablet (dose 50mcg or more)	0.769	124.9	0.164	-0.278	0.660	0.062	-0.532	0.618
Vaginal misoprostol (dose 50 mcg or more)	IV oxytocin	0.926	126.4	-0.024	-0.985	0.951	-0.076	-0.840	0.693
Vaginal misoprostol (dose 50 mcg or more)	Nitric oxide	0.21	125.5	-0.379	-1.280	0.528	0.302	-0.307	0.917
Vaginal misoprostol (dose 50 mcg or more)	Mechanical methods – Foley catheter	0.087	124.4	-0.838	-2.296	0.469	0.351	0.021	0.687
Vaginal misoprostol (dose 50 mcg or more)	Buccal/sublingual misoprostol	0.764	125.9	0.124	-0.513	0.774	-0.017	-0.692	0.686
Vaginal misoprostol (dose 50 mcg or more)	Vaginal PGE2 (gel)	0.5	125.2	0.168	-0.233	0.577	-0.028	-0.477	0.404
Vaginal misoprostol (dose 50 mcg or more)	Vaginal PGE2 (pessary – slow release)	0.478	126.3	0.392	-0.902	1.765	-0.101	-0.520	0.367

Oral misoprostol tablet (dose less than 50 mcg)	Mechanical methods – Foley catheter	0.885	126	0.362	-0.240	0.963	0.440	-0.458	1.319
Oral misoprostol tablet (dose less than 50 mcg)	Vaginal PGE2 (gel)	0.879	126.6	0.232	-0.590	1.082	0.159	-0.480	0.815
Oral misoprostol tablet (dose 50mcg or more)	Mechanical methods – Foley catheter	0.981	125.2	0.159	-0.401	0.727	0.148	-0.376	0.649
Oral misoprostol tablet (dose 50mcg or more)	Vaginal PGE2 (gel)	0.573	126.6	0.375	-1.169	1.945	-0.061	-0.460	0.306
Oral misoprostol tablet (dose 50mcg or more)	Vaginal misoprostol (dose less than 50 mcg)	0.917	126.2	0.057	-0.882	0.974	0.001	-0.438	0.475
Titrated (low dose) oral misoprostol solution	Sustained release misoprostol insert	0.806	125.8	-0.614	-1.595	0.330	-0.778	-1.697	0.182
Titrated (low dose) oral misoprostol solution	Vaginal PGE2 (gel)	0.937	125.8	-0.246	-0.842	0.339	-0.296	-1.521	0.841
Sustained release misoprostol insert	Vaginal PGE2 (pessary – slow release)	0.798	126.3	0.344	-0.278	0.968	0.181	-0.991	1.386
IV oxytocin	Vaginal misoprostol (dose less than 50 mcg)	0.922	126.9	0.214	-0.444	0.871	0.158	-0.844	1.176
Nitric oxide	Placebo	0.558	125.2	0.176	-0.491	0.859	0.500	-0.355	1.389
Nitric oxide	Vaginal PGE2 (gel)	0.576	125.8	-0.135	-0.786	0.526	0.126	-0.549	0.801
Mechanical methods – Foley catheter	Mechanical methods – laminaria including dilapan	0.847	126.4	-0.571	-1.329	0.197	-0.699	-1.798	0.383
Mechanical methods – Foley catheter	Mechanical methods – Double balloon or Cook's catheter	0.338	124	0.293	-0.126	0.723	0.749	-0.080	1.606
Mechanical methods – Foley catheter	Vaginal PGE2 (gel)	0.9	123	-0.199	-0.598	0.194	-0.231	-0.577	0.139
Mechanical methods – Foley catheter	Intracervical PGE2	0.112	125.2	0.951	-0.217	2.214	-0.149	-0.877	0.524
Mechanical methods – Foley catheter	Vaginal misoprostol (dose less than 50 mcg)	0.842	124.1	-0.120	-0.512	0.311	-0.186	-0.697	0.335
Mechanical methods – laminaria including dilapan	Vaginal PGE2 (tablet)	0.952	126.8	0.423	-1.597	2.684	0.364	-0.500	1.262
Mechanical methods – laminaria including dilapan	Vaginal PGE2 (gel)	0.848	127	0.517	-0.725	1.834	0.379	-0.378	1.141
Placebo	Vaginal PGE2 (gel)	0.084	123.4	-0.866	-1.715	-0.056	0.058	-0.618	0.753

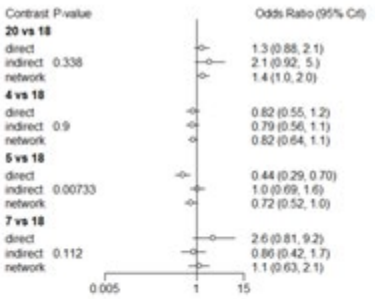
Placebo	Vaginal PGE2 (pessary – slow release)	0.148	125.9	0.262	-0.853	1.378	-0.679	-1.358	-0.006
Mechanical methods – Double balloon or Cook's catheter	Vaginal PGE2 (gel)	0.256	125.5	-0.125	-0.983	0.733	-0.677	-1.171	-0.222
Mechanical methods – Double balloon or Cook's catheter	Vaginal PGE2 (pessary – slow release)	0.265	125.6	-1.006	-1.742	-0.270	-0.513	-1.027	0.065
Buccal/sublingual misoprostol	Vaginal misoprostol (dose less than 50 mcg)	0.755	126.1	0.129	-0.426	0.682	-0.017	-0.753	0.750
Vaginal PGE2 (tablet)	Vaginal PGE2 (gel)	0.301	126.3	0.159	-0.443	0.755	-0.555	-1.856	0.669
Vaginal PGE2 (tablet)	Intracervical PGE2	0.237	125.3	-0.344	-1.745	1.028	0.622	-0.220	1.483
Vaginal PGE2 (gel)	Intracervical PGE2	0.578	126.7	0.201	-0.529	0.940	0.532	-0.385	1.470
Vaginal PGE2 (gel)	Vaginal misoprostol (dose less than 50 mcg)	0.288	125	-0.070	-0.488	0.354	0.243	-0.175	0.667

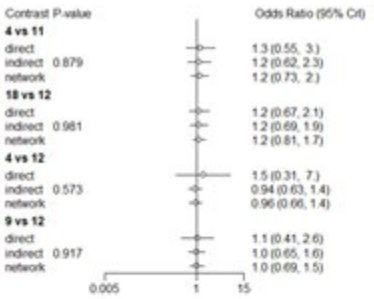
Forest plots, for outcome epidural, full dataset, highlighting contributions of direct and indirect evidence on the effect size estimated within each treatment comparison (contrast). 1 - No treatment, 2 – Placebo, 3 - Vaginal PGE2 (tablet), 4 - Vaginal PGE2 (gel), 5 - Vaginal PGE2 (pessary – slow release), 6 - PGF2 gel, 7 - Intracervical PGE2, 8 - Vaginal PGE2 pessary (normal release), 9 - Vaginal misoprostol (dose less than 50 mcg), 10 - Vaginal misoprostol (dose 50 mcg or more), 11 - Oral misoprostol tablet (dose less than 50 mcg), 12 - Oral misoprostol tablet (dose 50mcg or more), 13 - Titrated (low dose) oral misoprostol solution, 14 - Sustained release misoprostol insert, 15 - IV oxytocin, 16 – Amniotomy, 17 - IV oxytocin plus amniotomy, 18 - Nitric oxide, 19 – Mifepristone, 20 – Oestrogens, 21 – Relaxin, 22 - Mechanical methods – Foley catheter, 23 - Mechanical methods – laminaria including dilapan, 24 - Mechanical methods – Double balloon or Cook's catheter, 25 - Buccal/sublingual misoprostol.

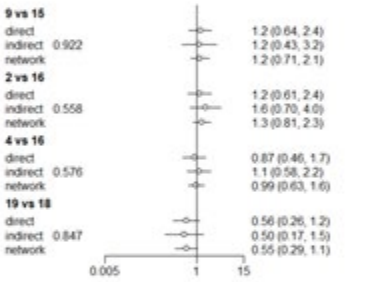


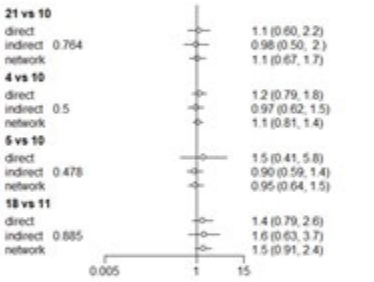


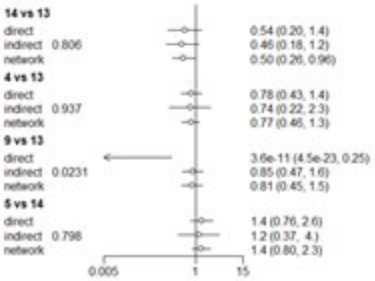
Forest plots, for outcome epidural, unfavourable cervix subgroup dataset, highlighting contributions of direct and indirect evidence on the effect size estimated within each treatment comparison (contrast). 1 - No treatment, 2 – Placebo, 3 - Vaginal PGE2 (tablet), 4 - Vaginal PGE2 (gel), 5 - Vaginal PGE2 (pessary – slow release), 6 - PGF2 gel, 7 - Intracervical PGE2, 8 - Vaginal PGE2 pessary (normal release), 9 - Vaginal misoprostol (dose less than 50 mcg), 10 - Vaginal misoprostol (dose 50 mcg or more), 11 - Oral misoprostol tablet (dose less than 50 mcg), 12 - Oral misoprostol tablet (dose 50mcg or more), 13 - Titrated (low dose) oral misoprostol solution, 14 - Sustained release misoprostol insert, 15 - IV oxytocin, 16 - Nitric oxide, 17 – Mifepristone, 18 - Mechanical methods (Foley catheter), 19 - Mechanical methods (laminaria including dilapan), 20 - Mechanical methods (Double balloon or Cook's catheter), 21 - Buccal/sublingual misoprostol.

