Induction of labour: towards a tailormade approach

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Methods for induction of labour

towards a tailormade approach

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Methods for induction of labour

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een oproep tot maatwerk

(met een samenvatting in het Nederlands)

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1 Chapter

General introduction and outline of this thesis

Induction of labour – "For the times they are a-changing"[1]

Labour induction is a common procedure, which was introduced in the 1780's into obstetric practice, initially for very limited medical indications [2]. For a long time induction of labour was only carried out in high-risk pregnancies in the interest of the patient and fetal wellbeing, when the risk of continuing pregnancy outweighed the benefits. However, in the last decades induction of labour is being utilised for less urgent medical indications. Also, the procedure is used more and more at request of patients to shorten the duration of pregnancy or to time the birth of the baby according to the convenience of the patient, partner and healthcare workers [3]. As a consequence worldwide, the numbers of labour induction have increased drastically. In the United States numbers have risen from 9.6% in 1990 to 31.4% in 2020 [4,5]. In the United Kingdom, in 2020, up to 33% of all labour was induced [6]. Also, in the Netherlands 27% of all deliveries are induced [7]. Although rates are generally lower in low- or middle income countries for various reasons, in some settings they can be as high as those observed in high income countries [3].

As the characteristics of patients being induced are changing, this also applies to the time in which we live. which we think is characterised by social engineering and abandoning paternalistic thinking. These changes also influence the decisions we make about the methods we choose to induce labour. In the past, when mainly patients with high risk pregnancies were induced, it was important that the method used for labour induction was fast and effective. Therefore, duration of induction and labour was a frequently chosen primary outcome in trials studying and comparing induction methods. Nowadays, in settings where labour is frequently induced in relatively low-risk pregnancies, safety outcomes of the patient and the neonate are becoming far superior to duration of labour, but also patient satisfaction with the method used becomes increasingly important. And with different induction methods to choose from, each with its own advantages and disadvantages, asks for a more tailor made approach in choosing the most suitable induction method instead of one method that suits all.

The three recommended induction methods in most recent guidelines are a balloon catheter, prostaglandin E2 (PGE2) or prostaglandin E1 (misoprostol) [3,8-10]. However, most of these guidelines are outdated and don't take into account characteristics of the person and unborn child, personal preferences, nor the option of counselling couples and helping them choose the optimal method for induction in their specific situation. But, to inform, advice and counsel people in choosing the most suitable induction method, a clinician has to know the advantages and disadvantages of the different methods at their disposal, but also how these methods perform in specific subgroup of pregnant individuals. The working mechanisms of the methods and their potential (dis)advantages will be shortly discussed below.

Balloon catheter

Mechanical methods were the first methods developed to ripen the cervix and induce labour [11]. Devices that were used in this context were the standard single balloon catheter (Foley balloon), specially developed double balloon catheters (Cook® balloon or ATAD® catheter) or laminaria tents [12]. These devices are introduced into the cervical canal or through the cervix into the extra-amniotic space. The balloon is then filled with fluid to keep in place, where in some clinics traction is applied (see figure 1). The goal of mechanical induction is to ripen the cervix, which can be achieved directly through dilatation of the cervix and indirectly by increasing prostaglandin or oxytocin secretion [13].

After partially being substituted by pharmacological methods in the 1970's, mechanical induction with a balloon catheter has gained popularity as more recent studies showed this method has a favourable safety profile [14,15]. The shifting in popularity began after the publication of the PROBAAT-study, a Dutch multicentred randomised controlled trial between a 30cc Foley balloon catheter and vaginal PGE2 regarding safety and efficiency. No difference was found in mode of delivery between the two methods, although uterine hyperstimulation occurred less often with the use of a Foley balloon catheter [14]. Even though the caesarean section rates were equal between the two methods, fewer caesarean sections were performed for fetal distress when a balloon catheter was used. The publication of this study was the instigator for more studies on mechanical induction with a balloon catheter. Nowadays, the balloon catheter has vastly grown out to be the number one used induction method in some countries, including the Netherlands [16].

Apart from the reduction in adverse events such as uterine hyperstimulation, and as a consequence having the potential to reduce fetal distress and improve neonatal outcomes , other advantages of this method is being widely available and low in cost. A disadvantage of induction with a balloon catheter is a potential longer induction to delivery interval, which is mainly caused by a prolonged stage of cervical ripening. During this period, patients are mostly admitted to the hospital for sometimes several days. Considering the safety of this method and the low risk of uterine hyperstimulation, especially during the stage of cervical ripening, provides an opportunity for induction in a combined hospital and outpatient setting (at home), which now also has become common practice in most Dutch clinics [16,17].

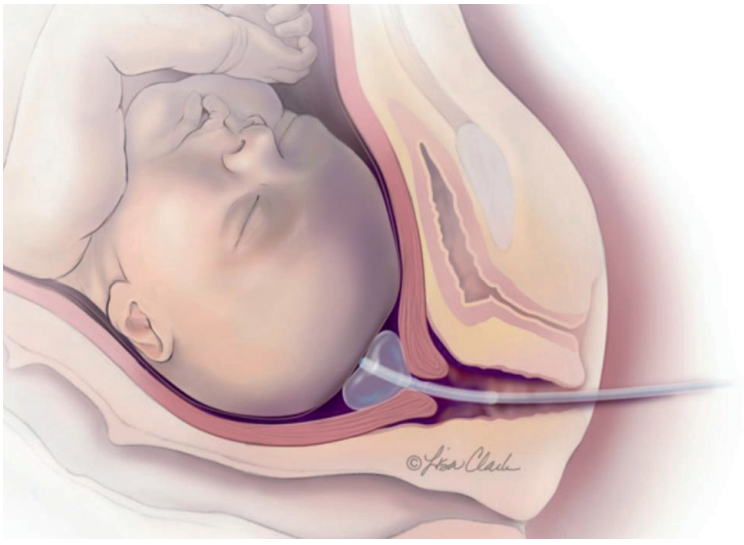

Figure 1: Foley balloon catheter placed beyond the internal ostium and filled with saline. (available from Clark medical illustrations)

Prostaglandin E2

Prostaglandins for induction of labour have been introduced in the 1970's [18,19]. Synthetic prostaglandins mimic the cervical ripening effect of endogenous prostaglandins, [20-22]. Although endogenous prostaglandins undergo rapid metabolism, synthetic prostaglandins have largely been designed to maintain a longer period of bioavailability [22,23]).

Until a decade ago, the most preferred method for induction was vaginal applied Prostaglandin E2, with the suggestion that it was effective in starting the onset of labour and being relatively safe [18,24-26]. However, it is known that the use of PGE2 can cause unwanted side-effects, such as excessive uterine contractions and as a result, fetal distress. The use of vaginal preparations (rather than oral or intravenous routes) for induction of labour aims to lessen these side-effects, although the risk of uterine hyperstimulation with fetal heartrate changes are still higher compared to spontaneous labour [18]. There are a number of different vaginal preparations of prostaglandins on the market, including gels, tablets, suppositories and pessaries.

An advantage of PGE2 is their effectiveness in achieving birth in a short timeframe after start of induction. Potential disadvantages other than the risk of uterine hyperstimulation, especially in low- and middle income countries, are their costs and the need to be stored refrigerated. Also, the risk of uterine hyperstimulation asks for close monitoring of the unborn child as well as the patient, which is not always available.

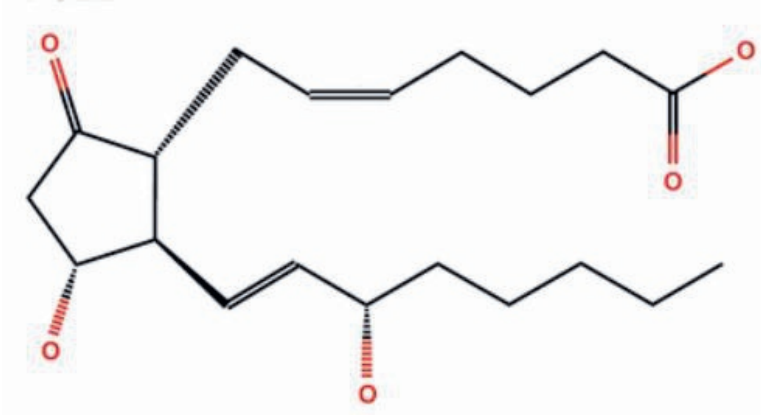

Figure 2. Chemical structure of synthetic Prostaglandin E2 (available from Archives of Gynaecology and Obstetrics)

Misoprostol

Just as PGE2, misoprostol or Prostaglandin E1 is a synthetic prostaglandin. Although misoprostol is widely used in obstetric as well as gynaecological practice because of the ability to both ripen the cervix and cause uterine contractions, it was initially developed and registered by the FDA for the prevention and treatment of gastrointestinal ulcers and peptic ulcer disease caused by prostaglandin inhibitors [23,27]. Despite having been studied for several reproductive health indications and recommended as an effective and safe induction method, misoprostol's licence has not extended in all countries [27,28]. However, since 2020, under the brand name Angusta®, low dose oral misoprostol is on the market for labour induction in the Netherlands, as well as other European countries [29].

Beside the oral route, misoprostol can also be administered vaginal [3,30]. However, meta-analyses showed that low dose oral misoprostol is as effective as vaginal misoprostol but lowers the risk of low Apgar scores and postpartum haemorrhage [28]. Therefore, low dose oral misoprostol seems to be superior compared to vaginal misoprostol and now is recommended above the vaginal route in the Dutch national guidelines , alongside induction of labour with a Foley balloon catheter [8].

The advantages of misoprostol are the costs, being stable in a wide temperature range, and that it does not require refrigeration. Another advantage of oral misoprostol is being more patient friendly, however, studies regarding patient satisfaction between a balloon catheter, oral misoprostol and PGE2 are still inconclusive [30-33]. Compared to vaginal inserted prostaglandins, oral misoprostol can lower the number of vaginal examinations during the induction period. Disadvantages of misoprostol could be the potential gastro-intestinal side-effect such as nausea and diarrhoea [34].

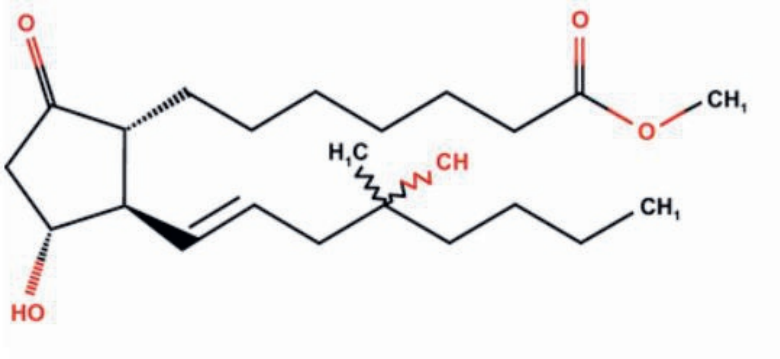

Figure 3: Chemical structure of synthetic prostaglandin E1 (misoprostol) (available from Archives of Gynaecology and Obstetrics)

Aim of this thesis

Although, much is already known on safety aspects of a balloon catheter by itself or in comparison to other recommended induction methods, several questions regarding perinatal safety aspect are still unanswered. This, because of the low prevalence of some adverse outcomes, such as neonatal asphyxia, and is therefore in most studies almost always underpowered. Systematic reviews with meta-analyses make it possible to pool low-prevalence outcomes and therefore increases the chance to make valid recommendation on these outcomes.

Some researched questions regarding safety of induction of labour with a balloon catheter, originated after the method was implemented in hospitals worldwide. A question that has been risen since, is if the mechanical stretch of the balloon on the cervix can increase the risk of preterm labour in a subsequent pregnancy. Therefore, some clinicians are ambivalent in introducing mechanical induction in practice and continue to use the methods they are familiar with. With a Foley balloon catheter being used worldwide, but also with preterm birth on the rise, it is important to rule out if there is any evidence for a relation between both [3].

While in the past mostly one method was available or the decision for a method was made by the clinician, nowadays shared decision making is becoming the standard as more and more healthcare organisations recommend this when counselling the patient and partner for induction of labour and the method used [35]. However, the information given on the methods available are predominantly derived from studies that were conducted in a general population and as a consequence, those answers cannot always be extrapolated to specific subgroups. For instance, what is the effect of a Foley Balloon catheter, PGE2 or oral misoprostol on small-for-gestational age (SGA) neonates (birthweight <10th percentile)? Although SGA neonates are at risk for fetal distress when labour is induced compared to non-SGA neonates, studies on the effect of different induction methods on perinatal outcomes in these pregnancies are limited [36,37].

And with the times that are changing, patient characteristics have also changed over the last decades, such as Body-Mass-Index (BMI). In the Netherlands, nearly 40% of all women between 25 and 45 years old are overweight (BMI ≥ 25 kg/m^2) and up to 15% have obesity [38]. The prevalence of obesity in the same age group in the USA is even up to 39% [39]. As it is known that obesity (BMI ≥ 30 kg/m^2) during pregnancy is associated with an increased risk on a caesarean section and haemorrhage postpartum, little is known what the effect is of different induction methods, especially mechanical induction, in this subgroup [40-42].

The aim of this thesis was to investigate obstetric and perinatal safety and effectiveness of induction of labour with a balloon catheter in comparison to other induction agents in a general population as well as in different subgroups .

Specific research questions

- Is there a difference between mechanical induction with a balloon catheter compared to PGE2 and low dose misoprostol regarding safety and effectiveness?
- Does a Foley balloon catheter have a better perinatal safety profile in pregnancies with a small-for-gestational age child compared to vaginal PGE2 and oral misoprostol
- How does a foley balloon catheter for induction of labour perform regarding safety and effectiveness for people in different weight groups compared to vaginal PGE2 and oral misoprostol.
- Does the use of a Foley balloon catheter increase the risk of a preterm birth in a subsequent pregnancy

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Chapter 2

Mechanical methods for induction of labour

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Abstract

Background:

Mechanical methods were the first methods developed to ripen the cervix and induce labour. During recent decades they have been substituted by pharmacological methods. Potential advantages of mechanical methods, compared with pharmacological methods may include reduction in side effects that could improve neonatal outcomes. This is an update of a review first published in 2001, last updated in 2012.

Objectives:

To determine the effectiveness and safety of mechanical methods for third trimester (> 24 weeks' gestation) induction of labour in comparison with prostaglandin E2 (PGE2) (vaginal and intracervical), low-dose misoprostol (oral and vaginal), amniotomy or oxytocin.

Search methods:

For this update, we searched Cochrane Pregnancy and Childbirth's Trials Register, ClinicalTrials.gov, the WHO International Clinical Trials Registry Platform (ICTRP), and reference lists of retrieved studies (9 January 2018). We updated the search in March 2019 and added the search results to the awaiting classification section of the review.

Selection criteria:

Clinical trials comparing mechanical methods used for third trimester cervical ripening or labour induction with pharmacological methods. Mechanical methods include: (1) the introduction of a catheter through the cervix into the extra-amniotic space with balloon insufflation; (2) introduction of laminaria tents, or their synthetic equivalent (Dilapan), into the cervical canal; (3) use of a catheter to inject fluid into the extra-amniotic space (EASI).This review includes the following comparisons: (1) specific mechanical methods (balloon catheter, laminaria tents or EASI) compared with prostaglandins (different types, different routes) or with oxytocin; (2) single balloon compared to a double balloon; (3) addition of prostaglandins or oxytocin to mechanical methods compared with prostaglandins or oxytocin alone.

Data collection and analysis:

Two review authors independently assessed trials for inclusion and assessed risk of bias. Two review authors independently extracted data and assessed the quality of the evidence using the GRADE approach.

Main results:

This review update includes a total of 112 trials (22,055 women) contributing data to 21 comparisons. Risk of bias of trials varied. Overall, the evidence was graded from very-low to moderate quality. All evidence was downgraded for lack of blinding and, for many comparisons, the effect estimates were too imprecise to make a valid judgement.

Balloon versus vaginal PGE2: there may be little or no difference in vaginal deliveries not achieved within 24 hours (average risk ratio (RR) 1.01, 95% confidence interval (CI) 0.82 to 1.26; 7 studies; 1685 women; I^2 = 79%; low-quality evidence) and there probably is little or no difference in caesarean sections (RR 1.00, 95% CI 0.92 to 1.09; 28 studies; 6619 women; moderate-quality evidence) between

induction of labour with a balloon catheter and vaginal PGE2. A balloon catheter probably reduces the risk of uterine hyperstimulation with fetal heart rate (FHR) changes (RR 0.35, 95% CI 0.18 to 0.67; 6 studies; 1966 women; moderate-quality evidence), serious neonatal morbidity or perinatal death (RR 0.48, 95% CI 0.25 to 0.93; 8 studies; 2757 women; moderate-quality evidence) and may slightly reduce the risk of an neonatal intensive care unit (NICU) admission (RR 0.82, 95% CI 0.65 to 1.04; 3647 women; 12 studies; low-quality evidence). It is uncertain whether there is a difference in serious maternal morbidity or death (RR 0.20, 95% CI 0.01 to 4.12; 4 studies; 1481 women) or five-minute Apgar score < 7 (RR 0.74, 95% CI 0.49 to 1.14; 4271 women; 14 studies) because the quality of the evidence was found to be very low and low, respectively.

Balloon versus low-dose vaginal misoprostol: it is uncertain whether there is a difference in vaginal deliveries not achieved within 24 hours between induction of labour with a balloon catheter and vaginal misoprostol (RR 1.09, 95% CI 0.85 to 1.39; 340 women; 2 studies; low-quality evidence). A balloon catheter probably reduces the risk of uterine hyperstimulation with FHR changes (RR 0.39, 95% CI 0.18 to 0.85; 1322 women; 8 studies; moderate-quality evidence) but may increase the risk of a caesarean section (average RR 1.28, 95% CI 1.02 to 1.60; 1756 women; 12 studies; I^2 = 45%; low-quality evidence). It is uncertain whether there is a difference in serious neonatal morbidity or perinatal death (RR 0.58, 95% CI 0.12 to 2.66; 381 women; 3 studies), serious maternal morbidity or death (no events; 4 studies, 464 women), both very low-quality evidence, and five-minute Apgar score < 7 (RR 1.00, 95% CI 0.50 to 1.97; 941 women; 7 studies) and NICU admissions (RR 1.00, 95% CI 0.61 to 1.63; 1302 women; 9 studies) both low-quality evidence.

Balloon versus low-dose oral misoprostol: a balloon catheter probably increases the risk of a vaginal delivery not achieved within 24 hours (RR 1.28, 95% CI 1.13 to 1.46; 782 women, 2 studies, and probably slightly increases the risk of a caesarean section (RR 1.17, 95% CI 1.04 to 1.32; 3178 women; 7 studies; both moderate-quality evidence) when compared to oral misoprostol. It is uncertain whether there is a difference in uterine hyperstimulation with FHR changes (RR 0.81, 95% CI 0.48 to 1.38; 2033 women; 2 studies), serious neonatal morbidity or perinatal death (RR 1.11, 95% CI 0.60 to 2.06; 2627 women; 3 studies), both low-quality evidence, serious maternal morbidity or death (RR 0.50, 95% CI 0.05 to 5.52; 2627 women; 3 studies), very low-quality evidence, five-minute Apgar scores < 7 (RR 0.71, 95% CI 0.38 to 1.32; 2693 women; 4 studies) and NICU admissions (RR 0.82, 95% CI 0.58 to 1.17; 2873 women; 5 studies) both low-quality evidence.

Authors' conclusions:
Low- to moderate-quality evidence shows mechanical induction with a balloon is probably as effective as induction of labour with vaginal PGE2. However, a balloon seems to have a more favourable safety profile. More research on this comparison does not seem warranted.

Moderate-quality evidence shows a balloon catheter may be slightly less effective as oral misoprostol, but it remains unclear if there is a difference in safety outcomes for the neonate. When compared to low-dose vaginal misoprostol, low-quality evidence shows a balloon may be less effective, but probably has a better safety profile.

Future research could be focused more on safety aspects for the neonate and maternal satisfaction

Summary of findings 1: Balloon (Foley or ATAD) compared to vaginal prostaglandin E2

Patient or population: third trimester labour induction in women with a viable fetus
Setting: Australia, China, Denmark, Iran, Jordan, India, Italy, Israel, Nigeria, Pakistan, Singapore, Sweden, the Netherlands, USA, UK
Intervention: balloon (Foley or ATAD)
Comparison: vaginal prostaglandin E2

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with vaginal prostaglandin E2	Risk with balloon (Foley or ATAD)				
Vaginal delivery not achieved in 24 hours	Study population 528 per 1000	533 per 1000 (433 to 665)	RR 1.01 (0.82 to 1.26)	1685 (7 RCTs)	⨁⨁⊖⊖ LOW [1,2]	
Uterine hyperstimulation with FHR changes	Study population 31 per 1000	11 per 1000 (6 to 21)	RR 0.35 (0.18 to 0.67)	1966 (6 RCTs)	⨁⨁⨁⊖ MODERATE [1]	
Caesarean section	Study population 238 per 1000	238 per 1000 (219 to 260)	RR 1.00 (0.92 to 1.09)	6619 (28 RCTs)	⨁⨁⨁⊖ MODERATE [1]	
Serious neonatal morbidity or perinatal death	Study population 20 per 1000	9 per 1000 (5 to 18)	RR 0.48 (0.25 to 0.93)	2757 (8 RCTs)	⨁⨁⨁⊖ MODERATE [1]	
Serious maternal morbidity or death	Study population 3 per 1000	1 per 1000 (0 to 11)	RR 0.20 (0.01 to 4.12)	1481 (4 RCTs)	⨁⊖⊖⊖ VERY LOW [1,3]	
Apgar score < 7 at 5 minutes	Study population 22 per 1000	16 per 1000 (11 to 25)	RR 0.74 (0.49 to 1.14)	4271 (14 RCTs)	⨁⨁⊖⊖ LOW [1,4]	
Neonatal intensive care unit admission	Study population 74 per 1000	60 per 1000 (48 to 77)	RR 0.82 (0.65 to 1.04)	3647 (12 RCTs)	⨁⨁⊖⊖ LOW [1,4]	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio

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

[1]We downgraded (1) level for serious limitation in study design due to lack of blinding (although not feasible due to nature of event)

[2]We downgraded (1) level for serious inconsistency due to evidence of statistical heterogeneity (I^2 = >30%)

[3]We downgraded (2) levels for very serious imprecision due to wide CI crossing the line of no effect and small number of events

[4]We downgraded (1) level for serious imprecision due to wide CI crossing the line of no effect

Summary of findings 2: Balloon (Foley or ATAD) compared to low-dose vaginal misoprostol

Patient or population: third trimester induction of labour in women with a viable fetus
Setting: Brazil, Egypt, India, Iran, Nigeria, the Netherlands, Sweden
Intervention: balloon (Foley or ATAD)
Comparison: low-dose vaginal misoprostol

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with low-dose vaginal misoprostol	Risk with balloon (Foley or ATAD)				
Vaginal delivery not achieved in 24 hours	Study population		RR 1.09 (0.85 to 1.39)	340 (2 RCTs)	⊕⊕⊖⊖ LOW [1,2]	
	412 per 1000	449 per 1000 (350 to 573)				
Uterine hyperstimulation with FHR changes	Study population		RR 0.39 (0.18 to 0.85)	1322 (8 RCTs)	⊕⊕⊕⊖ MODERATE [1]	
	33 per 1000	13 per 1000 (6 to 28)				
Caesarean section	Study population		RR 1.28 (1.02 to 1.60)	1756 (12 RCTs)	⊕⊕⊖⊖ LOW [1,3]	
	243 per 1000	311 per 1000 (247 to 388)				
Serious neonatal morbidity or perinatal death	Study population		RR 0.58 (0.12 to 2.66)	381 (3 RCTs)	⊕⊖⊖⊖ VERY LOW [1,4]	
	21 per 1000	12 per 1000 (2 to 55)				
Serious maternal morbidity or death	Study population		not estimable	464 (4 RCTs)	⊕⊖⊖⊖ VERY LOW [1,5]	no events occurred in included studies
	0 per 1000	0 per 1000 (0 to 0)				
Apgar score < 7 at 5 minutes	Study population		RR 1.00 (0.50 to 1.97)	941 (7 RCTs)	⊕⊕⊖⊖ LOW [1,2]	
	30 per 1000	30 per 1000 (15 to 59)				
Neonatal intensive care unit admission	Study population		RR 1.00 (0.61 to 1.63)	1302 (9 RCTs)	⊕⊕⊖⊖ LOW [1,2,6]	
	47 per 1000	47 per 1000 (29 to 77)				

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio

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

[1] We downgraded (1) level for serious limitation in study design due to lack of blinding (although not feasible due to nature of event)

[2] We downgraded (1) level for serious imprecision due to wide CI crossing the line of no effect

[3] We downgraded (1) level for serious inconsistency due to evidence of statistical heterogeneity (I^2 = >30%)

[4] We downgraded (2) levels for very serious imprecision due to wide CI crossing the line of no effect and small number of events

[5] We downgraded (2) levels for very serious imprecision due to wide CI crossing the line of no effect and no events reported in included studies

[6] Although there was some evidence suggesting small-study effect we did not downgrade for publication bias because individual studies did not reach statistical significance and there was low heterogeneity across all studies for this outcome. Also, no difference was found between fixed-effect or random-effect analyses

Summary of findings 3: Balloon (Foley or ATAD) compared to low-dose oral misoprostol

Patient or population: third trimester induction of labour in women with a viable fetus
Setting: Finland, India, Pakistan, Sri Lanka, the Netherlands
Intervention: balloon (Foley or ATAD)
Comparison: low-dose oral misoprostol

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with low-dose oral misoprostol	Risk with balloon (Foley or ATAD)				
Vaginal delivery not achieved within 24 hours	Study population 476 per 1000	609 per 1000 (538 to 695)	RR 1.28 (1.13 to 1.46)	782 (2 RCTs)	⊕⊕⊕⊖ MODERATE [1]	
Uterine hyperstimulation with FHR changes	Study population 29 per 1000	24 per 1000 (14 to 40)	RR 0.81 (0.48 to 1.38)	2033 (2 RCTs)	⊕⊕⊖⊖ LOW [1 2]	
Caesarean section	Study population 222 per 1000	259 per 1000 (230 to 293)	RR 1.17 (1.04 to 1.32)	3178 (7 RCTs)	⊕⊕⊕⊖ MODERATE [1 3]	
Serious neonatal morbidity or perinatal death	Study population 14 per 1000	16 per 1000 (9 to 30)	RR 1.11 (0.60 to 2.06)	2627 (3 RCTs)	⊕⊕⊖⊖ LOW [1 2 4]	
Serious maternal morbidity or death	Study population 2 per 1000	1 per 1000 (0 to 8)	RR 0.50 (0.05 to 5.52)	2627 (3 RCTs)	⊕⊖⊖⊖ VERY LOW [1 5]	
Apgar score < 7 after 5 minutes	Study population 18 per 1000	13 per 1000 (6 to 28)	RR 0.71 (0.38 to 1.32)	2693 (4 RCTs)	⊕⊕⊖⊖ LOW [1 2 4]	
Neonatal intensive care unit admission	Study population 46 per 1000	37 per 1000 (26 to 53)	RR 0.82 (0.58 to 1.17)	2873 (5 RCTs)	⊕⊕⊖⊖ LOW [1 2 4]	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio

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

[1]We downgraded (1) level for serious limitation in study design due to lack of blinding (although not feasible due to nature of event)

[2]We downgraded (1) level for serious imprecision due to wide CI crossing the line of no effect

[3] Trial of Mundle 2017 did not meet the pre-specified population as pregnancies with a non viable fetus were included. Sensitivity analyses did not alter the estimated effect size. Therefore we did not downgrade

[4] Trial of Mundle 2017 did not meet the pre-specified population as pregnancies with a non viable fetus were included. Sensitivity analysis did not change the direction of the effect size and numbers of events were not higher compared to other trials. Therefore we did not downgrade.

[5] We downgraded (2) levels for very serious imprecision due to wide CI crossing the line of no effect and small number of events

Introduction

The previous version of this review formed one of a series of reviews of methods for induction of labour that followed a standardised published 'generic' protocol Hofmeyr 2009). These reviews were initially developed to help inform the recommendations of the National Institute for Health and Care Excellence (NICE) clinical practice guidelines on induction of labour (NICE 2008). This review no longer strictly follows the original protocol and has been updated with the intention of being a stand-alone review. This is an update of a review first published in 2001 (Boulvain 2001), and last updated in 2012 (Jozwiak 2012).

Description of the condition

Labour induction is a common obstetric procedure, which is generally carried out when the risk of continuing pregnancy outweighs the benefits. Also, induction of labour is being used more and more at the request of pregnant women to shorten the duration of pregnancy or to time the birth of the baby according to the convenience of the mother and/or healthcare workers [5] (WHO 2011). In the USA, approximately one in four women are induced and in the last decade, the induction rate in the UK has risen up to almost 30% (NICE 2008; NHS 2017). Although rates are generally lower in developing countries, in some settings they can be as high as those observed in developed countries (WHO 2011). To maximise the success of induction of labour in women with an unfavourable cervix, various ripening methods are available.

Description of the intervention

Mechanical methods were the first methods developed to ripen the cervix and induce labour (Thiery 1989). Devices that were used in this context include various type of catheters and laminaria tents, introduced into the cervical canal or through the cervix into the extra-amniotic space. During recent decades they were partly substituted by pharmacological methods, including various prostaglandin E2 (PGE2) preparations (vaginal gel, tablets, inserts, intracervical gel), prostaglandin E1 (PGE1; misoprostol tablets, applied either orally or vaginally) and oxytocin. Pharmacological methods however, have a variety of effects at different sites and receptors in the body that can lead to unwanted side effects when used, such as uterine hyperstimulation (excessive contractions of the uterus) and as result, fetal distress. Therefore, mechanical induction methods are gaining in popularity as it has the potential to have a better safety profile compared to pharmacological methods, however possibly at the cost of a longer duration of labour. These factors need to be considered to determine the most appropriate methods depending on the clinical situation, with impact on labour duration possibly being of secondary importance as more women have labour induced for less urgent indications.

How the intervention might work

The goal of mechanical induction methods is to ripen the cervix, which can be achieved directly through dilatation of the canal, indirectly by increasing prostaglandin or oxytocin secretion, or both (Keirse 1983). In addition to the local effect, mechanisms which involve neuro-endocrine reflexes (the Ferguson reflex) may promote the onset of contractions, leading to labour onset (Krammer 1995b).

The standard Foley urinary catheter can be used, as well as a specially developed 'Atad' double-balloon catheter (Atad 1996) or Cook balloon. The catheter is introduced through the cervical canal to reach

the extra-amniotic space. The balloon is then inflated to keep the catheter in place. Traction is applied to the catheter in some cases. Another method involving catheters consists of infusing saline solution or prostaglandins through a catheter inserted, via the cervical canal, in the extra-amniotic space (EASI).

Laminaria tents, made from sterile sea-weed or synthetic hydrophilic materials (e.g. Lamicel), are introduced into the cervical canal. These devices increase in diameter because of their hydrophilic properties. This achieves a gradual stretching of the cervix.
Digital stripping or sweeping of the membranes is evaluated in a different review (Boulvain 2005).

Why it is important to do this review
Mechanical methods were never completely abandoned, but were substituted by pharmacological methods in recent decades. However, as induction rates rise and indications are often less urgent, the safety aspects of induction methods become more important, although this could be at the expense of effectiveness. Apart for being widely available and low in cost, potential advantages of mechanical methods over pharmacological ones may include a reduction in side effects, such as uterine hyperstimulation, thereby having the potential to improve neonatal outcomes.

Objectives
To determine the effectiveness and safety of mechanical methods for third trimester (> 24 weeks' gestation) induction of labour in comparison with prostaglandin E2 (PGE2) (vaginal and intracervical), low-dose misoprostol (oral and vaginal), amniotomy or oxytocin.

Methods

Criteria for considering studies for this review

Types of studies
Clinical trials, comparing mechanical methods for cervical ripening or labour induction with other induction methods. Quasi-randomised controlled trials and trials only reported as abstract were eligible for inclusion. Cluster-randomised trials are unlikely to be conducted in this area, however, if identified by a future search, they will be handled with appropriate methods.

Types of participants
Pregnant women due for third trimester induction of labour, carrying a viable fetus.
Predefined subgroup comparisons were: previous caesarean section or not, nulliparity or multiparity. Only those outcomes with data appear in the analyses tables.

Types of interventions
Different types of intervention have been considered as mechanical methods: (1) the introduction of a catheter (Foley single balloon, Atad/Cook double balloon or other type), through the cervix into the extra-amniotic space, either with or without traction; (2) introduction of laminaria tents, or their synthetic equivalent (Dilapan), into the cervical canal; (3) use of a catheter to inject fluids, usually saline water, in the extra-amniotic space (EASI).
Mechanical methods were compared with other induction methods (i.e. vaginal PGE2, intracervical PGE2, intravenous oxytocin, amniotomy, vaginal and oral misoprostol). For this update, the

comparison with placebo/no treatment was left out. When the protocol for reviews of induction methods was designed, it was relevant to know if cervical ripening before actual induction of labour (rupturing the membranes, and if needed, administer of oxytocin) was beneficial. Since we already know the advantages of cervical ripening in case of an unfavourable cervix, no future trials will be done to study the effect of cervical ripening with a mechanical method versus no ripening. Also, in the case of pharmacological methods, it is possible to perform a placebo-controlled study, but with mechanical methods of labour, this is not possible. Studies which do make this comparison between mechanical induction and no treatment, explore other objectives rather than the ones relevant for his review (induction of labour versus expectant management to improve birth outcome). Therefore, the choice was made to depart from the original research protocol and leave out this pre-specified comparison. For this update, we also chose only to include low-dose misoprostol (defined as ≤ 50 mcg every ≥ 4 hours) as evidence suggests low-dose misoprostol is superior to high-dose misoprostol regarding safety outcomes and being equally effective (Alfirevic 2014; Hofmeyr 2010).

In addition, other comparisons were made: (1) a single balloon compared to a double balloon; (2) laminaria tent compared to other hygroscopic dilatators; (3) addition of prostaglandins or oxytocin to mechanical methods compared with prostaglandins or oxytocin alone. These comparisons were not pre-specified in the generic protocol of induction of labour reviews (Hofmeyr 2009).

Types of outcome measures

We included all clinically relevant outcomes for trials of methods of cervical ripening/labour induction as had been pre-specified by two authors of the generic protocol for labour induction reviews (Justus Hofmeyr and Zarko Alfirevic). We added six more outcomes to the list of the original protocol. Differences were settled by discussion.