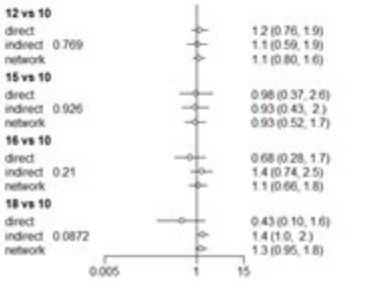

Contrast P-value
Odds Ratio (95% CrI)
20 vs 18
direct
1.3 (0.88, 2.1)
indirect 0.338
2.1 (0.92, 5.)
network
1.4 (1.0, 2.0)
4 vs 18
direct
0.82 (0.55, 1.2)
indirect 0.9
0.79 (0.56, 1.1)
network
0.82 (0.64, 1.1)
5 vs 18
direct
0.44 (0.29, 0.70)
indirect 0.00733
1.0 (0.69, 1.6)
network
0.72 (0.52, 1.0)
7 vs 18
direct
2.6 (0.81, 9.2)
indirect 0.112
0.86 (0.42, 1.7)
network
1.1 (0.63, 2.1)
0.005
1
15

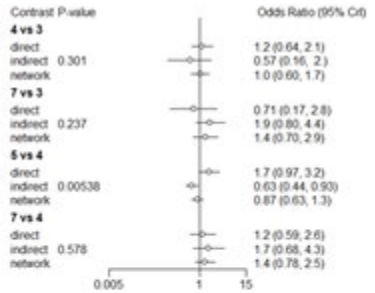

Contrast P-value
Odds Ratio (95% CrI)
4 vs 11
direct
1.3 (0.55, 3.)
indirect 0.879
1.2 (0.62, 2.3)
network
1.2 (0.73, 2.)
18 vs 12
direct
1.2 (0.67, 2.1)
indirect 0.981
1.2 (0.69, 1.9)
network
1.2 (0.81, 1.7)
4 vs 12
direct
1.5 (0.31, 7.)
indirect 0.573
0.94 (0.63, 1.4)
network
0.96 (0.66, 1.4)
9 vs 12
direct
1.1 (0.41, 2.6)
indirect 0.917
1.0 (0.65, 1.6)
network
1.0 (0.69, 1.5)
0.005
1
15

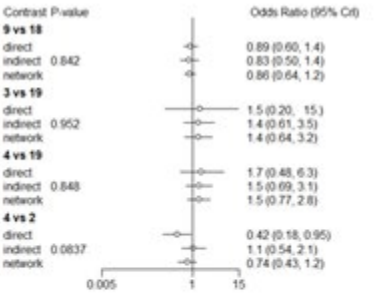

9 vs 15
direct
1.2 (0.64, 2.4)
indirect 0.922
1.2 (0.43, 3.2)
network
1.2 (0.71, 2.1)
2 vs 16
direct
1.2 (0.61, 2.4)
indirect 0.558
1.6 (0.70, 4.0)
network
1.3 (0.81, 2.3)
4 vs 16
direct
0.87 (0.46, 1.7)
indirect 0.576
1.1 (0.58, 2.2)
network
0.99 (0.63, 1.6)
19 vs 18
direct
0.56 (0.26, 1.2)
indirect 0.847
0.50 (0.17, 1.5)
network
0.55 (0.29, 1.1)
0.005
1
15

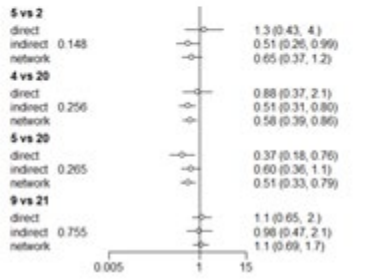

21 vs 10
direct
1.1 (0.60, 2.2)
indirect 0.764
0.98 (0.50, 2.)
network
1.1 (0.67, 1.7)
4 vs 10
direct
1.2 (0.79, 1.8)
indirect 0.5
0.97 (0.62, 1.5)
network
1.1 (0.81, 1.4)
5 vs 10
direct
1.5 (0.41, 5.8)
indirect 0.478
0.90 (0.59, 1.4)
network
0.95 (0.64, 1.5)
18 vs 11
direct
1.4 (0.79, 2.6)
indirect 0.885
1.6 (0.63, 3.7)
network
1.5 (0.91, 2.4)
0.005
1
15

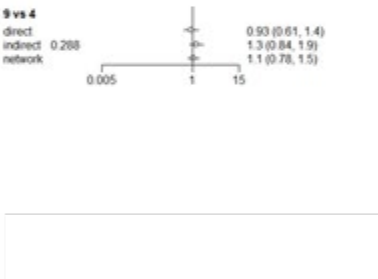

14 vs 13
direct
0.54 (0.20, 1.4)
indirect 0.806
0.46 (0.18, 1.2)
network
0.50 (0.26, 0.96)
4 vs 13
direct
0.78 (0.43, 1.4)
indirect 0.937
0.74 (0.22, 2.3)
network
0.77 (0.46, 1.3)
9 vs 13
direct
3.6e-11 (4.5e-23, 0.25)
indirect 0.0231
0.85 (0.47, 1.6)
network
0.81 (0.45, 1.5)
5 vs 14
direct
1.4 (0.76, 2.6)
indirect 0.798
1.2 (0.37, 4.)
network
1.4 (0.80, 2.3)
0.005
1
15


12 vs 10
direct
1.2 (0.76, 1.9)
indirect 0.769
1.1 (0.59, 1.9)
network
1.1 (0.80, 1.6)
15 vs 10
direct
0.98 (0.37, 2.6)
indirect 0.926
0.93 (0.43, 2.)
network
0.93 (0.52, 1.7)
16 vs 10
direct
0.68 (0.28, 1.7)
indirect 0.21
1.4 (0.74, 2.5)
network
1.1 (0.66, 1.8)
18 vs 10
direct
0.43 (0.10, 1.6)
indirect 0.0872
1.4 (1.0, 2.)
network
1.3 (0.95, 1.8)
0.005
1
15


Contrast P-value
Odds Ratio (95% CrI)
4 vs 3
direct
1.2 (0.64, 2.1)
indirect 0.301
0.57 (0.16, 2.)
network
1.0 (0.60, 1.7)
7 vs 3
direct
0.71 (0.17, 2.8)
indirect 0.237
1.9 (0.80, 4.4)
network
1.4 (0.70, 2.9)
5 vs 4
direct
1.7 (0.97, 3.2)
indirect 0.00538
0.63 (0.44, 0.93)
network
0.87 (0.63, 1.3)
7 vs 4
direct
1.2 (0.59, 2.6)
indirect 0.578
1.7 (0.68, 4.3)
network
1.4 (0.78, 2.5)
0.005
1
15


Contrast P-value
Odds Ratio (95% CrI)
9 vs 18
direct
0.89 (0.60, 1.4)
indirect 0.842
0.83 (0.50, 1.4)
network
0.86 (0.64, 1.2)
3 vs 19
direct
1.5 (0.20, 15.)
indirect 0.952
1.4 (0.61, 3.5)
network
1.4 (0.64, 3.2)
4 vs 19
direct
1.7 (0.48, 6.3)
indirect 0.848
1.5 (0.69, 3.1)
network
1.5 (0.77, 2.8)
4 vs 2
direct
0.42 (0.18, 0.95)
indirect 0.0837
1.1 (0.54, 2.1)
network
0.74 (0.43, 1.2)
0.005
1
15


5 vs 2
direct
1.3 (0.43, 4.)
indirect 0.148
0.51 (0.26, 0.99)
network
0.65 (0.37, 1.2)
4 vs 20
direct
0.88 (0.37, 2.1)
indirect 0.256
0.51 (0.31, 0.80)
network
0.58 (0.39, 0.86)
5 vs 20
direct
0.37 (0.18, 0.76)
indirect 0.265
0.60 (0.36, 1.1)
network
0.51 (0.33, 0.79)
9 vs 21
direct
1.1 (0.65, 2.)
indirect 0.755
0.98 (0.47, 2.1)
network
1.1 (0.69, 1.7)
0.005
1
15


9 vs 4
direct
0.93 (0.61, 1.4)
indirect 0.288
1.3 (0.84, 1.9)
network
1.1 (0.78, 1.5)
0.005
1
15

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Turner 2015

Turner R, Jackson D, Wei Y, Thompson S, Higgins J. Predictive distributions for between-study heterogeneity and simple methods for their application in Bayesian meta-analysis. Statistics in Medicine 2015;34:984-98.

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Codes

The codes below were originally based on information within the TSU evidence synthesis technical support documents (Dias 2011, Dias 2014).

WinBUGS code for fixed effect model

```
# Binomial likelihood, logit link
# Fixed effects model
model{                          # *** PROGRAM STARTS
for(i in 1:ns){                 # LOOP THROUGH STUDIES
    mu[i] ~ dnorm(0,.0001)      # vague priors for all trial baselines
   #mu[i] ~ dnorm(0,.01)        # uninformative, more precise prior for all trial baselines
    for (k in 1:na[i])  {       # LOOP THROUGH ARMS
        r[i,k] ~ dbin(p[i,k],n[i,k])    # binomial likelihood
# model for linear predictor
        logit(p[i,k]) <- mu[i] + d[t[i,k]] - d[t[i,1]]
# expected value of the numerators
        rhat[i,k] <- p[i,k] * n[i,k]
#Deviance contribution
        dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
             +  (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))
      }
# summed residual deviance contribution for this trial
    resdev[i] <- sum(dev[i,1:na[i]])
     }
totresdev <- sum(resdev[])      # Total Residual Deviance
d[1]<-0    # treatment effect is zero for reference treatment
# vague priors for treatment effects
for (k in 2:nt){  d[k] ~ dnorm(0,.0001) }
              # d[k] ~ dnorm(0,.01)         # alternative vague prior for treatment effects
# pairwise ORs and LORs for all possible pair-wise comparisons, if nt>2
for (c in 1:(nt-1)) {
for (k in (c+1):nt) {
     or[c,k] <- exp(d[k] - d[c])
     lor[c,k] <- (d[k]-d[c])
     }
}

# ranking on relative scale
for (k in 1:nt) {
# rk[k] <- nt+1-rank(d[],k) # assumes events are "good"
rk[k] <- rank(d[],k) # assumes events are "bad"
best[k] <- equals(rk[k],1) #calculate probability that treat k is best
for (h in 1:nt){ prob[h,k] <- equals(rk[k],h) } # calculates probability that treat k is h-th
best
}
}                                                       # *** PROGRAM ENDS
```