Primary outcomes

Five primary outcomes were chosen as being most representative of the clinically important measures of effectiveness and complications. Subgroup comparisons were limited to the primary outcomes:

1. vaginal delivery not achieved within 24 hours (from start cervical ripening);
2. uterine hyperstimulation with fetal heart rate (FHR) changes;
3. caesarean section;
4. serious neonatal morbidity or perinatal death (e.g. seizures, birth asphyxia defined by trialists, neonatal encephalopathy, disability in childhood);
5. serious maternal morbidity or death (e.g. uterine rupture, admission to intensive care unit, septicaemia).

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

Measures of effectiveness:

1. cervix unfavourable/unchanged after 12 to 24 hours;
2. oxytocin augmentation.

Complications:

1. uterine hyperstimulation without FHR changes;
2. uterine rupture;
3. epidural analgesia;
4. instrumental vaginal delivery;
5. meconium-stained liquor;
6. Apgar score less than seven at five minutes;
7. neonatal intensive care unit (NICU) admission;
8. neonatal encephalopathy;
9. perinatal death;
10. disability in childhood;
11. maternal side effects (all);
12. maternal nausea;
13. maternal vomiting;
14. maternal diarrhoea;
15. other maternal side effects;
16. postpartum haemorrhage (as defined by the trial authors);
17. serious maternal complications (e.g. intensive care unit admission, septicaemia but excluding uterine rupture);
18. maternal death.

Measures of satisfaction:

1. woman not satisfied;
2. caregiver not satisfied.

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

Search methods for identification of studies

The following methods section of this review is based on a standard template used by Cochrane Pregnancy and Childbirth.

Electronic searches

For this update, we searched Cochrane Pregnancy and Childbirth's Trials Register by contacting their Information Specialist (9 January 2018). We updated this search on 19 March 2019 and added the results to Studies awaiting classification for consideration in the next update.

The Register is a database containing over 25,000 reports of controlled trials in the field of pregnancy and childbirth. It represents over 30 years of searching. For full current search methods used to populate Pregnancy and Childbirth's Trials Register including the detailed search strategies for CENTRAL, MEDLINE, Embase and CINAHL; the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service, please follow this link. Briefly, Cochrane Pregnancy and Childbirth's Trials Register is maintained by their Information Specialist and contains trials identified from:

1. monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. weekly searches of MEDLINE (Ovid);
3. weekly searches of Embase (Ovid);
4. monthly searches of CINAHL (EBSCO);
5. handsearches of 30 journals and the proceedings of major conferences;
6. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Search results are screened by two people and the full text of all relevant trial reports identified through the searching activities described above is reviewed. Based on the intervention described, each trial report is assigned a number that corresponds to a specific Pregnancy and Childbirth review topic (or topics) and is then added to the Register. The Information Specialist searches the Register for each review using this topic number rather than keywords. This results in a more specific search set that has been fully accounted for in the relevant review sections (Included, Excluded, Awaiting Classification or Ongoing).
In addition, we searched ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP) for unpublished, planned and ongoing trial reports (19 March 2019) using the search methods detailed in Appendix 1.

Searching other resources
We searched the reference lists of retrieved studies. We did not apply any language or date restrictions.

Data collection and analysis
For methods used in the previous version of this review, *see* Jozwiak 2012. For this update, the following methods were used for assessing the 247 reports that were identified as a result of the updated search. The following methods section of this review is based on a standard template used by Cochrane Pregnancy and Childbirth.

Selection of studies
Two review authors (Marieke de Vaan and Mieke ten Eikelder) independently assessed all potential studies identified as a result of the search strategy for inclusion. Any disagreement was resolved through discussion, or if required, by involving a third review author (Marta Jozwiak).

Data extraction and management
We designed a form to extract data. For eligible studies, two groups of two review authors (Marieke de Vaan, Marta Jozwiak, Ben Willem Mol and Kirsten Palmer) extracted the data using the agreed form. We resolved discrepancies through discussion or, if required, we consulted a third review author. Data

were entered into Review Manager software (RevMan 2014) and checked by a second review author for accuracy. When information regarding any of the above was unclear, we contacted authors of the original reports to provide further details.

Assessment of risk of bias in included studies

Two review authors (Marieke de Vaan and Mieke ten Eikelder) independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Any disagreement was resolved by discussion or by involving a third assessor (Marta Jozwiak).

(1) Random sequence generation (checking for possible selection bias)

We described for each included study the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.

We assessed the method as:

- low risk of bias (any truly random process, e.g. random number table; computer random number generator);
- high risk of bias (any non-random process, e.g. odd or even date of birth; hospital or clinic record number);
- unclear risk of bias.

(2) Allocation concealment (checking for possible selection bias)

We described for each included study the method used to conceal allocation to interventions prior to assignment and assessed whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.

We assessed the methods as:

- low risk of bias (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
- high risk of bias (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
- unclear risk of bias.

(3.1) Blinding of participants and personnel (checking for possible performance bias)

We described for each included study the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We considered that studies were at low risk of bias if they were blinded, or if we judged that the lack of blinding unlikely to affect results. We assessed blinding separately for different outcomes or classes of outcomes.

We assessed the methods as:

- low, high or unclear risk of bias for participants;
- low, high or unclear risk of bias for personnel.

(3.2) Blinding of outcome assessment (checking for possible detection bias)

We described for each included study the methods used, if any, to blind outcome assessors from knowledge of which intervention a participant received. We assessed blinding separately for different outcomes or classes of outcomes.

We assessed methods used to blind outcome assessment as:

- low, high or unclear risk of bias.

(4) Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data)

We described for each included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We stated whether attrition and exclusions were reported and the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information was reported, or could be supplied by the trial authors, we planned to re-include missing data in the analyses which we undertook. We assessed methods as:

- low risk of bias (e.g. no missing outcome data; missing outcome data balanced across groups);
- high risk of bias (e.g. numbers or reasons for missing data imbalanced across groups; 'as treated' analysis done with substantial departure of intervention received from that assigned at randomisation);
- unclear risk of bias.

(5) Selective reporting (checking for reporting bias)

We described for each included study how we investigated the possibility of selective outcome reporting bias and what we found.

We assessed the methods as:

- low risk of bias (where it is clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review have been reported);
- high risk of bias (where not all the study's pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported);
- unclear risk of bias.

(6) Other bias (checking for bias due to problems not covered by (1) to (5) above)

We described for each included study any important concerns we had about other possible sources of bias.

Assessment of the quality of the evidence using the GRADE approach

For this update, the quality of the evidence was assessed for the comparisons relating to the most frequently used methods of cervical ripening (i.e. vaginal prostaglandin E2 (PGE2), vaginal misoprostol, and oral misoprostol) using the GRADE approach as outlined in the GRADE handbook in order to assess the quality of the body of evidence relating to the following outcomes.

1. Vaginal delivery not achieved within 24 hours
2. Uterine hyperstimulation with FHR changes
3. Caesarean section
4. Serious neonatal morbidity or perinatal death (e.g. seizures, birth asphyxia defined by trialists, neonatal encephalopathy, disability in childhood)
5. Serious maternal morbidity or death (e.g. uterine rupture, admission to intensive care unit, septicaemia)
6. Neonatal intensive care unit admission
7. Apgar score less than seven at five minutes

For the main comparisons we used GRADEpro Guideline Development Tool to import data from Review Manager 5.3 (RevMan 2014) in order to create 'Summary of findings' tables. A summary of the intervention effect and a measure of quality for each of the above outcomes was produced using the GRADE approach. The GRADE approach uses five considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of the body of evidence for each outcome. The evidence can be downgraded from 'high quality' by one level for serious (or by two levels for very serious) limitations, depending on assessments for risk of bias, indirectness of evidence, serious inconsistency, imprecision of effect estimates or potential publication bias.

Measures of treatment effect

Dichotomous data

For dichotomous data, we presented results as summary risk ratio with 95% confidence intervals.

Continuous data

No continuous data were analysed in this update. If outcomes using continuous data are included in future versions of this review, we will use the mean difference if outcomes are measured in the same way between trials. We will use the standardised mean difference to combine trials that measure the same outcome but use different methods.

Unit of analysis issues

Cluster-randomised trials

Cluster-randomised trials are eligible for inclusion in the analyses along with individually-randomised trials. None have currently been identified. If in the future such trials are identified, we will adjust their standard errors using the methods described in the Handbook (Higgins 2011) using an estimate of the intracluster correlation co-efficient (ICC) derived from the trial (if possible), from a similar trial or from a study of a similar population. If we use ICCs from other sources, we will report this and conduct sensitivity analyses to investigate the effect of variation in the ICC. If we identify both cluster-randomised trials and individually-randomised trials, we plan to synthesise the relevant information. We will consider it reasonable to combine the results from both if there is little heterogeneity between the study designs and the interaction between the effect of intervention and the choice of randomisation unit is considered to be unlikely. We will also acknowledge heterogeneity in the randomisation unit and perform a sensitivity analysis to investigate the effects of the randomisation unit.

Cross-over trials

Cross-over trials were not eligible for inclusion.

Other unit of analysis issues

Trials in pregnancy and childbirth may include outcomes for multiple pregnancies, but the trials identified to date have included singleton pregnancies only. Trials with multiple pregnancy will be included, but the outcomes relating to the babies will have to take account of clustering of events, as outlined in the Pregnancy and Childbirth Group Methodological Guidelines and the *Handbook* (Higgins 2011). Some trials are multi-arm studies, where this occurs only the intervention arms relevant to this review were included and this is noted in the Characteristics of included studies table.

Dealing with missing data

For included studies, levels of attrition were noted. In future updates, if more eligible studies are included, we will explore the impact of including studies with high levels of missing data in the overall assessment of treatment effect by using sensitivity analysis. For all outcomes, analyses were carried out, as far as possible, on an intention-to-treat basis, i.e. we attempted to include all participants randomised to each group in the analyses. The denominator for each outcome in each trial was the number randomised minus any participants whose outcomes were known to be missing.

Assessment of heterogeneity

We assessed statistical heterogeneity in each meta-analysis using the Tau^2, I^2 and Chi^2 statistics. We regarded heterogeneity as substantial if an I^2 was greater than 30% and either a Tau^2 was greater than zero, or there was a low P value (less than 0.10) in the Chi^2 test for heterogeneity. In the case of substantial heterogeneity (above 30%), if possible, we explored it by subgroup analyses.

Assessment of reporting biases

When there were 10 or more studies in the meta-analysis, we investigated reporting biases (such as publication bias) using funnel plots. We assessed funnel plot asymmetry visually. If asymmetry was suggested by a visual assessment, we performed exploratory analyses to investigate it.

Data synthesis

We carried out statistical analysis using the Review Manager software (RevMan 2014). We used fixed-effect meta-analysis for combining data where it was reasonable to assume that studies were estimating the same underlying treatment effect: i.e. where trials were examining the same intervention, and the trials' populations and methods were judged sufficiently similar.

If there was clinical heterogeneity sufficient to expect that the underlying treatment effects differed between trials, or if substantial statistical heterogeneity was detected, we used random-effects meta-analysis to produce an overall summary, if an average treatment effect across trials was considered clinically meaningful. The random-effects summary was treated as the average range of possible treatment effects and the clinical implications of treatment effects differing between trials is discussed. If the average treatment effect was not clinically meaningful, we did not combine trials. When random-effects analyses were used, the results were presented as the average treatment effect with 95% confidence intervals, and the estimates of Tau^2 and I^2.

Subgroup analysis and investigation of heterogeneity

We did not carry out formal subgroup analysis to investigate heterogeneity, but carried out additional analyses of subgroups of trials based on the following.

1. Previous caesarean section or not
2. Nulliparity or multiparity

The following outcomes were used in the subgroups.

1. Vaginal delivery not achieved within 24 hours
2. Uterine hyperstimulation with FHR changes
3. Caesarean section

4. Serious neonatal morbidity or perinatal death (e.g. seizures, birth asphyxia defined by trialists, neonatal encephalopathy, disability in childhood)
5. Serious maternal morbidity or death (e.g. uterine rupture, admission to intensive care unit, septicaemia)

Sensitivity analysis

We carried out sensitivity analyses to explore the effect of trial quality assessed by concealment of allocation, high attrition rates, or both, with poor quality studies being excluded from the analyses in order to assess whether this made any difference to the overall result.

Results

For this update, we identified 418 trial reports to assess in the search of 9 January 2018. One study (Pineda Rivas 2016) was retrieved through other sources. When exploring the included trial registration of this study, we found out that an abstract of this study was published.

We also reassessed the 17 reports awaiting classification and the four ongoing studies in the previous version of the review (Jozwiak 2012). One hundred and seventy-one reports were screened out because they did not meet the scope for this review or were not randomised controlled trials. We then assessed trial reports which related to 166 new trials (247 reports). We included 60 new trials (120 reports), added two trial reports to already included studies and excluded 74 trials (102 reports). Two trials from the January 2018 search are awaiting classification (Agboghoroma 2015; Mallah 2011), and 21 are ongoing (Argilagos 2016; Beckmann 2013; Bekele 2017; Berndl 2016; Bhide 2017; Eser 2016; Goli 2017; Goonewardene 2016; Gupta 2016; Hassanzadeh 2017; Igwe 2017; Lacarin 2017; Lauterbach 2017; Levy 2016; Osoti 2016; Park 2012; Perrotin 2016; Tagore 2015; Viteri 2015; Wise 2016; Yildirim 2017).

Of the 71 previous included studies, we excluded 18 trials because they were no longer within the scope of this review. Four studies were excluded because they compared a mechanical method with a placebo or no cervical ripening (De Oliveira 2003; Gilson 1996; Gower 1982; Lackritz 1979), 11 studies because of the use of high-dose misoprostol (Adeniji 2005b; Barrilleaux 2002a; Buccellato 2000; Chung 2003; Greybush 2001; Hill 2009; Kashanian 2006; Owolabi 2005; Rust 2001; Sciscione 2001; Vengalil 1998), two studies compared extra-amniotic space infusion (EASI) versus induction with a balloon or laminaria (El-Torkey 1995; Lin 1995), and one study compared a balloon versus prostaglandin F2alpha (Mawire 1999).

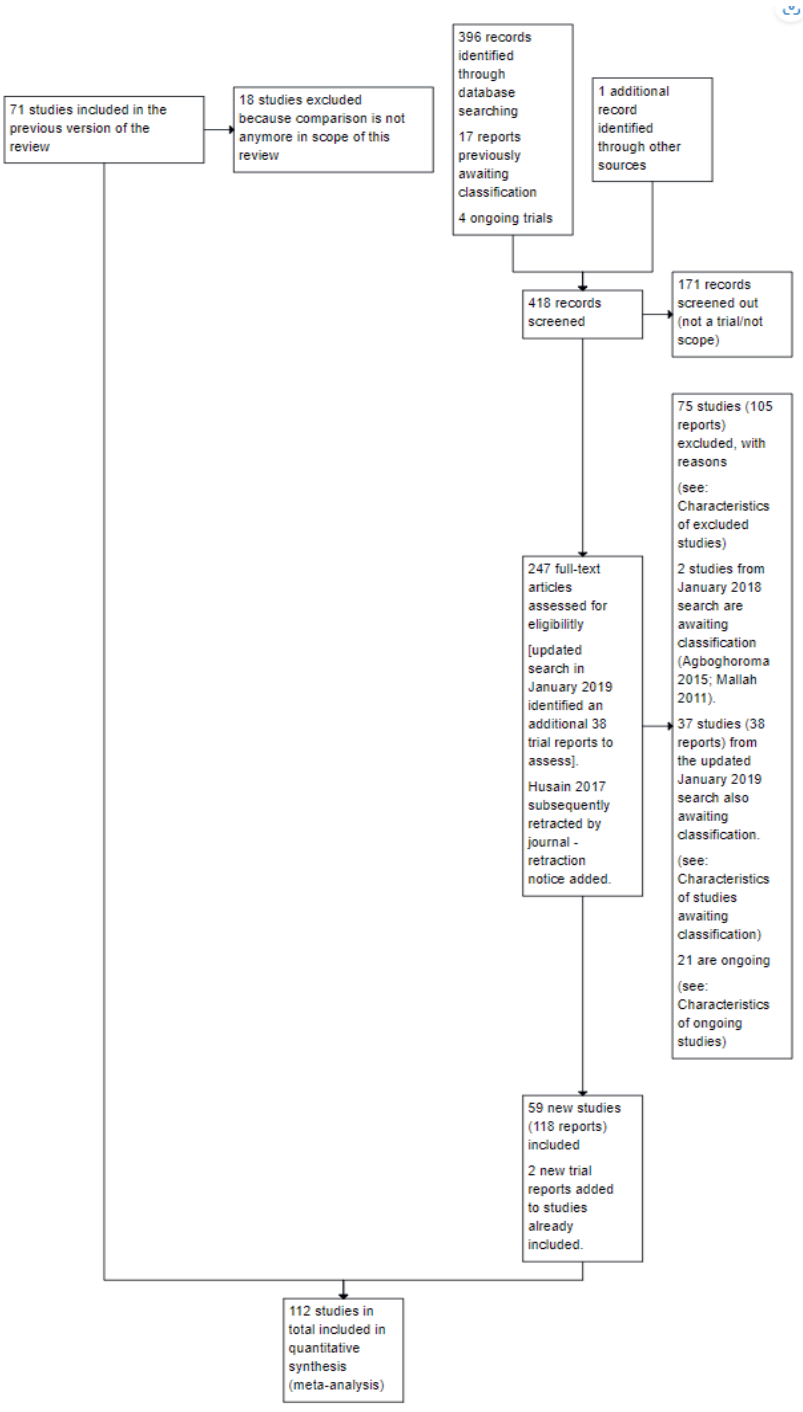


Figure 1: study flow diagram

In the updated search of 19 March 2019, we identified an additional 38 trial reports which were added to Studies awaiting classification for consideration in the next update. The references have been assessed but not incorporated into the review. Only seven of these trials are likely to contribute data for this review and are mainly small trials (Khatib 2019; Lim 2018; Osoti 2018; Souizi 2018; ten Eikelder 2017; Tulek 2018; Viteri 2019). We imputed the data for these trials and this resulted in no changes in terms of the direction or strength of the evidence. We will incorporate these studies fully at the next update.

March 2023: One included study has subsequently been retracted by the journal (Husain 2017) (identified by Cochrane Pregnancy and Childbirth's ongoing surveillance). This study has now been excluded

Included studies

Altogether, this review now comprises 112 included studies, 104 of which contributed data. The studies that contributed data involved 22,055 women (see Characteristics of included studies). Trials with more than two arms may be included in more than one comparison. No cluster-randomised trials were identified by the search.

Eight studies did not contribute any data to this review because the outcomes of interest were not reported, or reported in a format that could not be included in this review (Biron-Shental 2004; Deo 2013; Hughes 2002; Jalilian 2011; Peedicayil 1998; Qamar 2012; Thiery 1981; Zahoor 2014). These studies are therefore not included in the descriptions of study details and 'Risk of bias' assessment below.

Design

All included studies were randomised controlled trials although the randomisation method was not always well described and in three studies the allocation process was not truly random (Jagani 1982; Kandil 2012; Roztocil 1998). All studies involved two trial arms except for Aduloju 2016, Allouche 1993, Atad 1996, Browne 2011, Cromi 2011, Deo 2012, Dionne 2011, El Khouly 2017, Guinn 2000, Matonhodze 2003, Lewis 1983, Orhue 1995, Pennell 2009, Prager 2008, Saleem 2006, Sheikher 2009 and Yuen 1996, which had three arms. Gelisen 2005, Lyndrup 1989 and Roberts 1986 had four arms, and Jagani 1982 had five arms. Not all comparisons in these studies were relevant for this review and therefore one or more arms in the studies of Gelisen 2005, Jagani 1982, Lewis 1983 and Roberts 1986 were excluded.

Setting

Nine studies were multicentre studies (Edwards 2014c; Guinn 2000; Jozwiak 2012; Jozwiak 2013; Jozwiak 2014; Lokkegaard 2015; Mundle 2017; Sarreau 2016; ten Eikelder 2016), the remaining studies were single-centre studies.All studies took place in a hospital setting, except for Henry 2013, in which the period of cervical ripening took place in an outpatient setting.

The included studies were conducted in the following countries: Australia (Henry 2013; Pennell 2009), Brazil (Filho 2002; Oliveira 2010, Canada (Lemyre 2006; Pineda Rivas 2016; St Onge 1995), Czech Republic (Roztocil 1998), China (Wang 2012; Wang 2014; Wu 2017; Yuen 1996), Denmark (Lokkegaard 2015; Lyndrup 1989; Lyndrup 1994), Egypt (Ahmed 2016; El Khouly 2017; Kandil 2012), Finland (Kruit 2016), France (Allouche 1993; Sarreau 2016;), India (Chavakula 2015; Dalui 2005; Deo 2012; Deshmukh 2011; Goonewardene 2014; Gunawardena 2012; Joshi 2016; Kuppulakshmi

2016; Laddad 2013; Lanka 2014; Meetei 2015; Mundle 2017; Sheikher 2009), Iran (Moini 2003; Niromanesh 2003; Roudsari 2011; Sharami 2005) Italy (Cromi 2011; Cromi 2012), Israel (Atad 1996; Barda 2018; Ophir 1992; Shechter-Maor 2015; Salim 2011; Solt 2009), Jordan (Al-Taani 2004; Khamaiseh 2012), the Netherlands (Jozwiak 2012; Jozwiak 2013; Jozwiak 2014; ten Eikelder 2016), Nigeria (Aduloju 2016; Garba 2016; Orhue 1995; Tabowei 2003), Norway (Haugland 2012), Pakistan (Matonhodze 2003; Mazhar 2003; Saleem 2006), Russia (Glagoleva 1999), Rwanda (Gilson 2017), South Africa (Bagratee 1990; Jeeva 1982; Ntsaluba 1997), Singapore (Chua 1997), Sri Lanka (Rudra 2012; Somirathne 2017; Tan 2015), Sweden (Hemlin 1998; Prager 2008), Tunis (Benzineb 1996), Turkey (Gelisen 2005), the UK (Dionne 2011; Guinn 2000; Hay 1995; Johnson 1985; Lewis 1983), the USA (Al-Ibraheemi 2018; Amorosa 2017; Blumenthal 1990; Browne 2011; Carbone 2013; Casey 1995; Culver 2004; Edwards 2014c; Hibbard 1998; Hoppe 2016; Hudon 1999; Jagani 1982; Krammer 1995a; Mackeen 2018; Mullin 2002; Perry 1998; Ridgway 1991; Roberts 1986; Rouben 1993; Sanchez-Ramos 1992; Sciscione 1999; Suffecool 2014; Sullivan 1996; Tita 2006; Turnquest 1997).

Dates

The study of Blumenthal 1990 and Sanchez-Ramos 1992 took place between 1980 and 1989; the studies of Allouche 1993, Guinn 2000, Hemlin 1998, Hibbard 1998, Khamaiseh 2012, Lyndrup 1994, Orhue 1995, Perry 1998, Roudsari 2011, Roztocil 1998, Sciscione 1999, St Onge 1995, Sullivan 1996 and Turnquest 1997 between 1990 and 1999; the studies of Tabowei 2003, Culver 2004 and Mullin 2002 between 1998 and 2001; the studies of Al-Taani 2004, Cromi 2011, Deshmukh 2011, Dionne 2011, Filho 2002, Joshi 2016, Jozwiak 2012, Jozwiak 2013, Krammer 1995a, Lokkegaard 2015, Matonhodze 2003, Mazhar 2003, Moini 2003, Niromanesh 2003, Oliveira 2010, Pennell 2009, Prager 2008, Roudsari 2011, Rudra 2012, Saleem 2006, Sharami 2005 and Tita 2006 between 2000 and 2009; the studies of Jozwiak 2014 and Salim 2011 between 2008 and 2011; and the studies of Aduloju 2016, Ahmed 2016, Al-Ibraheemi 2018, Amorosa 2017, Barda 2018, Browne 2011, Carbone 2013, Chavakula 2015, Cromi 2012, Edwards 2014c, El Khouly 2017, Garba 2016, Goonewardene 2014, Haugland 2012, Henry 2013, Hoppe 2016, Kandil 2012, Kruit 2016, Kuppulakshmi 2016, Laddad 2013, Mundle 2017, Noor 2015, Sarreau 2016, Somirathne 2017, Suffecool 2014, ten Eikelder 2016, Wang 2014 and Wu 2017 between 2010 and the present day.

For the remaining studies, no study period was reported (Atad 1996; Bagratee 1990; Benzineb 1996; Casey 1995; Chua 1997; Dalui 2005; Deo 2012; Gelisen 2005; Gilson 2017; Glagoleva 1999; Gunawardena 2012; Hay 1995; Hudon 1999; Jagani 1982; Jeeva 1982; Johnson 1985; Lanka 2014; Lanka 2014; Lewis 1983; Lyndrup 1989; Ntsaluba 1997; Ophir 1992; Pineda Rivas 2016; Ridgway 1991; Roberts 1986; Rouben 1993; Solt 2009; Shechter-Maor 2015; Sheikher 2009; Tan 2015; Wang 2012; Yuen 1996).

Participants

Most studies included both nulliparous and multiparous women. Nine studies included only nulliparous women (Culver 2004; Deshmukh 2011; Gunawardena 2012; Johnson 1985; Kandil 2012; Pennell 2009; Sharami 2005; Suffecool 2014; Wang 2012) and two studies included only multiparous women (Al-Taani 2004; Garba 2016).

Thirteen studies included women with a specific indication for labour induction or specific patient groups, i.e. women with a hypertensive disease (Mundle 2017), women with a body mass index (BMI) greater than 30 (Pineda Rivas 2016), post-date pregnancies (Gelisen 2005; Goonewardene

2014; Gunawardena 2012; Kandil 2012; Somirathne 2017), oligohydramnios (Shechter-Maor 2015; Wang 2014) or pre labour rupture of membranes (PROM; Amorosa 2017; Kruit 2016; Mackeen 2018; Tita 2006). Most authors specified that only women with intact membranes were included, except for Prager 2008, in which this was not an exclusion criteria. Orhue 1995, Roudsari 2011 and Roztocil 1998 reported nothing on membrane status, so it was not clear if women with ruptured membranes could be included.
Most studies excluded women with a past history of caesarean section, although four studies only included women with a past history of caesarean section (Joshi 2016; Meetei 2015; Sarreau 2016; Tabowei 2003). Three studies did not exclude women with a past history of caesarean section, but did not specify the outcomes for this subgroup of women separately (Mackeen 2018; Tabowei 2003; Tita 2006). Benzineb 1996, Cromi 2011, Deo 2012, Guinn 2000, Haugland 2012, Lyndrup 1994, Pineda Rivas 2016, Rouben 1993, and Wu 2017 reported nothing on previous caesarean section in their inclusion and exclusion criteria.

The majority of studies included women with a gestational age beyond 37 weeks, except for Edwards 2014c and Hemlin 1998 who reported a minimal gestational age of 36 weeks, Amorosa 2017, Chavakula 2015, Cromi 2011, Cromi 2012, Mackeen 2018Matonhodze 2003, Pennell 2009; Roudsari 2011 and Sharami 2005 of 34 weeks, Dalui 2005 of 33 weeks, Lokkegaard 2015 of 32 weeks, Culver 2004, Lanka 2014 and El Khouly 2017 of 28 weeks, Browne 2011 of 26 weeks, Carbone 2013 of 24 weeks and Mundle 2017 of 20 weeks, although in this last study, no women with a gestational age below 28 weeks were included.

Twenty-four studies were not clear on their inclusion and exclusion criteria: Gilson 2017, Jeeva 1982 and Kuppulakshmi 2016 reported no inclusion or exclusion criteria. Jagani 1982, Rudra 2012 and Turnquest 1997 only reported that women with intact membranes were included. Glagoleva 1999 only reported that women with a previous caesarean section were excluded. Bagratee 1990, Dionne 2011, Johnson 1985, Lyndrup 1989, Ridgway 1991, Solt 2009; Sullivan 1996 reported that only women with an indication for labour induction with an unfavourable cervix were included. Hemlin 1998 reported nothing on membrane status or previous caesarean section. Casey 1995, Garba 2016, Hudon 1999, Krammer 1995a, Lemyre 2006, Lewis 1983 and Saleem 2006 reported nothing on fetal presentation, membrane status or previous caesarean section. Chua 1997 and Ophir 1992 reported nothing on gestational age, fetal presentation, membrane status or previous caesarean section.

Interventions and comparisons
The protocol of administration in the intervention and in the control groups varied between studies. Different mechanical devices were evaluated (i.e. balloon catheter, laminaria tents, and extra-amniotic infusion). Prostaglandins (intracervical or intravaginal PGE2, and oral or vaginal misoprostol) were used with different protocols of administration. We regrouped these protocols as follows: (1) balloon catheter versus other interventions; (2) laminaria tent versus other interventions: (3) extra-amniotic infusion versus other interventions; (4) any mechanical method combined with other (non-mechanical) intervention versus other interventions. For this last group of comparisons, we considered both PGE2 (intracervical or intravaginal PGE2) and misoprostol (oral or vaginal misoprostol) as a single intervention. The information on comparisons made in each trial, used device and balloon size is summarised below.

Studies evaluating laminaria or Dilapan were considered together, irrespective of the number of devices inserted. Similarly, evaluations of a Foley catheter (regardless of sizes and amount of liquid used to inflate the balloon and traction applied on the catheter) and a specially designed double-balloon catheter (ATAD or Cook catheter), we considered as similar interventions. However, when a catheter was used to perform extra-amniotic saline infusion (EASI), we considered these studies separately. Despite having regrouped similar interventions, this review still includes a large number of comparisons.

Most of the studies included in the review examined a balloon and compared it with either vaginal PGE2 or with vaginal or oral misoprostol. A smaller number of studies examined a balloon versus either intracervical PGE2 or oxytocin. Since the last update, no more studies have been published about induction of labour with a Laminaria tent or with EASI. None of the included studies examined the combination of a mechanical method with amniotomy.
The following comparisons were made in this review.

1. Balloon comparisons

Balloon (Foley or ATAD) versus vaginal prostaglandin E2

PGE2 tablets: Al-Taani 2004 (50 cc); Atad 1996 (double balloon); Barda 2018 (80 cc); Khamaiseh 2012 (50 cc to 60 cc); Lokkegaard 2015 (double balloon); Niromanesh 2003 (30 cc); Ophir 1992 (40 cc); Pennell 2009 (30 cc and double balloon); Tan 2015 (double balloon).
PGE2 gel: Browne 2011 (40 cc); Deo 2012 (30 cc); Deshmukh 2011 (balloon size unknown); Henry 2013 (30 cc); Jozwiak 2012 (30 cc); Orhue 1995 (30 cc); Prager 2008 (30 cc); Rouben 1993 (30 cc); Rudra 2012 (40 cc).
*PGE2 vaginal insert:*Cromi 2011 (50 cc; for this comparison the two groups of Foley catheter (12 hours and 24 hours) were combined); Cromi 2012 (double balloon); Edwards 2014c (30 cc); Jozwiak 2013 (30 cc); Lewis 1983 (30 cc); Lyndrup 1994 (30 cc); Pineda Rivas 2016 (balloon size unknown); Saleem 2006 (40 cc to 50cc); Shechter-Maor 2015 (double balloon); Suffecool 2014 (double balloon); Wang 2012 (80 cc); Wang 2014 (double balloon); Yuen 1996 (double balloon).

Balloon (Foley or ATAD) versus intracervical prostaglandin E2

PGE2 intracervical gel:Allouche 1993 (50 cc); gel: Benzineb 1996 (40 cc); Dalui 2005 (30 cc); Gunawardena 2012 (balloon size unknown); Hudon 1999 (40 cc); Kuppulakshmi 2016 (30 cc); Laddad 2013: (balloon size unknown); Moini 2003 (30 cc); Ntsaluba 1997 (30 cc); Sciscione 1999 (30 cc); St Onge 1995 (30 cc); Yuen 1996 (double balloon).

Balloon (Foley or ATAD) versus low-dose vaginal misoprostol

Misoprostol tablets: Aduloju 2016 (30 cc); Chavakula 2015 (30 cc); Filho 2002 (30 cc); Jozwiak 2014 (30 cc); Kandil 2012 (30 cc); Lemyre 2006 (balloon size unknown); Noor 2015 (50 cc); Oliveira 2010 (30 cc); Prager 2008 (30 cc); Roudsari 2011 (50 cc); Sheikher 2009 (30 cc); Tabowei 2003 (50 cc).

Balloon (Foley or ATAD) versus low-dose oral misoprostol

*Misoprostol tablets:*Goonewardene 2014 (balloon size unknown); Kruit 2016 (50 cc to 60 cc); Mundle 2017 (30 cc); Saleem 2006 (40 cc to 50 cc); Sheikher 2009 (30 cc); Somirathne 2017 (60 cc);ten Eikelder 2016 (30 cc). *misoprostol solution:*Matonhodze 2003 (50 cc).

Balloon (Foley or ATAD) versus oxytocin
Amorosa 2017 (60 cc); Atad 1996 (double balloon); El Khouly 2017 (30 cc); Gelisen 2005 (50 cc); Jagani 1982 (70 to 80 cc); Joshi 2016; (30 cc); Meetei 2015 (30 cc); Orhue 1995 (30 cc); Sarreau 2016 (50 cc).

Balloon (Foley or ATAD) versus amniotomy
Jagani 1982 (70 cc to 80 cc).

Single balloon (Foley versus double balloon (ATAD)
Ahmed 2016 (50 cc); Haugland 2012 (size unknown); Hoppe 2016 (30 cc); Pennell 2009 (30 cc); Salim 2011 (60 cc); Solt 2009 (balloon size unknown). No studies were found for the comparison of a balloon versus oxytocin with amniotomy.

2. Laminaria comparisons
Laminaria tent versus vaginal prostaglandin E2
*PGE2 tablets:*Bagratee 1990 (Lamicel); Hay 1995 (Dilapan); Jeeva 1982; (laminaria).
*PGE2 gel:*Johnson 1985 (Lamicel); Roudsari 2011 (Dilapan); Sanchez-Ramos 1992 (Dilapan).

Laminaria tent versus intracervical prostaglandin E2
*PGE2 intracervical gel:*Chua 1997 (Dilapan); Glagoleva 1999 (Dilapan); Krammer 1995a; (Dilapan); Roztocil 1998 (Dilapan).

Laminaria tent versus oxytocin
Jagani 1982 (70 to 80 cc); Roberts 1986 (Lamicel).

Laminaria tent versus amniotomy
Jagani 1982 (70 to 80 cc).

Laminaria tent versus other hygroscopic dilator
Blumenthal 1990 (Dilapan versus laminaria tent).
No studies were found for the comparison of laminaria tent versus oxytocin with amniotomy or laminaria tent versus vaginal or oral misoprostol.