WinBUGS code for random effects model

```
# Binomial likelihood, logit link
# Random effects model for multi-arm trials
model{                                  # *** PROGRAM STARTS
for(i in 1:ns){                         # LOOP THROUGH STUDIES
    w[i,1] <- 0    # adjustment for multi-arm trials is zero for control arm
```

```
    delta[i,1] <- 0             # treatment effect is zero for control arm
    mu[i] ~ dnorm(0,.0001)           # vague priors for all trial baselines
   #mu[i] ~ dnorm(0,.01)        # uninformative, more precise prior for all trial baselines
    for (k in 1:na[i]) {             # LOOP THROUGH ARMS
        r[i,k] ~ dbin(p[i,k],n[i,k]) # binomial likelihood
        logit(p[i,k]) <- mu[i] + delta[i,k]  # model for linear predictor
        rhat[i,k] <- p[i,k] * n[i,k] # expected value of the numerators
#Deviance contribution
        dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
            +  (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))         }
#  summed residual deviance contribution for this trial
    resdev[i] <- sum(dev[i,1:na[i]])
    for (k in 2:na[i]) {             # LOOP THROUGH ARMS
# trial-specific LOR distributions
        delta[i,k] ~ dnorm(md[i,k],taud[i,k])
# mean of LOR distributions (with multi-arm trial correction)
        md[i,k] <-  d[t[i,k]] - d[t[i,1]] + sw[i,k]
# precision of LOR distributions (with multi-arm trial correction)
        taud[i,k] <- tau *2*(k-1)/k
# adjustment for multi-arm RCTs
        w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]])
# cumulative adjustment for multi-arm trials
        sw[i,k] <- sum(w[i,1:k-1])/(k-1)
      }
  }
totresdev <- sum(resdev[])           # Total Residual Deviance
d[1]<-0       # treatment effect is zero for reference treatment
# vague priors for treatment effects
for (k in 2:nt){  d[k] ~ dnorm(0,.0001)
               # d[k] ~ dnorm(0,.01)         # alternative vague prior for treatment effects
}

# Between-study variance with vague prior
# Comment out to use informative prior instead (below in purple)
sd ~ dunif(0,5)     # vague prior for between-trial SD
tau <- pow(sd,-2)   # between-trial precision = (1/between-trial variance)

#informative prior on between-study variance based on Turner 2015
#outcome: Obstetric outcomes
#intervention type: non-pharma vs. pharma
#tausq.prec <- pow(1.50,-2)           # precision of informative distribution
#tausq ~ dlnorm(-2.49,tausq.prec)     # prior on between-trial variance
#sd <- pow(tausq,0.5)                 # between-trial SD
#tau <- pow(tausq,-1)                 # between-trial precision

# pairwise ORs and LORs for all possible pair-wise comparisons, if nt>2
for (c in 1:(nt-1)) {
for (k in (c+1):nt) {
     or[c,k] <- exp(d[k] - d[c])
     lor[c,k] <- (d[k]-d[c])
     }
}

# ranking on relative scale
for (k in 1:nt) {
# rk[k] <- nt+1-rank(d[],k) # assumes events are "good"
rk[k] <- rank(d[],k) # assumes events are "bad"
best[k] <- equals(rk[k],1) #calculate probability that treat k is best
for (h in 1:nt){ prob[h,k] <- equals(rk[k],h) } # calculates probability that treat k is h-th
best
}

}                                    # *** PROGRAM ENDS
```

WinBUGS code for fixed effect inconsistency model

```
# Binomial likelihood, logit link, inconsistency model
# Fixed effects model
```

```
model{                          # *** PROGRAM STARTS
for(i in 1:ns){                 # LOOP THROUGH STUDIES
    mu[i] ~ dnorm(0,.0001)  # vague priors for trial baselines
   #mu[i] ~ dnorm(0,.01)        # uninformative, more precise prior for all trial baselines
    for (k in 1:na[i])  {   # LOOP THROUGH ARMS
        r[i,k] ~ dbin(p[i,k],n[i,k])    # binomial likelihood
        logit(p[i,k]) <- mu[i] + d[t[i,1],t[i,k]]  # model for linear predictor
#Deviance contribution
        rhat[i,k] <- p[i,k] * n[i,k] # expected value of the numerators
        dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
          +  (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))
      }
# summed residual deviance contribution for this trial
   resdev[i] <- sum(dev[i,1:na[i]])
  }
totresdev <- sum(resdev[])   # Total Residual Deviance
for (k in 1:nt) { d[k,k] <- 0 } # set effects of k vs k to zero
for (c in 1:(nt-1)) {  # priors for all mean treatment effects
    for (k in (c+1):nt)  {
                        d[c,k] ~ dnorm(0,.0001)
                        #d[c,k] ~ dnorm(0,.01)        # alternative vague prior
                        lor[c,k] <- d[c,k]
                        }
  }
} # *** PROGRAM ENDS
```

WinBUGS code for random effects inconsistency model

```
# Binomial likelihood, logit link, inconsistency model
# Random effects model
model{                          # *** PROGRAM STARTS
for(i in 1:ns){                 # LOOP THROUGH STUDIES
    delta[i,1]<-0           # treatment effect is zero in control arm
    mu[i] ~ dnorm(0,.0001)  # vague priors for trial baselines
# mu[i] ~ dnorm(0,.01)        # alternative vague prior for trial baselines
    for (k in 1:na[i])  {   # LOOP THROUGH ARMS
        r[i,k] ~ dbin(p[i,k],n[i,k]) # binomial likelihood
        logit(p[i,k]) <- mu[i] + delta[i,k]  # model for linear predictor
#Deviance contribution
        rhat[i,k] <- p[i,k] * n[i,k] # expected value of the numerators
        dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
          +  (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))
      }
# summed residual deviance contribution for this trial
   resdev[i] <- sum(dev[i,1:na[i]])
   for (k in 2:na[i]) {  # LOOP THROUGH ARMS
# trial-specific LOR distributions
        delta[i,k] ~ dnorm(d[t[i,1],t[i,k]] ,tau)
      }
  }
totresdev <- sum(resdev[])   # Total Residual Deviance
for (c in 1:(nt-1)) {  # priors for all mean treatment effects
    for (k in (c+1):nt)  {
                        d[c,k] ~ dnorm(0,.0001)
          # d[c,k] ~ dnorm(0,.01)            # alternative vague prior for treatment
                        lor[c,k] <- d[c,k]
                        or[c,k] <- exp(d[c,k])
                        }
  }
# Between-study standard deviation with vague prior
# Comment out to use informative prior instead (below in purple)
sd ~ dunif(0,5)  # vague prior for between-trial standard deviation
var <- pow(sd,2) # between-trial variance
tau <- 1/var     # between-trial precision

#informative prior on between-study variance based on Turner 2015
#outcome: Obstetric outcomes
#intervention type: non-pharma vs. pharma
```

```
#tausq.prec <- pow(1.50,-2)          # precision of informative distribution
#tausq ~ dlnorm(-2.49,tausq.prec)    # prior on between-trial variance
#sd <- pow(tausq,0.5)                # between-trial SD
#tau <- pow(tausq,-1)                # between-trial precision
} # *** PROGRAM ENDS
```

Appendix Q – Threshold analysis

Threshold analysis for review question: What are the benefits and harms of pharmacological and mechanical methods in induction of labour?

TSU, Unversity of Bristol (Beatrice Downing, Nicky J. Welton, David Phillippo, Hugo Pedder)

Introduction

The TSU was invited to explore the application of the threshold analysis method (Phillippo 2018, Phillippo 2019) in the Inducing Labour guideline, and to apply the method where relevant. Threshold analysis can be used to assess the robustness of recommendations made to potential limitations in the evidence, when the recommendations are based on an NMA. Such limitations arise because the observed estimates differ from the true effects of interest, for example due to study biases, sampling variation, or issues of relevance. Threshold analysis quantifies precisely how much the evidence could change before the recommendation changes, and what the revised recommendation would be.

Requirements for use of the method are that there is a clear decision rule that is used to base the recommendations on the NMA results. For example: choose the intervention with the highest estimated chance of achieving a vaginal birth in 24 hours of inducing labour. Or: of those interventions with a high chance of achieving vaginal birth in 24 hours, choose the intervention with the lowest risk of hyperstimulation. Currently the methods are only available to be used on one outcome at a time.

In this report, we begin by summarising the preliminary recommendations made by the committee. We then discuss the links between the recommendations and the NMA results to identify decision rules that could be used in the threshold method. For those recommendations where a decision rule could be identified, we perform the threshold analysis and present the results. We end with a brief summary of our findings.

Preliminary recommendations following the committee meeting on 12th February 2021

Explain to the woman that her possible choices of treatment will depend on the readiness of her cervix (recorder as the Bishop score), determined by vaginal examination.

Discuss with the woman the risks of pharmacological methods to induce labour. Include that:

- uterine activity and fetal condition must be monitored regularly
- both dinoprostone and misoprostol can cause hyperstimulation, but the risk may be higher with misoprostol

- if hyperstimulation does occur, further administration should be avoided (either by giving no further oral tablets, or by removal of vaginally administered products when possible)
- there are differences in the ease with which different vaginal products can be removed
- hyperstimulation can be treated with tocolysis, but hyperstimulation caused by misoprostol may be more difficult to reverse.

Follow the manufacturers' guidance on the use of dinoprostone and misoprostol preparations for the induction of labour, including when to remove dinoprostone controlled-release vaginal delivery systems.

For women with a Bishop score of 6 or less, offer induction of labour with dinoprostone as vaginal tablet, vaginal gel or controlled-release vaginal delivery system

For women with a Bishop score of 6 or less, consider a mechanical method to induce labour (for example, a balloon catheter) if:

- pharmacological methods are not suitable (for example, in women with a higher risk of hyperstimulation or those who have had a previous caesarean birth) or
- the woman chooses to use a mechanical method.