3. EASI comparisons
The only studies which were found compared EASI with PGE2.

EASI versus vaginal prostaglandin E2
*Vaginal insert:*Mazhar 2003.

EASI versus intracervical prostaglandin E2
*Intracervical gel:*Hemlin 1998.

4. Any mechanical combined with prostaglandin E2 comparisons
Any mechanical method combined with prostaglandin E2 versus prostaglandin E2 alone
*PGE2 intracervical gel:*Allouche 1993 (50 cc); Casey 1995 (50 cc); Ridgway 1991 (Lamicel); Sullivan 1996 (50 cc).

*PGE2 vaginal gel:*Browne 2011 (40 cc); Hibbard 1998 (Dilapan); Lyndrup 1989; (Lamicel); Turnquest 1997 (Laminaria)

Any mechanical method combined with prostaglandin E2 versus low-dose misoprostol alone
*Vaginal misoprostol:*Perry 1998.

Any mechanical method combined with prostaglandin E2 versus oxytocin alone
Lyndrup 1989 (Lamicel).
No studies were found which compared a mechanical method combined with PGE2 with amniotomy or oxytocin with amniotomy

5. Any mechanical combined with low-dose misoprostol comparisons
Any mechanical method combined with low-dose misoprostol versus prostaglandin E2 alone
Oral misoprostol: Matonhodze 2003.

Any mechanical method combined with low-dose misoprostol versus low-dose misoprostol alone
*Vaginal misoprostol:*Aduloju 2016 (30 cc); Al-Ibraheemi 2018 (60 cc); Carbone 2013 (60 cc); Dionne 2011 (balloon size and dosage of misoprostol unknown); Lanka 2014 (30 cc).
Oral misoprostol: Matonhodze 2003 (50 cc).
No studies were found which compared a mechanical method combined with low-dose misoprostol with amniotomy, oxytocin or oxytocin with amniotomy.

6. Any mechanical method combined with oxytocin comparisons
Any mechanical method combined with oxytocin versus prostaglandin E2 alone
*PGE2 intracervical gel:*Guinn 2000 (laminaria + oxytocin and EASI + oxytocin); Lyndrup 1989 (Lamicel); Sharami 2005 (EASI).

Any mechanical method combined with oxytocin versus low-dose misoprostol alone
*Vaginal misoprostol:*Culver 2004 (30 cc); Dionne 2011 (balloon size unknown); Gilson 2017 (30 cc); Garba 2016 (balloon size and dosage of misoprostol unknown); Mullin 2002.

Any mechanical method combined with oxytocin versus oxytocin alone
El Khouly 2017 (30 cc); Lyndrup 1989 (Lamicel); Mackeen 2018 (30 cc); Tita 2006 (balloon size unknown); Wu 2017 (double balloon). No studies were found which compared a mechanical method combined with oxytocin to amniotomy or oxytocin with amniotomy.

Outcomes
The study authors frequently reported on continuous outcome measures such as change in the cervical status or time to onset of labour, but also mean Apgar score after five minutes and mean pH in the umbilical artery. As these were not pre-specified in our protocol, we have not included these results in the review. In several studies, the only pre-specified result available was the number of women delivered by caesarean section. Maternal or neonatal death were infrequently pre-specified by the authors and therefore not specifically reported. Therefore, these outcomes could not be included in this review.

Maternal satisfaction was reported in seven studies (Ahmed 2016; Chavakula 2015; Gilson 2017; Henry 2013; Lyndrup 1994; Mundle 2017; Shechter-Maor 2015). Of these seven studies, only three studies contributed data for the meta-analysis (Gilson 2017; Lyndrup 1994; Mundle 2017). The other four studies reported on maternal satisfaction with continuous data. Because of the importance of this outcome, we decided to report these results in narrative form.

Source of trial funding

Only 14 trials provided details for their funding sources: Filho 2002 received financial support from CAPES. Guinn 2000 reported that UpJohn Pharmaceuticals provided funds to purchase study drugs. Kruit 2016 received a grand from the Finnish medical society Duodecim and Helsinky university central hospital. Lokkegaard 2015 reported the randomisation procedure was funded by Snedkermester Sophus Jacobsen & Astrid Jacobsens fond and the Danish Toyota Foundation. Mackeen 2018 received a small internal grant to assist with the conduct and statistical analyses for the entire study. Mundle 2017 received funding from the Department for International Development, Medical Research Council, and Wellcome Trust Joint Global Health Trials Scheme. The study of Pennell 2009 was supported by a grant from the Women and Infants Research Foundation and Adeza Biomedical Corporation contributed support for the fetal fibronectin test kits. Roberts 1986 and Sullivan 1996 stated they were supported by the Vicksburg hospital medical foundation. Salim 2011 received funding from the Emek medical centre. Tan 2015 reported that the double balloons were provided by Cook medical. ten Eikelder 2016 received funding from Fonds Nuts Ohra. Wang 2014 received financial support of The People's Liberation Army. Wu 2017 received a grant from the Nature Science Foundation of China.

Thirteen studies reported they received no funding (Aduloju 2016; El Khouly 2017; Garba 2016; Hoppe 2016; Jozwiak 2012; Jozwiak 2013; Jozwiak 2014; Laddad 2013; Lanka 2014; Meetei 2015; Shechter-Maor 2015; Somirathne 2017). All other studies did not provide information on received funding.

Declarations of interest

Thirty-five studies declared no conflict of interest (Aduloju 2016; Ahmed 2016; Al-Ibraheemi 2018; Amorosa 2017; Barda 2018; Chavakula 2015; Cromi 2012; Edwards 2014c; El Khouly 2017; Filho 2002; Garba 2016; Goonewardene 2014; Henry 2013; Hoppe 2016; Jozwiak 2012; Jozwiak 2013; Jozwiak 2014; Kandil 2012; Kruit 2016; Laddad 2013; Lanka 2014; Lewis 1983; Lokkegaard 2015; Mackeen 2018; Meetei 2015; Noor 2015; Pennell 2009; Salim 2011; Shechter-Maor 2015; Somirathne 2017;Tan 2015; ten Eikelder 2016; Wang 2014; Wu 2017).

Two studies reported they had conflicts of interest. Atad 1996 stated that the first author has a patent licensing arrangement for Atad ripening device and thus has the potential gain from its sales. Mundle 2017 reported that one of the authors was a scientific adviser to Azanta, a Danish pharmaceutical company.The remaining studies did not report whether any conflicts of interest were present.

Excluded studies

In total, 138 studies were excluded (see Characteristics of excluded studies), 74 studies (102 reports) in this update. In this update, most of the excluded trials (54 studies) made comparisons not within the scope of this review (Ahmad 2015; Arsenijevic 2012; Arshad 2016; Caughey 2007; Connolly 2016; Connolly 2017; Demirel 2015; Edwards 2017; El-Khayat 2016; El Shaky 2017; Forgie

2016; Forooshani 2011; Fruhman 2017; Gadel 2015; Ghanaei 2009; Ghanaie 2013; Gibson 2013; Gu 2015; Haghighi 2015; Hallak 2008; He 2000; Hill 2013; Hussein 2012; Ifnan 2006; Jonsson 2011; Kehl 2012; Kehl 2015; Lam 2006; Leong 2017; Levine 2016; Lutgendorf 2012; Manish 2016; Mattingly 2015; McGee 2016; Mei-Dan 2012a; Mei-Dan 2014; Movahed 2016; Mullin 2014; Neethurani 2013; Rameez 2007; Rezk 2014; Saad 2016; Salmeen 2012; Sandberg 2017; Schoen 2017; Sharma 2015a; Sharma 2017; Siddiqui 2013; Torbenson 2015;Walfisch 2015; Wickramasinghe 2014; Wilkinson 2015; Yaddehige 2015; Zakaria 2017).

Four studies were not randomised trials (Du 2015; Miller 2015; Naseem 2007; Nasir 2012) and one study did a cross-over after 24 hours (Ugwu 2013). Thirteen trial registration were excluded because they exceeded the participated end date by more than two years and it was presumed the trial was terminated before enrolment (Anabosy 2014; Baacke 2006; Behrashi 2013; Cullimore 2009; Dias 2008EUCTR 2012; Kamilya 2011; Mei-Dan 2012; Park 2011Pathiraja 2014; Reif 2012; Yazdani 2011; Zhang 2014). For more information, see Characteristics of excluded studies.

Risk of Bias

The quality assessments are graphically summarised in Figure 2 and Figure 3.

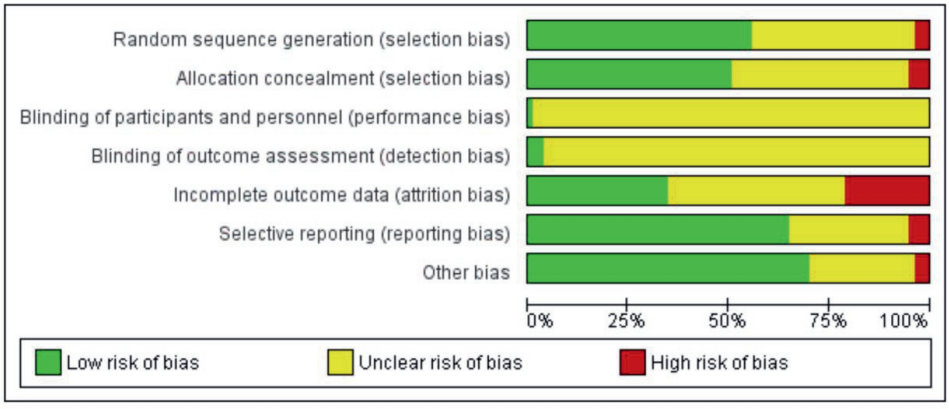


Figure 2: 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies

Allocation

Sequence generation

We judged 62 trials to be at low risk of selection bias, reporting some form of adequate random sequencing such as a computer-generated sequence or a list of random numbers (Aduloju 2016; Ahmed 2016; Al-Ibraheemi 2018; Al-Taani 2004; Amorosa 2017; Atad 1996; Bagratee 1990; Blumenthal 1990; Browne 2011; Carbone 2013; Chavakula 2015; Chua 1997; Cromi 2011; Cromi 2012; Culver 2004; Deo 2012; Edwards 2014c; El Khouly 2017; Filho 2002; Garba 2016; Gelisen 2005; Goonewardene 2014; Guinn 2000; Henry 2013; Hibbard 1998; Johnson 1985; Jozwiak 2012; Jozwiak 2013; Jozwiak 2014; Khamaiseh 2012; Krammer 1995a; Lanka 2014; Lokkegaard 2015; Mackeen 2018; Matonhodze 2003; Mazhar 2003; Meetei 2015; Mullin 2002; Mundle

2017; Niromanesh 2003; Oliveira 2010; Ophir 1992; Orhue 1995; Perry 1998; Prager 2008; Rouben 1993; Salim 2011; Sanchez-Ramos 1992; Sciscione 1999; Sharami 2005; Shechter-Maor 2015; Solt 2009; Somirathne 2017; St Onge 1995; Suffecool 2014; Tabowei 2003; Tan 2015; ten Eikelder 2016; Turnquest 1997; Wang 2012; Yuen 1996).

Three trials were classified as high risk because they were quasi-randomised trials. Jagani 1982 randomised by last digit of the chart number, Kandil 2012 randomised by odd or even admission date and Roztocil 1998 randomised by week of admission.

We judged the remaining 40 trials to be at unclear risk of selection bias, as they did not report on how a random sequence was generated (Allouche 1993; Barda 2018; Benzineb 1996; Casey 1995; Dalui 2005; Deshmukh 2011; Dionne 2011; Gilson 2017; Glagoleva 1999; Gunawardena 2012; Haugland 2012; Hay 1995; Hemlin 1998; Hoppe 2016; Hudon 1999; Jeeva 1982; Joshi 2016; Kruit 2016; Kuppulakshmi 2016; Laddad 2013; Lemyre 2006; Lewis 1983; Lyndrup 1989; Lyndrup 1994; Moini 2003; Noor 2015; Ntsaluba 1997; Pennell 2009; Pineda Rivas 2016; Ridgway 1991; Roberts 1986; Roudsari 2011; Rudra 2012; Saleem 2006; Sarreau 2016; Sheikher 2009; Sullivan 1996;Tita 2006; Wang 2014; Wu 2017).

Allocation concealment

Fifty-five studies reported a method of allocation concealment likely to have a low risk of bias, either by central randomisation or sequentially numbered, sealed, opaque envelopes (Aduloju 2016; Ahmed 2016; Al-Ibraheemi 2018; Amorosa 2017; Blumenthal 1990; Browne 2011; Carbone 2013; Chavakula 2015; Cromi 2012; Culver 2004; Deo 2012; Edwards 2014c; El Khouly 2017; Filho 2002; Gelisen 2005; Goonewardene 2014; Guinn 2000; Hemlin 1998; Henry 2013; Hibbard 1998; Hoppe 2016; Jozwiak 2012; Jozwiak 2013; Jozwiak 2014; Kruit 2016; Lanka 2014; Lokkegaard 2015; Lyndrup 1989; Lyndrup 1994; Matonhodze 2003; Mullin 2002; Mundle 2017; Niromanesh 2003; Ntsaluba 1997; Oliveira 2010; Orhue 1995; Pennell 2009; Perry 1998; Prager 2008; Roberts 1986; Rouben 1993; Salim 2011; Sciscione 1999; Sharami 2005; Somirathne 2017; St Onge 1995; Suffecool 2014; Sullivan 1996; Tabowei 2003; Tan 2015; ten Eikelder 2016; Turnquest 1997; Wang 2014; Yuen 1996).

Five studies were judged to be high risk. In the quasi-randomised trials of Jagani 1982, Kandil 2012 and Roztocil 1998 no measures were taken to conceal the allocation; Mackeen 2018 stated that the allocation was not concealed and Ophir 1992 allocated women by odd or even randomisation number.

The remaining 45 studies did not report a method for concealing allocation and were judged as being at unclear risk of bias (Allouche 1993; Al-Taani 2004; Atad 1996; Bagratee 1990; Barda 2018; Benzineb 1996; Casey 1995; Chua 1997; Cromi 2011; Dalui 2005; Deshmukh 2011; Dionne 2011; Garba 2016; Gilson 2017; Glagoleva 1999; Gunawardena 2012; Haugland 2012; Hay 1995; Hudon 1999; Jeeva 1982; Johnson 1985; Joshi 2016; Khamaiseh 2012; Krammer 1995a; Kuppulakshmi 2016; Laddad 2013; Lemyre 2006; Lewis 1983; Mazhar 2003; Meetei 2015; Moini 2003; Noor 2015; Pineda Rivas 2016; Ridgway 1991; Roudsari 2011; Rudra 2012; Saleem 2006; Sanchez-Ramos 1992; Sarreau 2016; Shechter-Maor 2015; Sheikher 2009; Solt 2009; Tita 2006; Wang 2012; Wu 2017).

Blinding

Performance bias

Given the nature of the intervention (mechanical methods for induction of labour) and comparison (pharmacological methods for induction of labour), it was not possible for women or clinicians to be blinded to the treatment group in any of the trials. For the more objective outcomes such as perinatal death, the lack of blinding is unlikely to be a major source of bias. Therefore, risk of performance bias was judged as unclear in all studies, but was a reason to downgrade the quality of evidence from high to moderate.

Detection bias

It would have been possible for outcome assessment to have been undertaken by someone blinded to allocation groups. However, only four trials reported blinded outcome assessment (rated as low risk of bias). Gelisen 2005 blinded only for the outcome of hyperstimulation. In the studies of Pennell 2009 and Gelisen 2005, data were collected by research midwives who were blinded to the intervention. Rudra 2012 and Haugland 2012 both stated they performed a double blind-trial but provided too little information to assess how this was done. The remaining 101 trials did not detail whether outcome assessment was blinded, and thus we judged risk of detection bias to be unclear. Measurement of outcomes such as perinatal death are unlikely to be biased by lack of blinding.

Incomplete outcome data

We considered 38 studies to be at low risk of attrition bias with data analyses according to intention-to-treat and minimal/no loss to follow-up or exclusion of women (Aduloju 2016; Al-Ibraheemi 2018; Al-Taani 2004; Amorosa 2017; Atad 1996; Carbone 2013; Chavakula 2015; Chua 1997; Cromi 2011; Culver 2004; Dalui 2005; Deshmukh 2011; Edwards 2014c; El Khouly 2017; Filho 2002; Guinn 2000; Henry 2013; Jeeva 1982; Jozwiak 2012; Jozwiak 2013; Jozwiak 2014; Lanka 2014; Lokkegaard 2015; Mackeen 2018; Mullin 2002; Mundle 2017; Noor 2015; Ntsaluba 1997; Oliveira 2010; Pennell 2009; Perry 1998; Prager 2008; Roberts 1986; Roztocil 1998; Suffecool 2014; Sullivan 1996; ten Eikelder 2016; Wu 2017).

Forty-three studies were judged to be at unclear risk of attrition bias, mainly because it was not clear if intention-to-treat analyses was used (Allouche 1993; Benzineb 1996; Garba 2016; Gelisen 2005; Hemlin 1998; Hibbard 1998; Hoppe 2016; Jagani 1982; Johnson 1985; Joshi 2016; Khamaiseh 2012; Laddad 2013; Lewis 1983; Matonhodze 2003; Meetei 2015; Niromanesh 2003; Roudsari 2011; Salim 2011; Sanchez-Ramos 1992; Sharami 2005; Shechter-Maor 2015; Somirathne 2017; St Onge 1995), or there was too little information to judge attrition bias (Barda 2018; Casey 1995; Dionne 2011; Gilson 2017; Glagoleva 1999; Gunawardena 2012; Haugland 2012; Hay 1995; Hudon 1999; Kuppulakshmi 2016; Lemyre 2006; Mazhar 2003; Moini 2003; Pineda Rivas 2016; Ridgway 1991; Rudra 2012; Saleem 2006; Sarreau 2016; Solt 2009; Tabowei 2003). Twenty-four studies were classified as high risk for attrition bias. In the studies of Ahmed 2016, Cromi 2012 and Wang 2014, women were excluded because of failed placement of the balloon. Kandil 2012 also excluded nine patients because of failed placement of the Foley catheter, but replaced them with women who did receive a Foley catheter. Deo 2012 analysed data as treated and also four cases went missing without a given explanation. Kruit 2016, Lyndrup 1989, Sciscione 1999, Tan 2015, Turnquest 1997, Wang 2012 and Yuen 1996 excluded cases because of protocol violation and Krammer 1995a reported they analysed intention-to-treat, but eventually excluded women because of protocol violation or if they

delivered within six hours after induction had started. Goonewardene 2014 also excluded women if they went into spontaneous labour after the intervention. Lyndrup 1994 excluded women if they delivered after 48 hours of induction had started. Orhue 1995 excluded women if they had an unfavourable cervix after 12 hours of induction. Rouben 1993 excluded women after failed induction. The studies of Bagratee 1990, Blumenthal 1990, Browne 2011, Ophir 1992, Sheikher 2009, Tita 2006 were judged to be of high risk for attrition bias because cases were missing without a given explanation.

Selective reporting

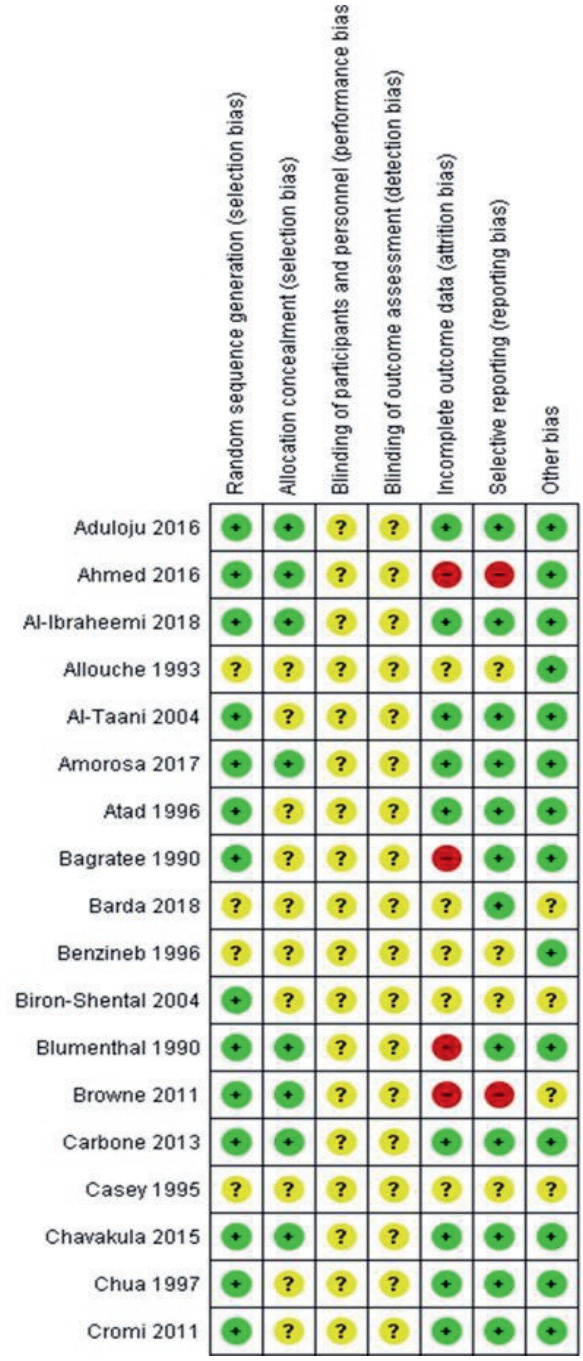
Seventy-two studies were judged to be at low risk of reporting bias as all pre-specified outcomes were reported (Aduloju 2016; Al-Ibraheemi 2018; Al-Taani 2004; Amorosa 2017; Atad 1996; Bagratee 1990; Barda 2018; Blumenthal 1990; Carbone 2013; Chavakula 2015; Chua 1997; Cromi 2011; Cromi 2012; Culver 2004; Dalui 2005; Deo 2012; Deshmukh 2011; Edwards 2014c; El Khouly 2017; Filho 2002; Garba 2016; Gelisen 2005; Goonewardene 2014; Guinn 2000; Hemlin 1998; Henry 2013; Hibbard 1998; Hoppe 2016; Jagani 1982; Johnson 1985; Joshi 2016; Jozwiak 2012; Jozwiak 2013; Jozwiak 2014; Kandil 2012; Khamaiseh 2012; Krammer 1995a; Kruit 2016; Kuppulakshmi 2016; Lanka 2014; Lokkegaard 2015; Lyndrup 1994; Mackeen 2018; Matonhodze 2003; Mazhar 2003; Meetei 2015; Mullin 2002; Mundle 2017; Noor 2015; Ntsaluba 1997;Oliveira 2010; Ophir 1992; Orhue 1995; Pennell 2009; Perry 1998; Prager 2008; Rouben 1993; Roztocil 1998; Salim 2011; Sciscione 1999; Sharami 2005; Solt 2009; Somirathne 2017; St Onge 1995; Suffecool 2014; Sullivan 1996; Tabowei 2003; ten Eikelder 2016; Turnquest 1997; Wang 2012;Wu 2017; Yuen 1996). It is important to note that not all studies had a trial protocol available and therefore it was not possible to check if there were other pre-specified outcomes not reported in the method section of the article.

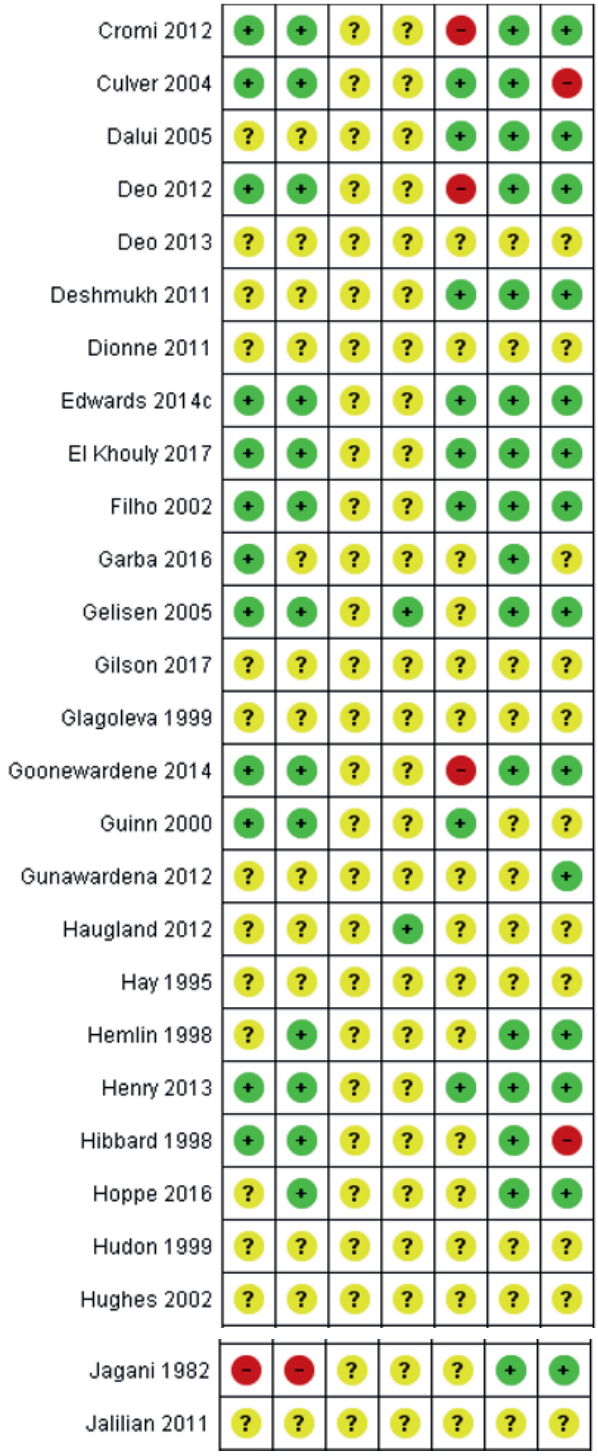
Twenty-eight studies were judged to be of unclear risk of reporting bias. In 10 studies no outcomes were pre-specified in the methods section (Allouche 1993; Benzineb 1996; Jeeva 1982; Laddad 2013; Lewis 1983; Lyndrup 1989; Roberts 1986; Sanchez-Ramos 1992; Tan 2015; Wang 2014 and in 18 studies there was too little information to judge reporting bias (Casey 1995; Dionne 2011; Gilson 2017; Glagoleva 1999; Guinn 2000; Gunawardena 2012; Haugland 2012; Hay 1995; Hudon 1999; Lemyre 2006; Moini 2003; Niromanesh 2003; Pineda Rivas 2016; Ridgway 1991; Roudsari 2011; Rudra 2012; Saleem 2006; Sarreau 2016). The studies of Ahmed 2016, Browne 2011, Shechter-Maor 2015, Sheikher 2009 and Tita 2006 were judged as high risk as not all pre-specified outcomes were reported in the results section.

Other potential sources of bias

For 24 studies it was not clear if there was another source of bias and these were therefore judged as unclear. For one study (Barda 2018), only a manuscript with no tables was available. Two trials (Browne 2011; Tita 2006) were not published, but the results of the primary outcome and adverse events were reported in the trial registration. Guinn 2000 stopped recruiting women for one arm of the study without an explanation. Mullin 2002 calculated a sample size of 140 women but included 200 women without explanation. Prager 2008 included patients who did not meet inclusion criteria. Eighteen studies were only published as abstracts, or there was too little information provided and so it was not possible to judge the risk of bias (Casey 1995; Dionne 2011; Garba 2016; Gilson 2017; Glagoleva 1999; Haugland 2012; Hay 1995; Hudon 1999; Lemyre 2006; Oliveira 2010; Pineda Rivas

2016; Ridgway 1991; Rudra 2012; Sarreau 2016; Shechter-Maor 2015; Solt 2009; Tabowei 2003; Wang 2012). The studies of Culver 2004, Hibbard 1998, and Kruit 2016 were judged as high risk for other potential sources of bias as they were terminated early before the required sample size was recruited




Cromi 2012
Culver 2004
Dalui 2005
Deo 2012
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Deshmukh 2011
Dionne 2011
Edwards 2014c
El Khouly 2017
Filho 2002
Garba 2016
Gelisen 2005
Gilson 2017
Glagoleva 1999
Goonewardene 2014
Guinn 2000
Gunawardena 2012
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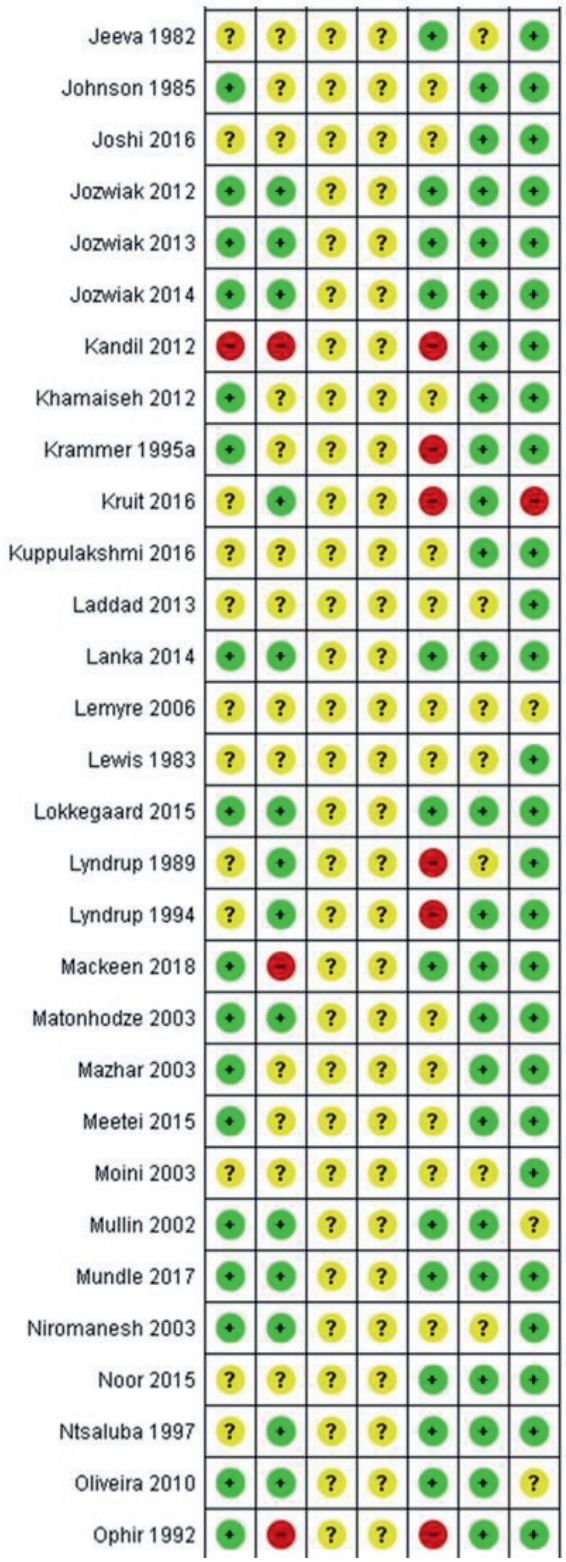
Hay 1995
Hemlin 1998
Henry 2013
Hibbard 1998
Hoppe 2016
Hudon 1999
Hughes 2002
Jagani 1982
Jalilian 2011


Jeeva 1982
Johnson 1985
Joshi 2016
Jozwiak 2012
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Kandil 2012
Khamaiseh 2012
Krammer 1995a
Kruit 2016
Kuppulakshmi 2016
Laddad 2013
Lanka 2014
Lemyre 2006
Lewis 1983
Lokkegaard 2015
Lyndrup 1989
Lyndrup 1994
Mackeen 2018
Matonhodze 2003
Mazhar 2003
Meetei 2015
Moini 2003
Mullin 2002
Mundle 2017
Niromanesh 2003
Noor 2015
Ntsaluba 1997
Oliveira 2010
Ophir 1992


Orhue 1995
Peedicayil 1998
Pennell 2009
Perry 1998
Pineda Rivas 2016
Prager 2008
Qamar 2012
Ridgway 1991
Roberts 1986
Rouben 1993
Roudsari 2011
Roztocil 1998
Rudra 2012
Saleem 2006
Salim 2011
Sanchez-Ramos 1992
Sarreau 2016
Sciscione 1999
Sharami 2005
Shechter-Maor 2015
Sheikher 2009
Solt 2009
Somirathne 2017
St Onge 1995
Suffecool 2014
Sullivan 1996
Tabowei 2003
Tan 2015
ten Eikelder 2016
Thiery 1981

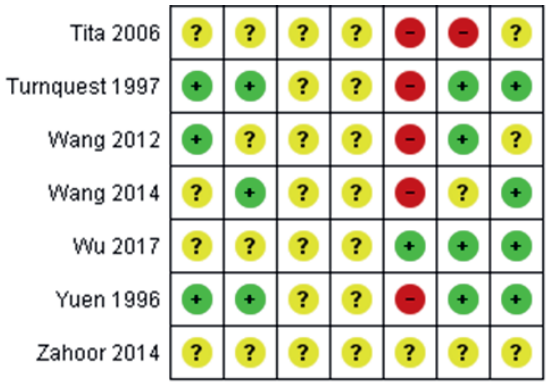


***Figure 3**: 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.*

This review update includes nine comparisons with more than 10 studies, of which we constructed funnel plots (Figure 4; Figure 5; Figure 6; Figure 7; Figure 8; Figure 9; Figure 10; Figure 11; Figure 12). Visual inspection of one funnel plot (Figure 5) was somewhat asymmetrical suggesting some form of publication bias for this outcome (oxytocin augmentation) for the comparison of a balloon versus vaginal PGE2. Visual assessment of the other funnel plots did not show asymmetry, suggesting there is no publication bias for these comparisons.