For women with a Bishop score of 6 or less who wish to continue with induction of labour in preference to a caesarean birth when induction with dinoprostone has not led to an adequate change in the Bishop score, consider misoprostol.

For women with a Bishop score of more than 6, offer induction of labour with amniotomy and an intravenous oxytocin infusion.

Threshold analysis

The committee were asked which interventions were relevant decision options in the UK. They did not consider mifeprostol or NO to be decision options. These options are excluded from the discussions below, although are retained in the evidence base for the NMA.

Recommendation: For women with a Bishop score of 6 or less who wish to continue with induction of labour in preference to a caesarean birth when induction with dinoprostone has not led to an adequate change in the Bishop score, consider misoprostol.

Decision rule linking recommendations to NMA results

This recommendation was informed by the high hyperstimulation risk associated with misoprostol, whilst recognising its efficacy for achieving a vaginal birth. There is a high degree of uncertainty in the relative intervention effect estimates for hyperstimulation (Fig 1), caused partly by low event rates. The NMA evidence for misoprostol included a wide variety of doses and modes of delivery including: Vaginal misoprostol <50mcg; Vaginal misoprostol>50mcg; Oral misoprostol<50mcg; Oral misoprostol>50mcg; Titrated oral misoprostol; Sustained release misoprostol; Buccal misoprostol. For some of the misoprostol interventions the NMA estimated a high risk of hyperstimulation (Buccal misoprostol, Sustained release misoprostol, Vaginal misoprostol>50mcg) compared with placebo.

However, the other misoprostol interventions had a similar hyperstimulation risk to the prostaglandin interventions, with slightly improved efficacy for achieving a vaginal birth within 24 hours. IV oxytocin and amniotomy also had a high hyperstimulation risk, but was still recommended for the subgroup with Bishop score > 6 (see below) due to it being more effective at achieving a vaginal birth within 24 hours than the other interventions.

We were unable to identify a clear decision rule linking the recommendation to the NMA evidence for hyperstimulation. The high degree of uncertainty in the NMA estimates for hyperstimulation and the considerable number of loops of evidence in which inconsistency was identified make it difficult to use these results for decision making. The recommendations were based on a consideration of multiple outcomes, together with clinical experience of hyperstimulation risk with the misoprostol options available in the UK.

We therefore do not feel it is possible or helpful to conduct a threshold analysis for this recommendation. However, we note that the very wide credible intervals around the effect estimates, and high degree of overlap, indicate that the determination of the "worst" interventions for the hyperstimulation outcome are likely to be sensitive to potential changes or biases in the evidence. We also note that misoprostol is not a single intervention, but can be delivered in various forms, and efficacy and safety varies across these different modes of intervention.

Recommendation: For women with Bishop score of 6 or less offer induction of labour with dinoprostone as tablet, gel or controlled-release vaginal delivery system

For women with a Bishop score of 6 or less, consider a mechanical method to induce labour (for example, a balloon catheter) if:

- **pharmacological methods are not suitable (for example, in women with a higher risk of hyperstimulation or those who have had a previous caesarean birth) or**
- **the woman chooses to use a mechanical method.**

Decision rule linking recommendations to NMA results

For the subgroup of women with Bishop score ≤ 6, having excluded misoprostol in the earlier recommendation, of the remaining interventions the following were recommended: all PGE2 interventions as well as double balloon/Cooks catheter and Foley catheter (representing 7 interventions from the NMA recommended in total). Laminaria tent was also recommended, but there is no evidence from the NMA on vaginal delivery within 24 hours for this intervention. Interventions in the set of decision options not recommended for this subgroup are: IV oxytocin on the basis of both hyperstimulation and poor outcomes for vaginal delivery in 24h and IV oxytocin + amniotomy on the basis of hyperstimulation and lack of evidence for vaginal delivery in 24h. This recommendation is in line with the NMA evidence (Fig 2) if misoprostol is excluded from consideration.

To assess the robustness of the decision to the NMA evidence, a threshold analysis was conducted on the No Vaginal Delivery within 24 hours outcome in the unfavourable cervix sub-group (excluding misoprostol, mifepristone, and NO), where the decision rule is to recommend the top 7 interventions. If the top 7 interventions change, this implies that one of the non-recommended interventions would be recommended in place of one of the currently recommended interventions. This allows us to assess how robust this recommendation is to changes in the evidence.

Threshold analysis results

The threshold analysis results are presented in Fig. 3, which shows, for: (a) each study (Fig 3a); and (b) each pair of interventions ("contrast") where we have evidence (Fig. 3b); the range of values for which the evidence from that contrast could change without changing the recommendations. Fig 3 also shows the intervention the recommendation would switch to, in this case the intervention that would replace the top seven interventions. Fig 3 highlights in pink where the recommendations change for (a) study estimates or (b) contrast estimates that are within their credibility limits (ie within sampling error). It can be seen that the recommendations are robust to changes in individual study estimates (fig 3a), but sensitive to plausible changes in the contrast-level evidence for IV Oxytocin vs vPGE2_gel; IV Oxytocin vs vMiso_a50; vMiso_a50 vs vPGE2_tab; and IV Oxytocin vs vMiso_b50 (Fig 3b). In each case the recommendation is likely to change to the inclusion of IV Oxytocin in the recommendation. All remaining contrasts have thresholds larger than a factor of 3 on the odds ratio scale (1.11 on log OR scale); any changes to the evidence on these contrasts are unlikely to affect the recommendation.

Recommendation: For women with a Bishop score of 6 or less, consider a mechanical method to induce labour (for example, a balloon catheter) if:

- **pharmacological methods are not suitable (for example, in women with a higher risk of hyperstimulation or those who have had a previous caesarean birth) or**
- **the woman chooses to use a mechanical method.**

Decision rule linking recommendations to NMA results

The second part of this recommendation links to the NMA results for hyperstimulation, which show that double balloon/Cooks catheter, laminaria tent, and Foley catheter are the top 3 interventions for avoiding hyperstimulation, when NO is excluded as a decision option (Fig 4). We can therefore conduct a threshold analysis on the hyperstimulation outcome in the subgroup of women with Bishop score ≤ 6 (excluding misoprostol, mifepristone, and NO), where the decision rule is to recommend the top 3 interventions. Placebo and no treatment were also excluded from this analysis, as they were not found to be effective, and are not expected to have a hyperstimulation risk. If the top 3 interventions change, this implies that one of the non-recommended interventions would become recommended in place of one of the currently recommended interventions. This allows us to assess how robust this recommendation is to changes in the evidence.

Foley catheter appears to have a slightly higher hyperstimulation risk than double balloon and laminaria tent, and so an additional threshold analysis was conducted where the decision rule is to recommend the top 2 interventions (double balloon/Cooks catheter and laminaria tent).

Threshold analysis results

It was not possible to obtain reliable results from the threshold analysis at the contrast level for the hyperstimulation outcome. This is due to the very high levels of heterogeneity, together with the high levels of uncertainty in the NMA estimates (due to the low event count in many of the included studies). It was possible to conduct threshold analyses at the study level using continuity-corrected data, reported in Fig. 5 for the top 3 decision rule (Fig 5a) and the top 2 decision rule (Fig 5b), which show that the decision is sensitive to changes in the study estimates. When using the top 3 decision rule (double balloon/Cooks catheter, laminaria tent, and Foley catheter) the recommendation is most likely to change to IV

Oxytocin + amniotomy in the top 3. When using the top 2 decision rule (double balloon/Cooks catheter and laminaria tent) the recommendation is most likely to change to Foley catheter or IV Oxytocin + amniotomy in the top 2.

Recommendation: For women with Bishop score of more then 6, offer induction of labour with amniotomy and intravenous oxytocin infusion

Decision rule linking recommendations to NMA results

For subgroup of women with Bishop score > 6, less weight was placed on the risk of hyperstimulation, and therefore the recommendation to offer IV oxytocin + amniotomy was based on the No Vaginal Delivery within 24 hours outcome, where this intervention was seen to be most effective in achieving a vaginal delivery within 24 hours (Fig 6). We can therefore conduct a threshold analysis on the No Vaginal Delivery within 24 hours outcome (excluding misoprostol, mifepristone, and NO), where the decision rule is to recommend the top 1 intervention. If the top intervention changes, this implies one of the non-recommended interventions would be recommended in place of the currently recommended intervention. This allows us to assess how robust this recommendation is to changes in the evidence.

Threshold analysis results

The threshold analysis results are presented in Fig. 7, which shows, for (a) each study and (b) each pair of interventions ("contrast") where we have evidence, the range of values for which the evidence from that (a) study or (b) contrast could change without changing the recommendations. Fig 7 also shows the intervention the recommendation would switch to. Fig 7 highlights in pink where the recommendations change for (a) study estimates and (b) contrast estimates that are within their credibility limits (ie within sampling error). It can be seen that the recommendations are robust to changes in the individual study estimates, but sensitive to changes in the contrast-level evidence for Foley Catheter vs vPGE2_norm; oMiso_tit vs vPGE2_norm; and bMiso vs IV Oxytocin + Amniotomy. In each case the recommendation is likely to change to vPGE2_norm in the recommendation. Thresholds for all other contrasts correspond to a factor of 2.7 or greater on the odds ratio scale (0.98 on the log OR scale), and so any changes in the evidence on these contrasts are unlikely to affect the recommendation.

Conclusions

The evidence relating to hyperstimulation is very uncertain and heterogeneous, and it is difficult to make robust recommendations based on the NMA evidence alone. The conclusion that double balloon/cooks catheter, laminaria tent, and Foley catheter have lower hyperstimulation risk than other induction options is sensitive to changes in the evidence. The recommendation is most likely to change to IV oxytocin + amniotomy, however we note that this is likely due to the very wide credible intervals for this intervention, and so simply reflects the high level of uncertainty.

For the subgroup of women with Bishop score ≤ 6, the recommendation to offer PGE2 (or Balloon catheter or laminaria tent if the risks of hyperstimulation are high) was sensitive to changes in the evidence, with the most likely change in the recommendation being to include IV oxytocin.