Effects of interventions

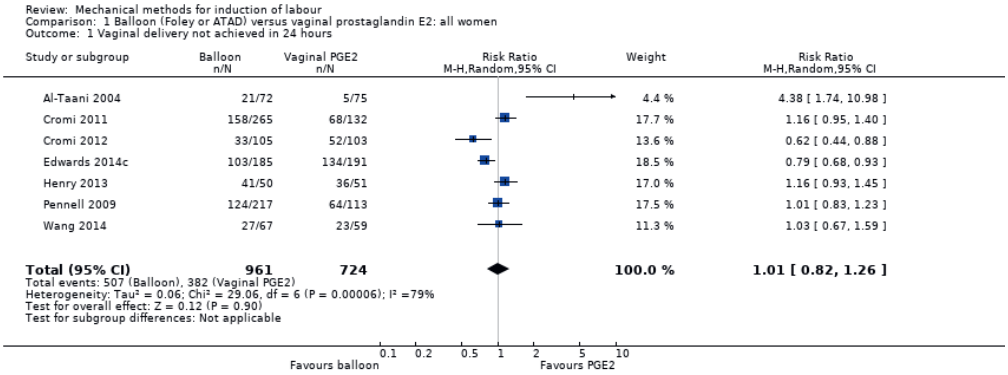
See: **Summary of findings for the main comparison** Balloon (Foley or ATAD) compared to vaginal prostaglandin E2 for third trimester labour induction in women with a viable fetus; **Summary of findings 2** Balloon (Foley or ATAD) compared to low-dose vaginal misoprostol for third trimester induction of labour in women with a viable fetus; **Summary of findings 3** Balloon (Foley or ATAD) compared to low-dose oral misoprostol for third trimester induction of labour in women with a viable fetus

Balloon (single or double) versus vaginal prostaglandin E2 (28 trials involving 6619 women)

Primary outcomes

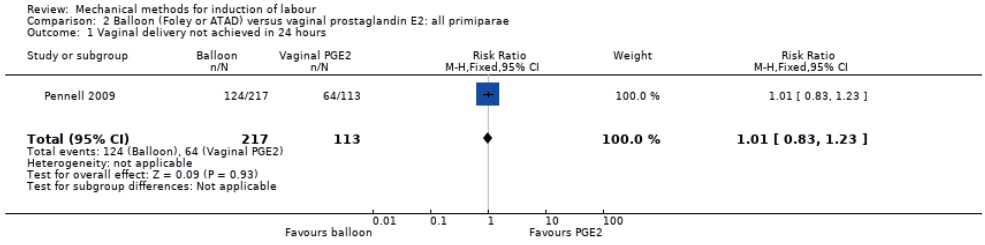
Vaginal delivery not achieved within 24 hours

There may be little or no difference in vaginal deliveries not achieved within 24 hours between induction of labour with a balloon catheter and vaginal PGE2 (average risk ratio (RR) 1.01, 95% confidence interval (CI) 0.82 to 1.26; 7 studies; 1685 women; low-quality evidence; Analysis 1.1), although there was substantial heterogeneity for this outcome ($Tau^2 = 0.06$; $Chi^2 = 29.06$, df = 6 (P =< 0.0001); $I^2 = 79\%$). A sensitivity analysis, after eliminating the two trials assessed as having a potentially higher risk of concealment or attrition bias (Cromi 2012; Wang 2014), did not change the effect observed, despite the result becoming less precise (average RR 1.10, 95% CI 0.86 to 1.41; 1351 women; 5 studies; $I^2 = 82\%$).

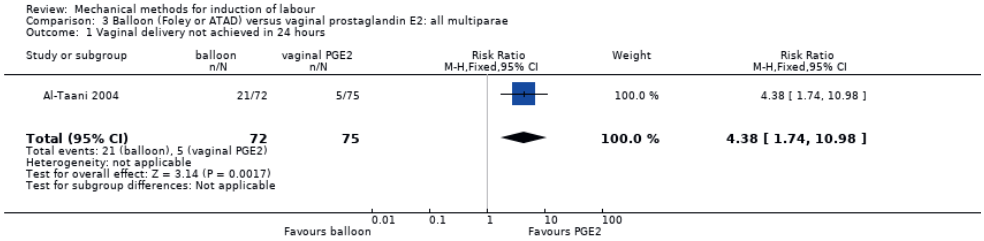


Analysis 1.1: *Comparison 1 Balloon (Foley or ATAD) versus vaginal prostaglandin E2: all women, Outcome 1 Vaginal delivery not achieved in 24 hours*

The same result was seen on a subgroup comparison for primiparous women (RR 1.01, 95% CI 0.83 to 1.23; 330 women; 1 study; Analysis 2.1). While for multiparous women, a balloon catheter may increase the risk of a vaginal delivery not being achieved within 24 hours (RR 4.38, 95% CI 1.74 to 10.98; 147 women; 1 study; Analysis 3.1).



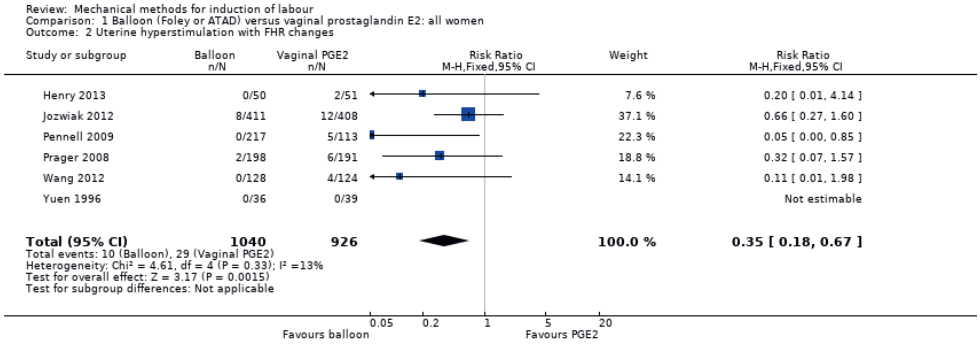
Analysis 2.1*: Comparison 2 Balloon (Foley or ATAD) versus vaginal prostaglandin E2: all primiparae, Outcome 1 Vaginal delivery not achieved in 24 hours.*



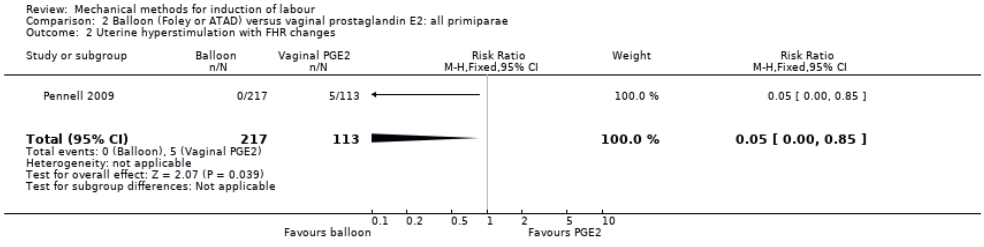
Analysis 3.1: *Comparison 3 Balloon (Foley or ATAD) versus vaginal prostaglandin E2: all multiparae, Outcome 1 Vaginal delivery not achieved in 24 hours.*

Uterine hyperstimulation with fetal heart rate (FHR) changes

A balloon catheter probably reduces the risk of uterine hyperstimulation with FHR changes when compared to vaginal PGE2 (RR 0.35, 95% CI 0.18 to 0.67; 6 studies; 1966 women; moderate-quality evidence; Analysis 1.2), the absolute effect being 21 less per 1000 deliveries.The same result was seen on a subgroup comparison for primiparous women (RR 0.05, 95% CI 0.00 to 0.85; 330 women; 1 study; Analysis 2.2). For multiparous women, no outcomes were reported.



Analysis 1.2*: Comparison 1 Balloon (Foley or ATAD) versus vaginal prostaglandin E2: all women, Outcome 2 Uterine hyperstimulation with FHR changes.*



Analysis 2.2*: Comparison 2 Balloon (Foley or ATAD) versus vaginal prostaglandin E2: all primiparae, Outcome 2 Uterine hyperstimulation with FHR changes*.

Caesarean section

There probably is little or no difference in caesarean sections between both induction methods (RR 1.00, 95% CI 0.92 to 1.09; 28 studies; 6619 women; moderate-quality evidence; Analysis 1.3). Visual inspection of the funnel plot associated with this outcome does not suggest any evidence of publication bias (Figure 4).

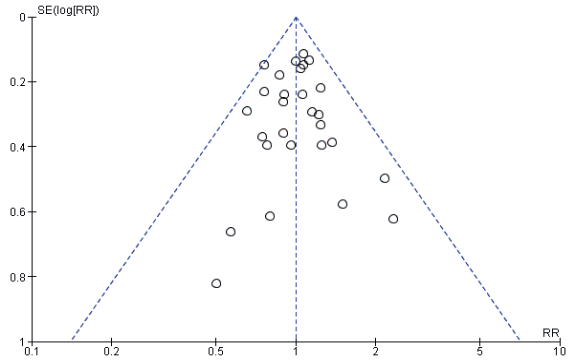
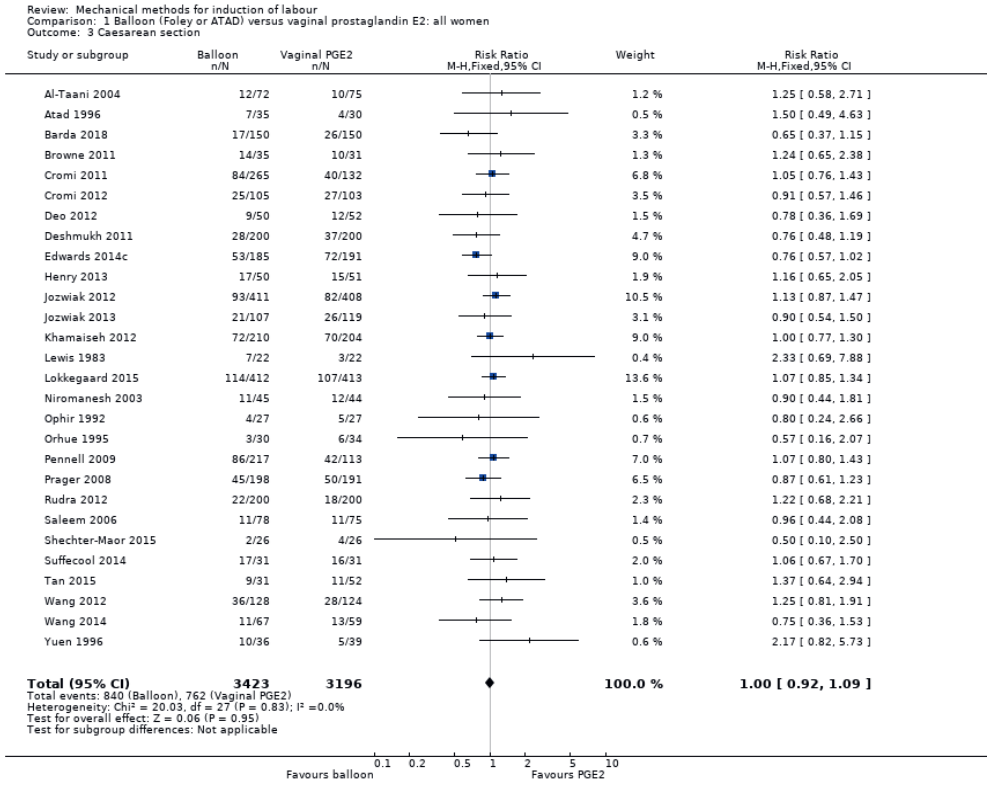
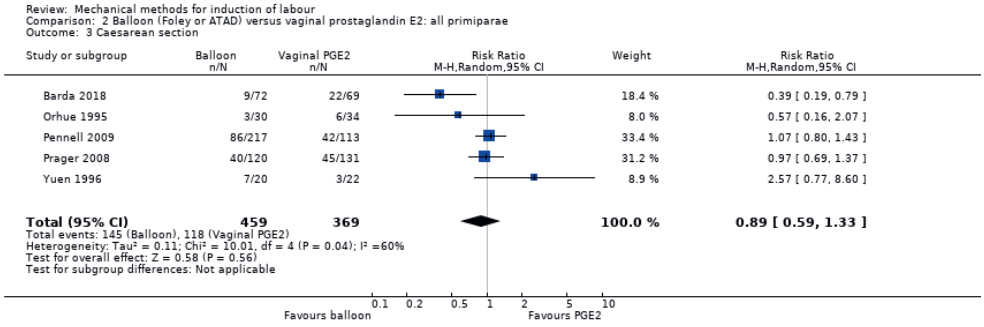


Figure 4: *Funnel plot of comparison: 1 Balloon (Foley or ATAD) versus vaginal Prostaglandin E2: all women, outcome: 1.3 Caesarean section*

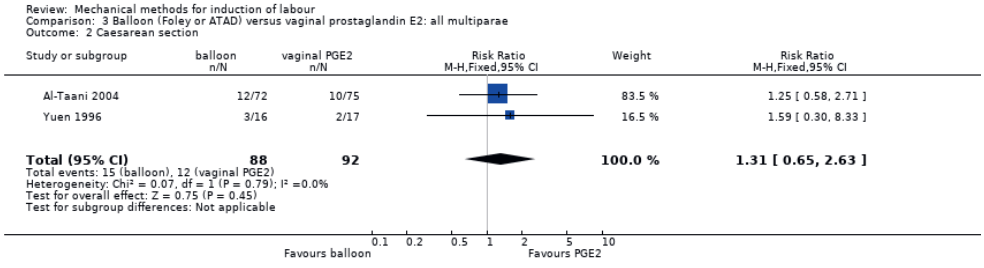


Analysis 1.3: *Comparison 1 Balloon (Foley or ATAD) versus vaginal prostaglandin E2: all women, Outcome 3 Caesarean section.*

It is uncertain whether there is a difference in caesarean sections between both induction methods on subgroups for both primiparous women (average RR 0.89, 95% CI 0.59 to 1.33; 828 women; 5 studies; Analysis 2.3) and multiparous women (RR 1.31, 95% CI 0.65 to 2.63; 180 women; 2 studies; Analysis 3.2) as the results of these outcomes were imprecise. Furthermore, for the primiparous group, there was also substantial heterogeneity ($Tau^2 = 0.11$; $Chi^2 = 10.01$, df = 4 (P = 0.04); $I^2 = 60\%$).



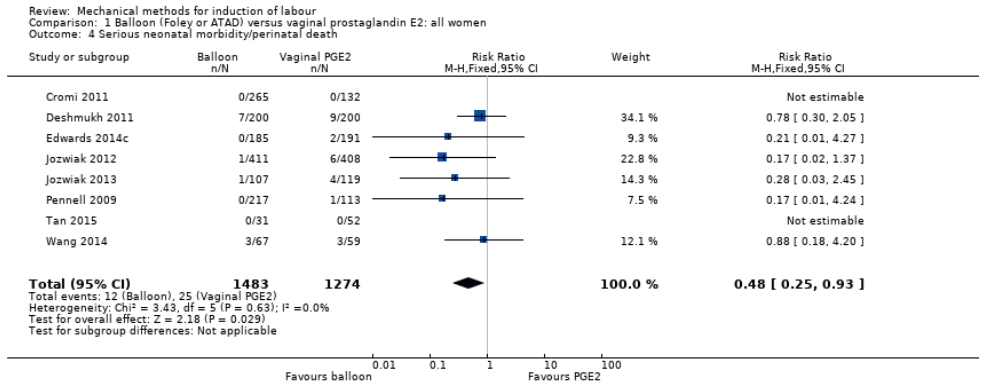
Analysis 2.3: *Comparison 2 Balloon (Foley or ATAD) versus vaginal prostaglandin E2: all primiparae, Outcome 3 Caesarean section.*



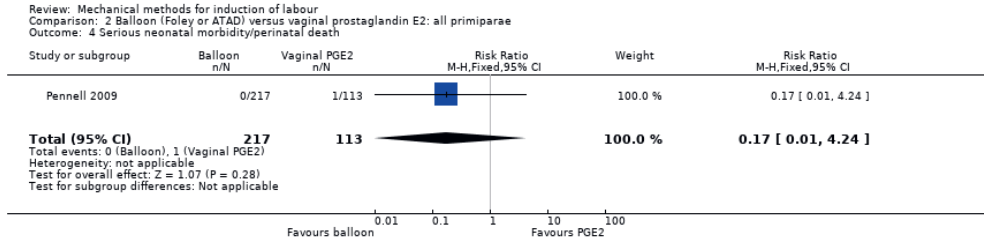
Analysis 3.2: *Comparison 3 Balloon (Foley or ATAD) versus vaginal prostaglandin E2: all multiparae, Outcome 2 Caesarean section.*

Serious neonatal morbidity or perinatal death

A balloon catheter probably reduces the risk of serious neonatal morbidity or perinatal death when compared to vaginal PGE2 (RR 0.48, 95% CI 0.25 to 0.93; 8 studies; 2757 women; moderate-quality evidence; Analysis 1.4). However, numbers are low (12/1483 versus 25/1274, respectively) and almost all of these numbers were cases of birth asphyxia. Only two perinatal deaths were reported, both in the PGE2 group (Edwards 2014c). No heterogeneity was seen for this outcome. For primiparous women, it is uncertain whether there is a difference in effect as the result for this outcome was imprecise (RR 0.17, 95% CI 0.01 to 4.24; 330 women; 1 study; Analysis 2.4). For multiparous women, no outcomes were reported.