For the subgroup of women with Bishop score > 6, the recommendation to offer Amniotomy + IV Oxytocin was found to be sensitive to changes in the evidence, with the most likely change in the recommendation being to vaginal PGE2 pessary "normal".

References

Phillippo 2018
Phillippo DM, Dias S, Ades AE, Didelez V, Welton NJ. *Sensitivity of treatment recommendations to bias in network meta-analysis*. JRSSA. 2018. 181:843-867. https://doi.org/10.1111/rssa.12341

Phillippo 2019

Phillippo DM, Dias S, Welton NJ, Caldwell DM, Taske N, Ades AE. *Confidence in recommendations based on Network Meta-Analysis: threshold analysis as an alternative to GRADE NMA in guideline development.* Annals of Internal Medicine 2019. 170: 538-546. DOI: 10.7326/M18-3542

Figures

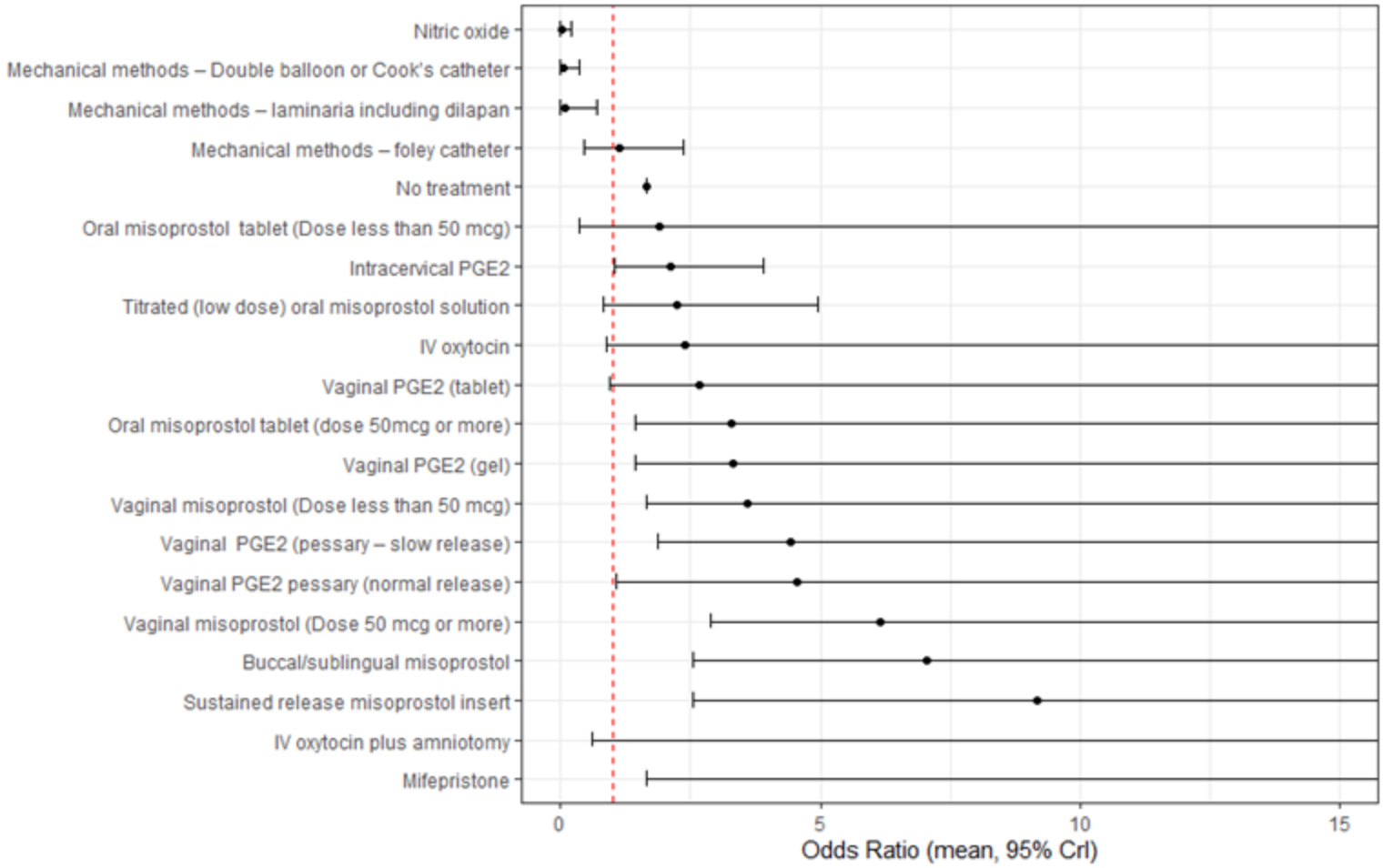

Fig.1 *Odds Ratios relative to placebo for the Hyperstimulation outcome from the Network Meta-Analysis, all women. Note that due to low event rates are the estimated odds ratios for IV oxytocin with amniotomy and mifepristone are too large to be plotted with very wide uncertainty limits (effectively not these effects are not estimable).*

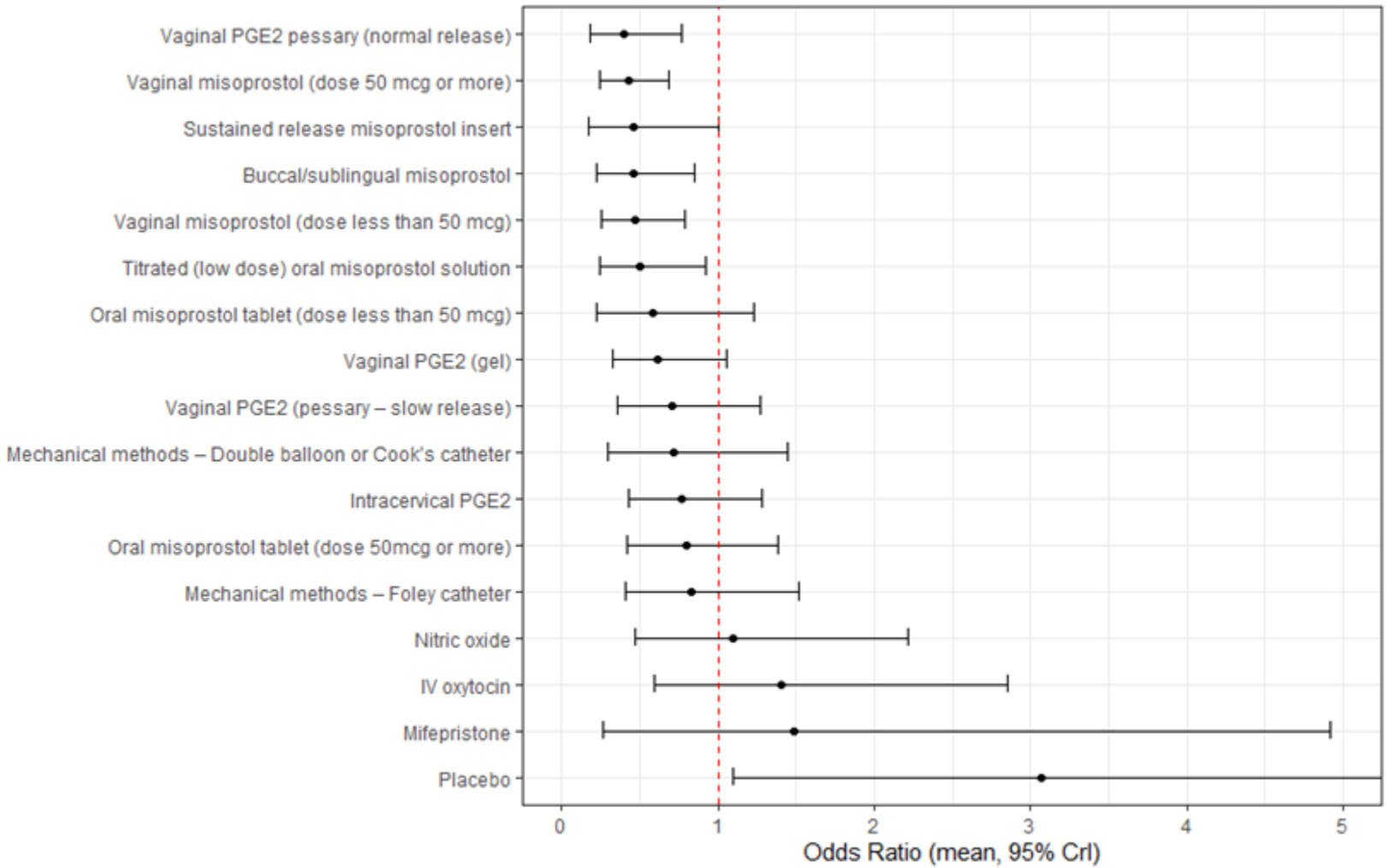

Fig 2 *Odds ratios relative to vaginal PGE2 tablet for the No Vaginal Delivery within 24 hours outcome in the subgroup of women with Bishop score ≤ 6*

Fig 3a

Study (Contrast)	Log−odds ratio	95% Confidence Interval		Invariant Interval	
Sifakis 2007. (8 vs. 2)	−0.40	(−0.81, 0.01)	13	(−2.69, NT)	–
Jackson 1994. (13 vs. 3)	0.65	(0.02, 1.29)	13	(−1.75, 199.20)	1
Kim 2000. (8 vs. 2)	−1.08	(−1.99, −0.18)	13	(−3.86, NT)	–
Rix 1996. (5 vs. 2)	0.25	(−0.30, 0.80)	13	(−2.70, NT)	–
Tabasi 2007. (13 vs. 8)	1.24	(0.44, 2.03)	13	(−1.83, NT)	–
Nayak 2015. (5 vs. 2)	−1.65	(−2.45, −0.86)	13	(−4.77, NT)	–
De Aquino 2003. (13 vs. 7)	0.88	(0.25, 1.51)	13	(−2.30, 84.16)	1
Aalami−Harandi 2013. (13 vs. 11)	0.89	(0.33, 1.45)	13	(−2.45, 183.04)	1
Charoenkul 2000. (8 vs. 2)	−0.30	(−1.01, 0.40)	13	(−4.00, NT)	–
Al−Sebai 1993. (3 vs. 2)	−0.53	(−1.48, 0.42)	13	(−4.54, NT)	–
Bollapragada 2009. (14 vs. 1)	−0.09	(−0.64, 0.47)	–	(NT, 6.50)	1
Moodley 2003. (7 vs. 3)	−0.00	(−0.49, 0.48)	–	(NT, 7.23)	13
Nigam 2004. (13 vs. 10)	−0.37	(−2.23, 1.48)	13	(−8.21, 1194.66)	1
Papanikolaou 2004. (8 vs. 2)	−1.82	(−3.96, 0.32)	13	(−10.31, NT)	–

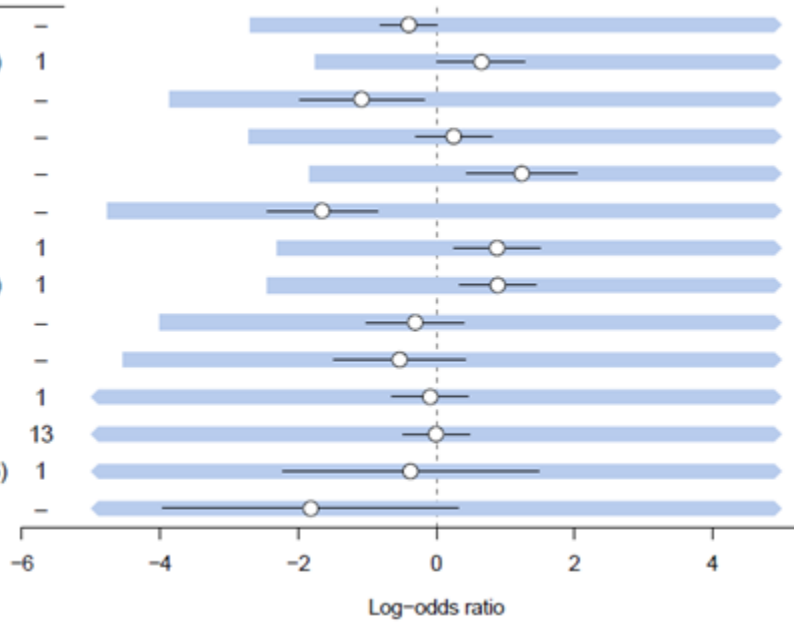

Fig 3b

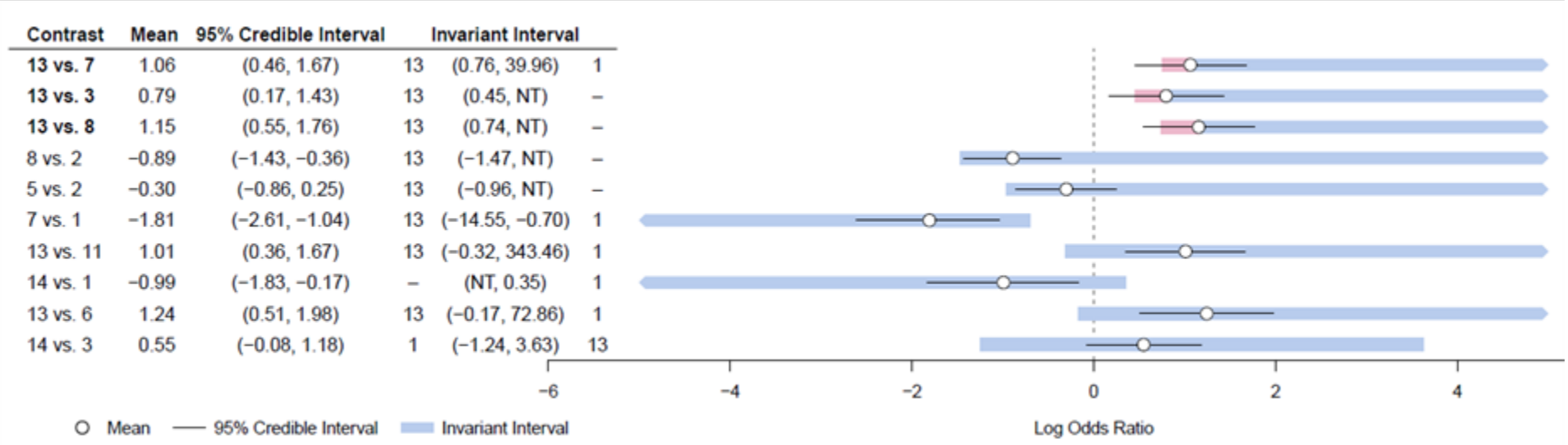

Fig. 3b *Threshold analysis results by (a) study and (b) contrast for: No Vaginal Delivery within 24 hours in the subgroup of women with Bishop score ≤ 6, by intervention contrast, sorted by increasing threshold magnitude. The optimal decision rule is to recommend all PGE2 interventions as well as double balloon/Cooks catheter and Foley catheter. The study / contrast estimate (labelled "Mean") and credible intervals are shown by the black lines. The blue shaded areas show the invariant interval where the optimal set of recommended interventions does not change, and the intervention that would enter the recommended intervention set is indicated by the figures either side of the invariant interval. The pink area indicates where the recommendations changes within the credible limits of the current estimates. Intervention codes are: 1=Plac, 2=vPGE2_tab, 3=vPGE2_gel, 4=vPGE2_slow, 5=icPGE2, 6=vPGE2_norm, 7=vMiso_b50, 8=vMiso_a50, 9=oMiso_b50, 10=oMiso_a50, 11=oMiso_tit, 12=iMiso, 13=ivOxy, 14=NO, 15=Mife, 16=mFolCat, 17=mDblBal, 18=bMiso. NT = No Threshold, no change to the evidence in this direction could lead to a new decision.*

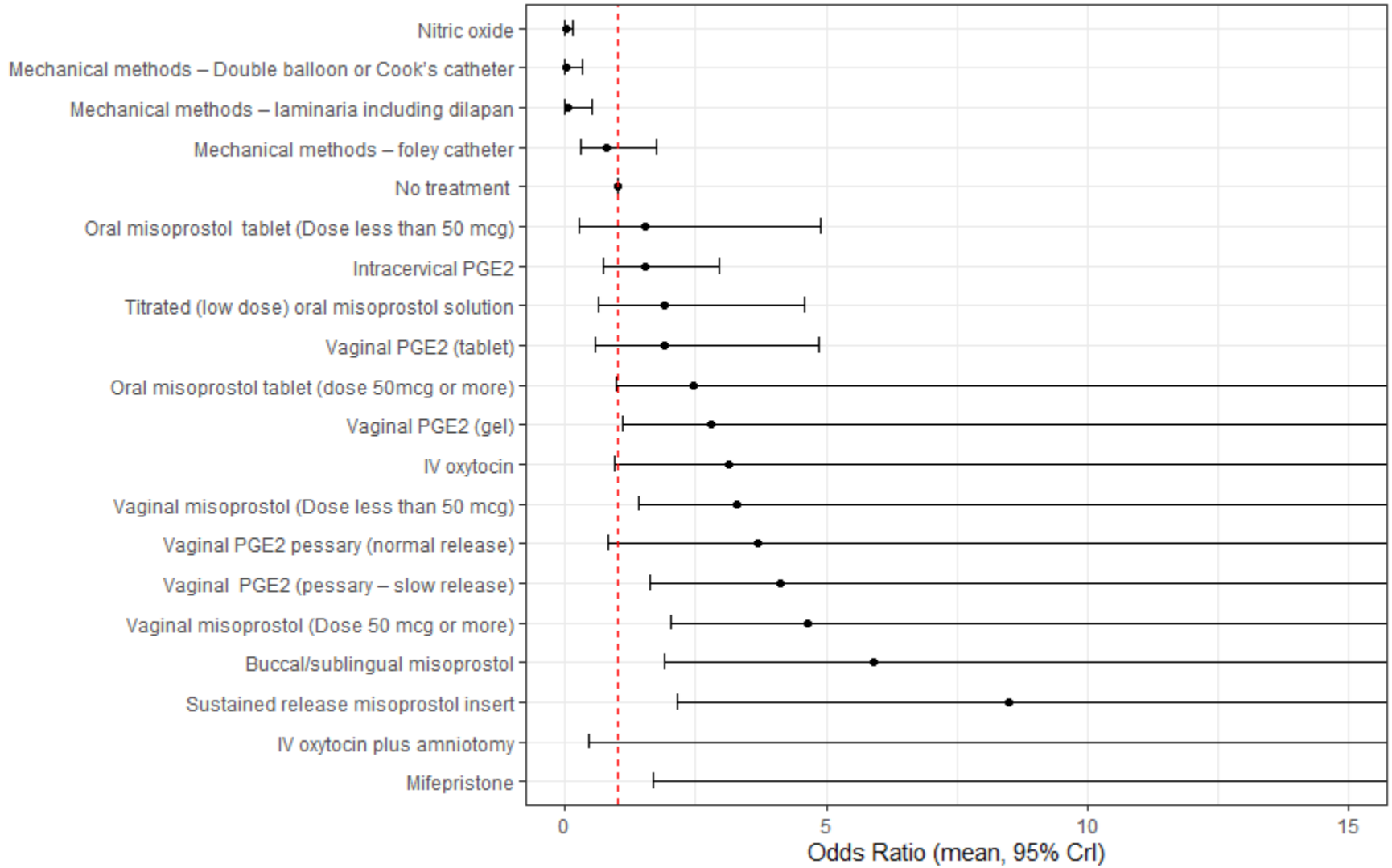

Fig. 4 *Odds Ratios relative to placebo for Hyperstimulation from the Network Meta-Analysis in subgroup of women with Bishop score ≤ 6*

Fig 5a

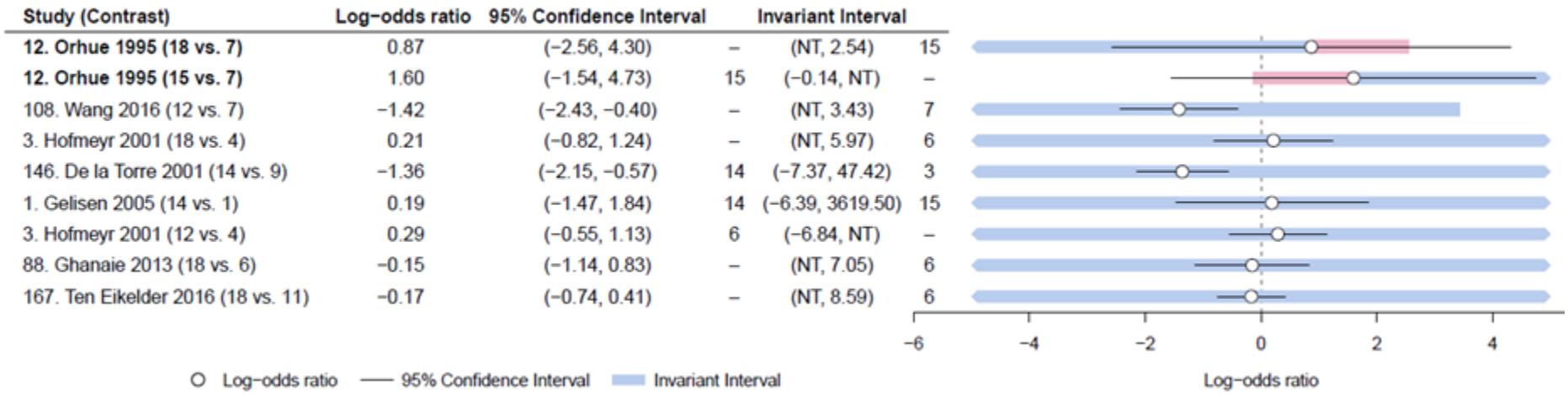

Fig 5b

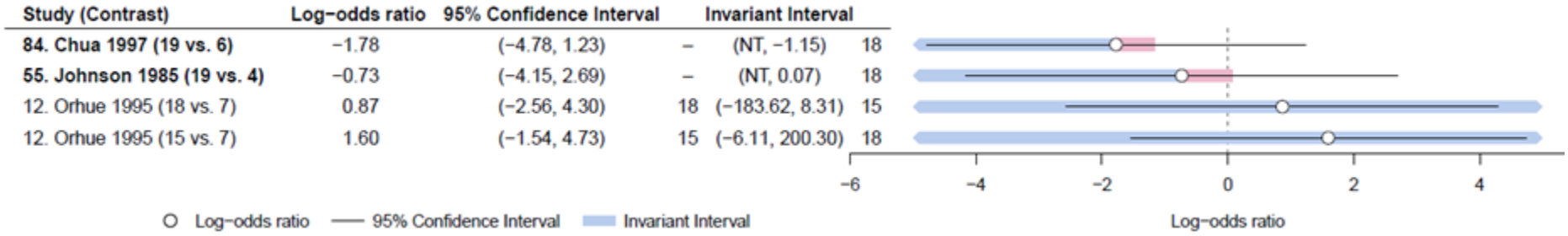

Fig. 5 *Threshold analysis results by study for Hyperstimulation, all women, sorted by increasing threshold magnitude. The optimal decision rule is to recommend (a) "top 3": double balloon/Cooks catheter, laminaria tent, and Foley catheter, and (b) "top 2": double balloon/Cooks catheter and laminaria tent. The study estimate (labelled "Mean") and credible intervals are shown by the black lines. The blue shaded areas show the invariant interval where the optimal set of recommended interventions does not change, and the intervention that would enter the recommended intervention set is indicated by the figures either side of the invariant interval. The pink area indicates where the recommendations changes within the credible limits of the current estimates. Intervention codes are: 1=Placebo, 2=NoTrt, 3=vPGE2_tab, 4=vPGE2_gel, 5=vPGE2_slow, 6=icPGE2, 7=vPGE2_norm, 8=vMiso_b50, 9=vMiso_a50, 10=oMiso_b50, 11=oMiso_a50, 12=oMiso_tit, 13=iMiso, 14=ivOxy, 15=ivOxyAmnio, 16=NO, 17=Mife, 18=mFolCat, 19=mLam, 20=mDblBal, 21=bMiso. NT = No Threshold, no change to the evidence in this direction could lead to a new decision.*

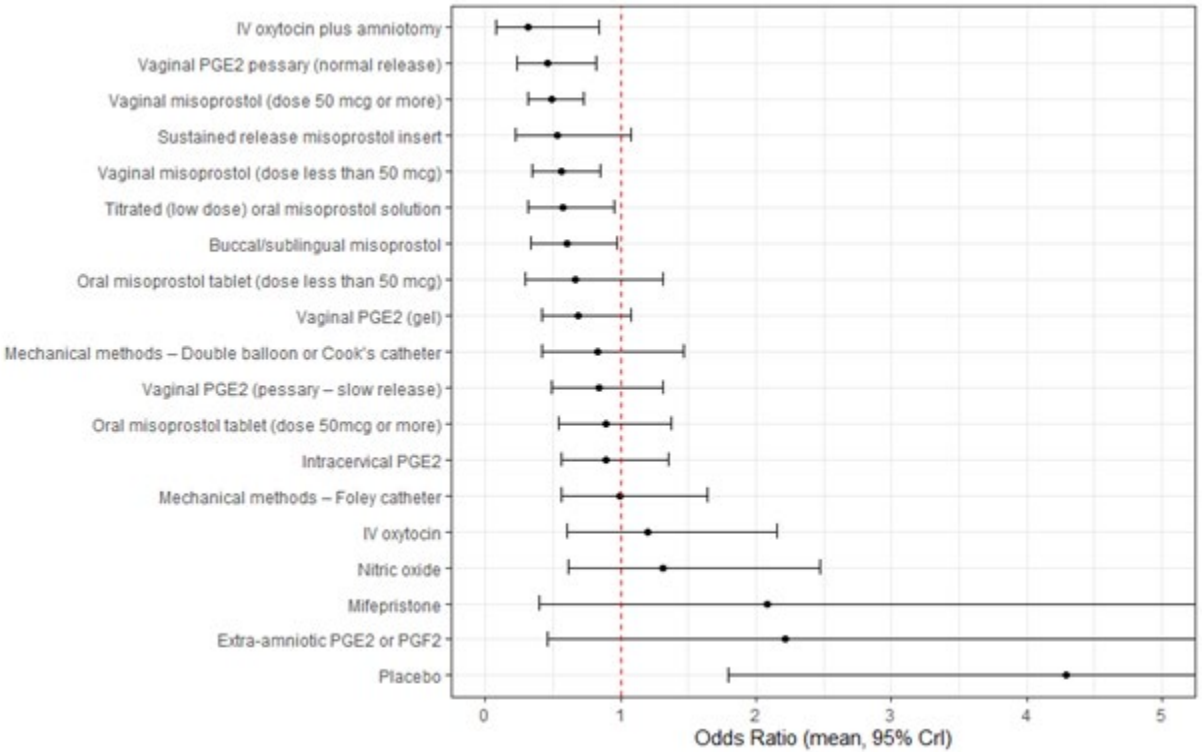

***Fig 6**. Odds Ratios relative to vaginal PGE2 tablet for the No Vaginal Delivery within 24 hours outcome from the Network Meta-Analysis in all women*

Fig 7a

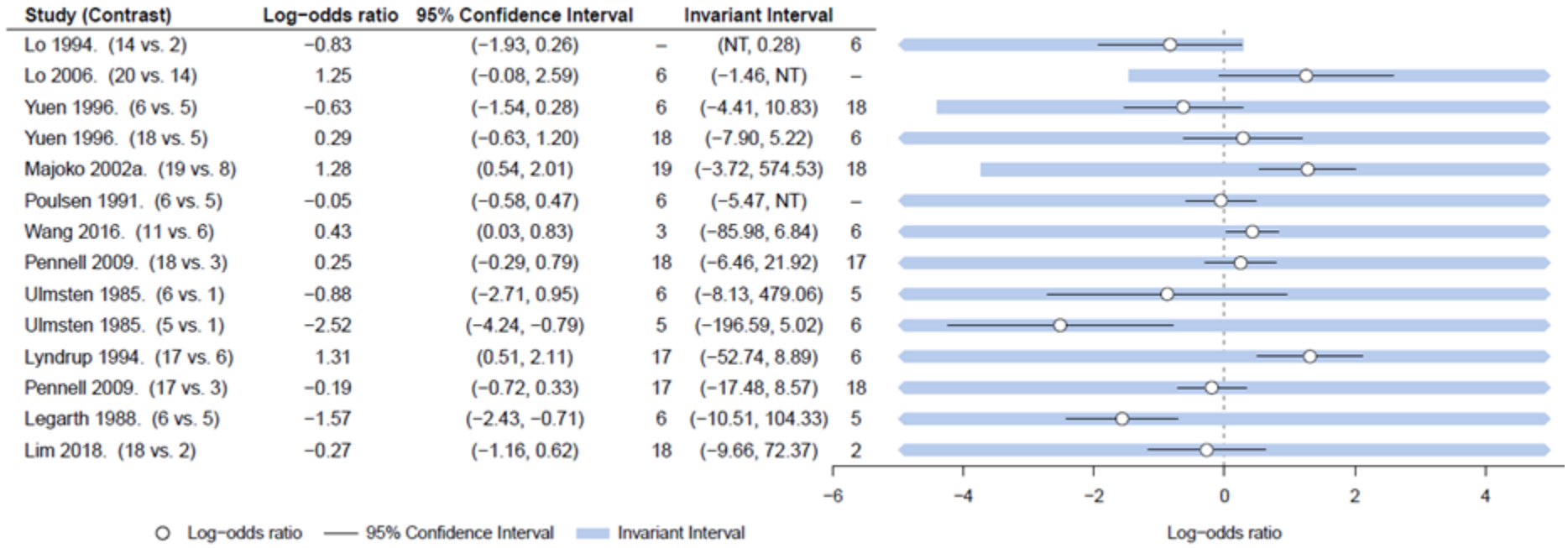
Study (Contrast)
Log−odds ratio
95% Confidence Interval
Invariant Interval
Lo 1994. (14 vs. 2) −0.83 (−1.93, 0.26) – (NT, 0.28) 6
Lo 2006. (20 vs. 14) 1.25 (−0.08, 2.59) 6 (−1.46, NT) –
Yuen 1996. (6 vs. 5) −0.63 (−1.54, 0.28) 6 (−4.41, 10.83) 18
Yuen 1996. (18 vs. 5) 0.29 (−0.63, 1.20) 18 (−7.90, 5.22) 6
Majoko 2002a. (19 vs. 8) 1.28 (0.54, 2.01) 19 (−3.72, 574.53) 18
Poulsen 1991. (6 vs. 5) −0.05 (−0.58, 0.47) 6 (−5.47, NT) –
Wang 2016. (11 vs. 6) 0.43 (0.03, 0.83) 3 (−85.98, 6.84) 6
Pennell 2009. (18 vs. 3) 0.25 (−0.29, 0.79) 18 (−6.46, 21.92) 17
Ulmsten 1985. (6 vs. 1) −0.88 (−2.71, 0.95) 6 (−8.13, 479.06) 5
Ulmsten 1985. (5 vs. 1) −2.52 (−4.24, −0.79) 5 (−196.59, 5.02) 6
Lyndrup 1994. (17 vs. 6) 1.31 (0.51, 2.11) 17 (−52.74, 8.89) 6
Pennell 2009. (17 vs. 3) −0.19 (−0.72, 0.33) 17 (−17.48, 8.57) 18
Legarth 1988. (6 vs. 5) −1.57 (−2.43, −0.71) 6 (−10.51, 104.33) 5
Lim 2018. (18 vs. 2) −0.27 (−1.16, 0.62) 18 (−9.66, 72.37) 2
−6
−4
−2
0
2
4
Log−odds ratio
Log−odds ratio
95% Confidence Interval
Invariant Interval
Log−odds ratio

Fig 7b

Contrast	Mean	95% Credible Interval		Invariant Interval	
17 vs. 6	0.79	(0.22, 1.35)	17	(−1.18, 1.17)	6
11 vs. 6	0.23	(−0.33, 0.79)	3	(−10.73, 0.69)	6
14 vs. 2	−1.33	(−2.52, −0.17)	–	(NT, −0.84)	6
20 vs. 14	0.78	(−0.40, 1.96)	6	(0.04, NT)	–
18 vs. 4	−0.03	(−0.59, 0.54)	18	(−0.96, 2.93)	4
6 vs. 5	−0.69	(−1.17, −0.20)	6	(−1.87, 27.32)	5
13 vs. 7	0.74	(0.23, 1.25)	13	(−1.05, 33.90)	5
19 vs. 8	1.30	(0.03, 2.58)	19	(−0.55, 1117.48)	18
18 vs. 5	−0.10	(−0.66, 0.45)	18	(−2.34, 13.18)	5
13 vs. 8	0.87	(0.35, 1.39)	13	(−1.43, 23.68)	19
4 vs. 3	0.19	(−0.20, 0.58)	4	(−2.24, 2.79)	3
10 vs. 2	−0.15	(−0.61, 0.31)	6	(−2.82, 6.72)	2
5 vs. 2	−0.13	(−0.58, 0.30)	6	(−3.04, 10.96)	2
13 vs. 6	0.95	(0.29, 1.62)	13	(−8.43, 4.08)	6
8 vs. 2	−0.74	(−1.16, −0.32)	6	(−3.99, 8.07)	2
18 vs. 3	0.17	(−0.39, 0.72)	18	(−3.27, 11.68)	3
15 vs. 1	−1.17	(−1.95, −0.41)	19	(−69.47, 2.83)	1
3 vs. 2	−0.40	(−0.88, 0.07)	6	(−5.48, 16.14)	2
18 vs. 2	−0.24	(−0.87, 0.38)	18	(−5.40, 31.42)	2
17 vs. 4	0.17	(−0.27, 0.62)	17	(−5.26, 7.57)	4
20 vs. 8	0.19	(−0.17, 0.56)	–	(NT, 5.66)	6
7 vs. 4	−0.40	(−0.74, −0.05)	13	(−79.09, 5.53)	4
20 vs. 13	−0.68	(−1.25, −0.11)	–	(NT, 6.03)	13
5 vs. 1	−1.51	(−2.22, −0.83)	5	(−75.99, 5.50)	1
11 vs. 10	−0.45	(−0.88, −0.02)	6	(−7.68, NT)	–
11 vs. 7	0.01	(−0.37, 0.40)	6	(−7.26, 3415.88)	1
15 vs. 3	0.61	(0.01, 1.21)	1	(−10.58, 8.02)	3
5 vs. 3	0.27	(−0.06, 0.59)	5	(−15.83, 7.98)	3
7 vs. 1	−1.99	(−2.71, −1.30)	17	(−806.56, 6.13)	1
13 vs. 3	0.53	(0.00, 1.07)	13	(−8.51, 20.85)	3

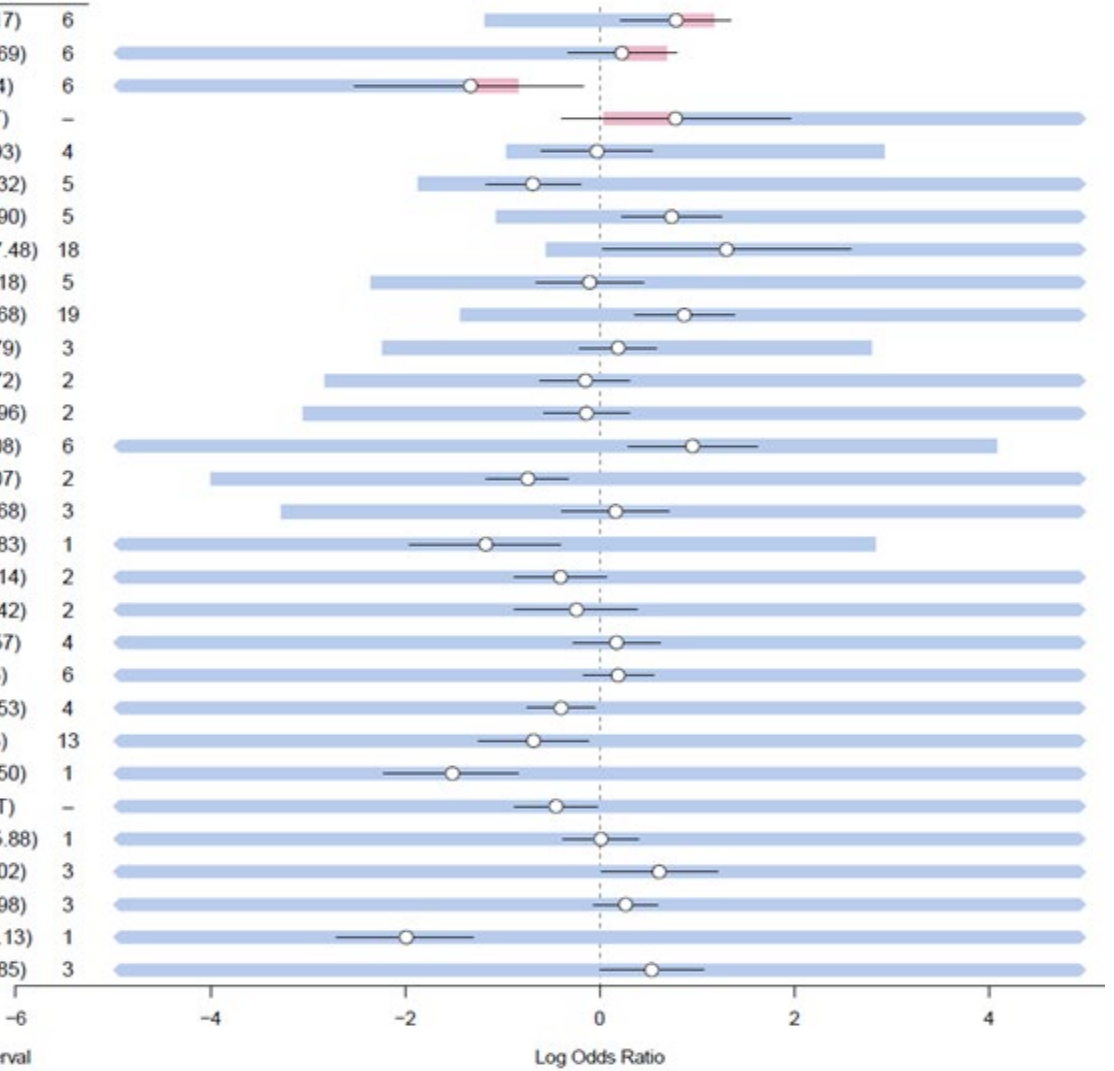

Fig. 7 *Threshold analysis results for No Vaginal Delivery within 24 hours (all women) by (a) study and (b) intervention contrast, sorted by increasing threshold magnitude. The optimal decision rule is to recommend Amniotomy + IV Oxytocin. The study / contrast estimate (labelled "Mean") and credible intervals are shown by the black lines. NT = No Threshold, no change to the evidence in this direction could lead to a new decision. The intervention that would enter the recommended intervention set is indicated by the figures either side of the invariant interval. The blue shaded areas show the invariant interval where the optimal decision set does not change. The pink area indicates where the recommendations changes within the credible limits of the current estimates. Intervention codes are: 1=Plac, 2=vPGE2_tab, 3=vPGE2_gel, 4=vPGE2_slow, 5=icPGE2, 6=vPGE2_norm, 7=vMiso_b50, 8=vMiso_a50, 9=oMiso_b50, 10=oMiso_a50, 11=oMiso_tit, 12=iMiso, 13=ivOxy, 14=ivOxyAmnio, 15=NO, 16=Mife, 17=mFolCat, 18=mDblBal, 19=eaPGE2PGF2, 20=bMiso*