Analysis 1.4*: Comparison 1 Balloon (Foley or ATAD) versus vaginal prostaglandin E2: all women, Outcome 4 Serious neonatal morbidity/perinatal death*

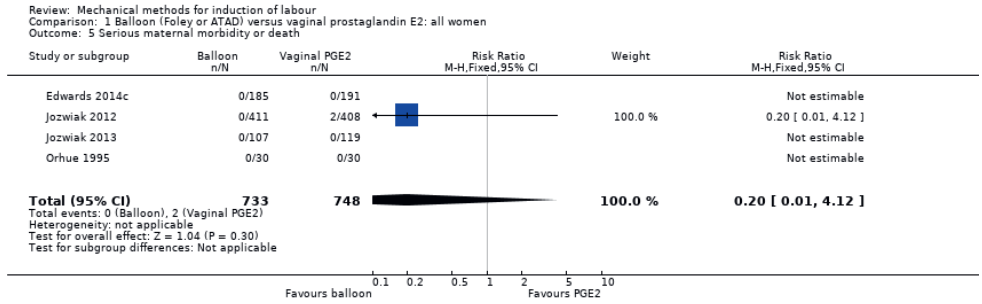


Analysis 2.4: *Comparison 2 Balloon (Foley or ATAD) versus vaginal prostaglandin E2: all primiparae, Outcome 4 Serious neonatal morbidity/perinatal death.*

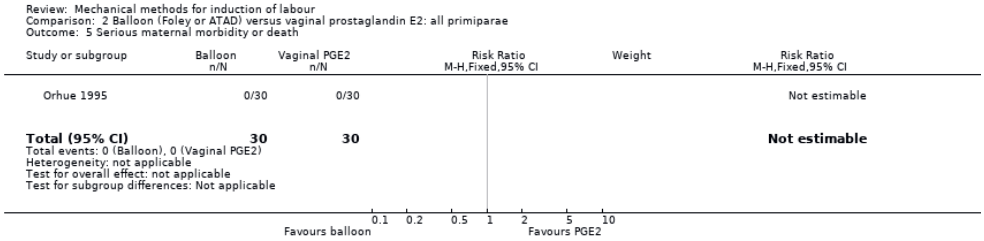
Serious maternal morbidity or death

It is uncertain whether there is a difference in serious maternal morbidity or death between both induction methods (RR 0.20, 95% CI 0.01 to 4.12; 4 studies; 1481 women; very low-quality evidence; Analysis 1.5). Of all the 28 studies included for this comparison, only four studies reported on this composite outcome. No events were reported in the balloon group. One author (Jozwiak 2012) reported two events in the PGE2 group, both events being uterine rupture.

Only one study (60 women) reported on this outcome in primiparous women, in which no events were seen (Analysis 2.5). For multiparous women, no outcomes were reported.



Analysis 1.5: *Comparison 1 Balloon (Foley or ATAD) versus vaginal prostaglandin E2: all women, Outcome 5 Serious maternal morbidity or death*



***Analysis 2.5**: Comparison 2 Balloon (Foley or ATAD) versus vaginal prostaglandin E2: all primiparae, Outcome 5 Serious maternal morbidity or death.*

Secondary outcomes

Cervix unfavourable/unchanged after 24 hours

Not reported.

Oxytocin augmentation

Induction of labour with a balloon catheter may increase the risk of oxytocin augmentation when compared to vaginal PGE2 (average RR 1.54, 95% CI 1.35 to 1.76; 4828 women; 16 studies; Analysis 1.6), although there was substantial heterogeneity for this outcome ($Tau^2 = 0.05$; $Chi^2 = 141.47$, df = 15 (P = < 0.0001); $I^2 = 89\%$). Visual inspection of the funnel plot was somewhat asymmetrical, suggesting some form of publication bias (Figure 5).

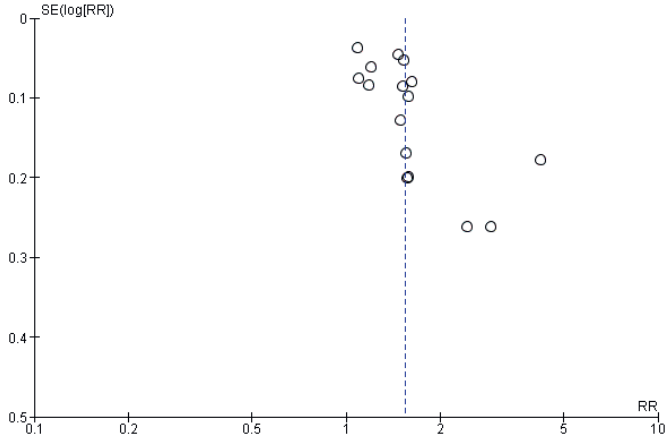
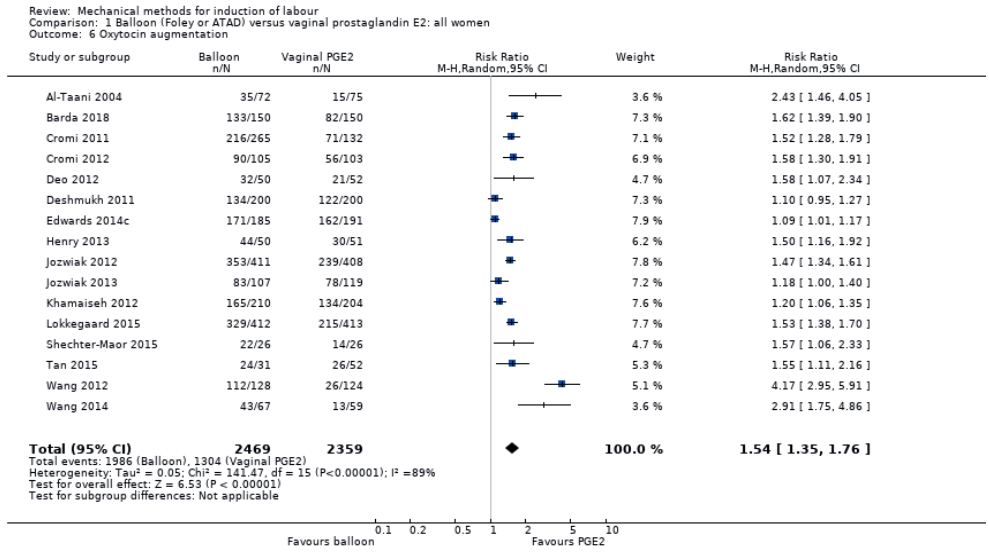


***Figure 5:** Funnel plot of comparison: 1 Balloon (Foley or ATAD) versus vaginal Prostaglandin E2: all women, outcome: 1.6 Oxytocin augmentation*

A sensitivity analysis, after eliminating the five trials assessed as having a potentially higher risk of allocation or attrition bias (Cromi 2012; Deo 2012; Tan 2015; Wang 2012; Wang 2014), did not alter the result, nor did it lower heterogeneity (average RR 1.37, 95% CI 1.21 to 1.54; 4005 women; 11 studies; $I^2 = 87\%$).



Analysis 1.6: *Comparison 1 Balloon (Foley or ATAD) versus vaginal prostaglandin E2: all women, Outcome 6 Oxytocin augmentation.*

Uterine hyperstimulation without FHR changes

A balloon catheter may reduce the risk of uterine hyperstimulation without FHR changes when compared to vaginal PGE2 (average RR 0.27, 95% CI 0.11 to 0.66; 2444 women; 15 studies; Analysis 1.7), although there was moderate heterogeneity for this outcome ($Tau^2 = 1.13$; $Chi^2 = 22.28$, df = 12 (P = 0.03); $I^2 = 46\%$). Visual inspection of the funnel plot associated with this outcome does not suggest any evidence of publication bias (Figure 6). A sensitivity analysis, after eliminating the seven trials assessed as having a potentially higher risk of allocation or attrition bias (Deo 2012; Orhue 1995; Shechter-Maor 2015; Tan 2015; Wang 2012; Wang 2014; Zahoor 2014), made this result less precise and therefore raises uncertainty as to whether there is a difference in uterine hyperstimulation without FHR changes (average RR 0.26, 95% CI 0.06 to 1.05; 1694 women; 8 studies; $I^2 = 62\%$).

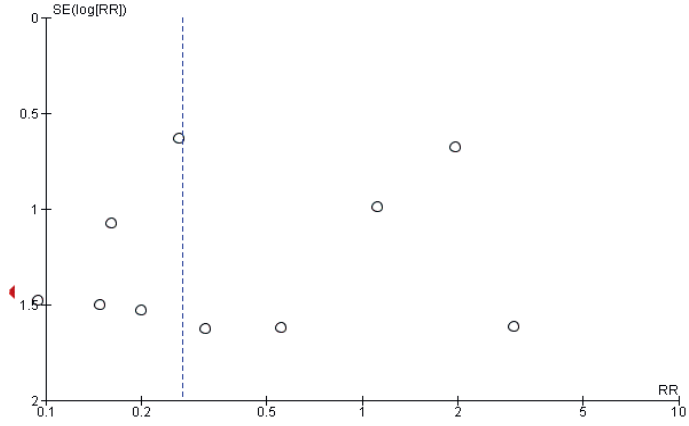
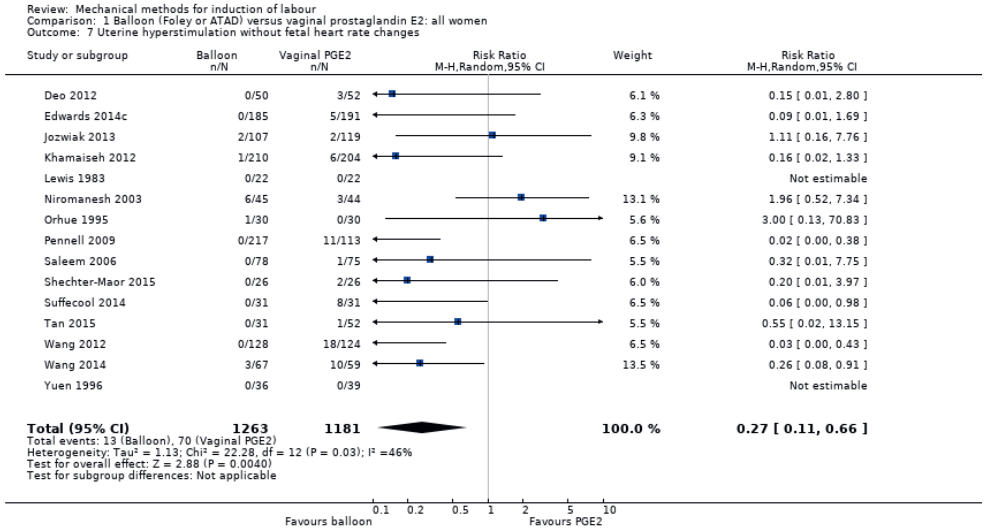


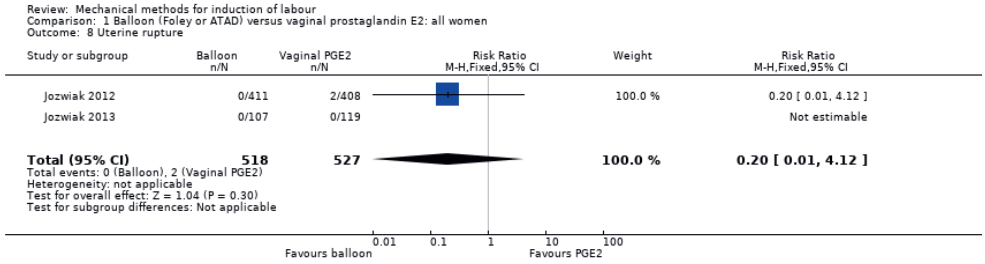
Figure 6: *Funnel plot of comparison: 1 Balloon (Foley or ATAD) versus vaginal Prostaglandin E2: all women, outcome: 1.7 Uterine hyperstimulation without fetal heart rate changes*



Analysis 1.7: *Comparison 1 Balloon (Foley or ATAD) versus vaginal prostaglandin E2: all women, Outcome 7 Uterine hyperstimulation without fetal heart rate changes.*

Uterine rupture

It is uncertain whether there is a difference in uterine rupture between both induction methods (RR 0.20, 95% CI 0.01 to 4.12; 1045 women; 2 studies; Analysis 1.8). Only two cases of uterine rupture were reported, both in the PGE2 group in the study of Jozwiak 2012. Uterine rupture was defined by the authors as a separation of the uterine wall, and in one case this was caused by inserting an intrauterine pressure catheter.

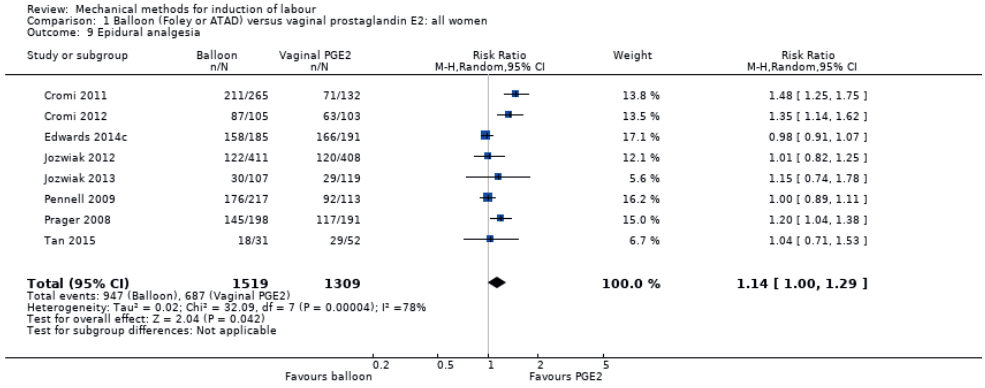


Analysis 1.8: *Comparison 1 Balloon (Foley or ATAD) versus vaginal prostaglandin E2: all women, Outcome 8 Uterine rupture.*

Epidural analgesia

A balloon catheter may slightly increase the use of epidural analgesia during labour when compared to vaginal PGE2 (average RR 1.14, 95% CI 1.00 to 1.29; 2828 women; 8 studies; Analysis 1.9). However, there was substantial heterogeneity for this outcome ($Tau^2 = 0.02$; $Chi^2 = 32.09$, df = 7 (P = < 0.0001); $I^2 = 78\%$).

A sensitivity analysis, after eliminating the two trials assessed as having a potentially higher risk of allocation or attrition bias (Cromi 2012; Tan 2015), did not alter the result, nor did it lower heterogeneity (average RR 1.11, 95% CI 0.97 to 1.28; 2537 women; 6 studies; I^2 = 80%).



Analysis 1.9: *Comparison 1 Balloon (Foley or ATAD) versus vaginal prostaglandin E2: all women, Outcome 9 Epidural analgesia.*

Instrumental vaginal delivery

There probably is little or no difference in instrumental vaginal deliveries between both induction methods (RR 0.93, 95% CI 0.79 to 1.09; 4514 women; 16 studies; Analysis 1.10). Visual inspection of the funnel plot associated with this outcome does not suggest any evidence of publication bias (Figure 7).

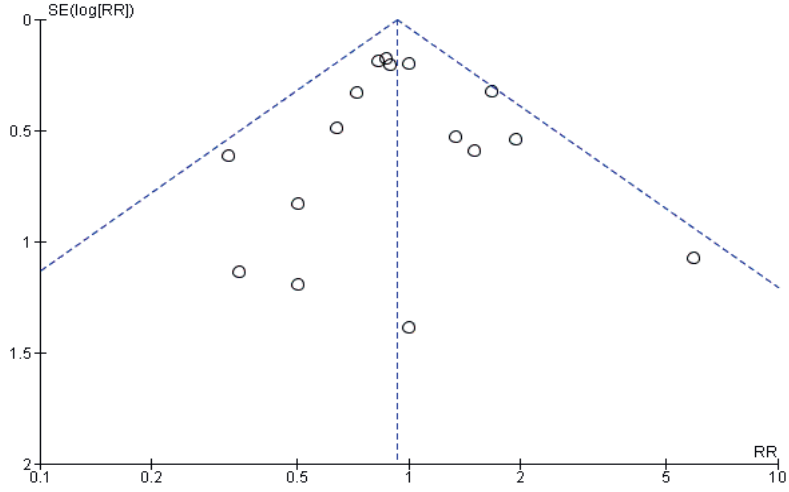
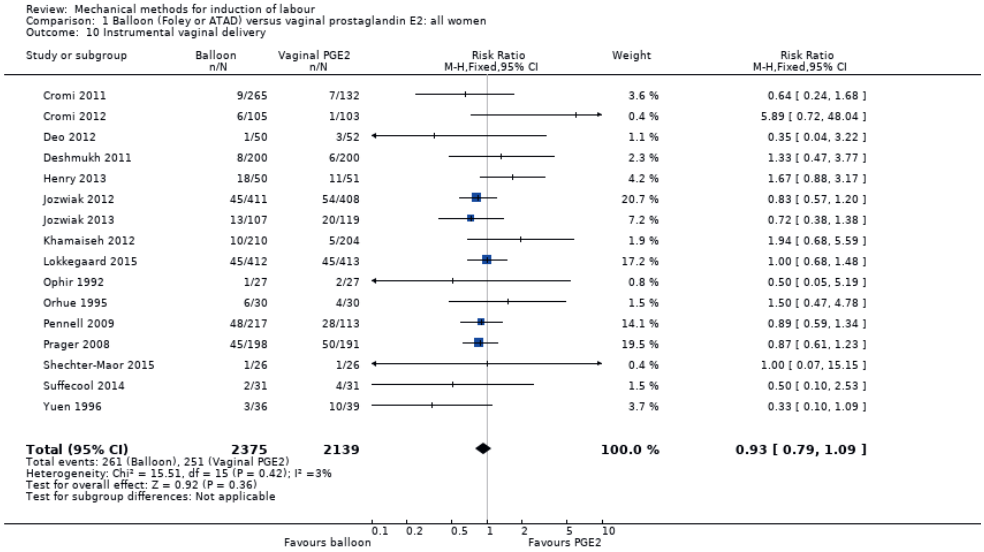


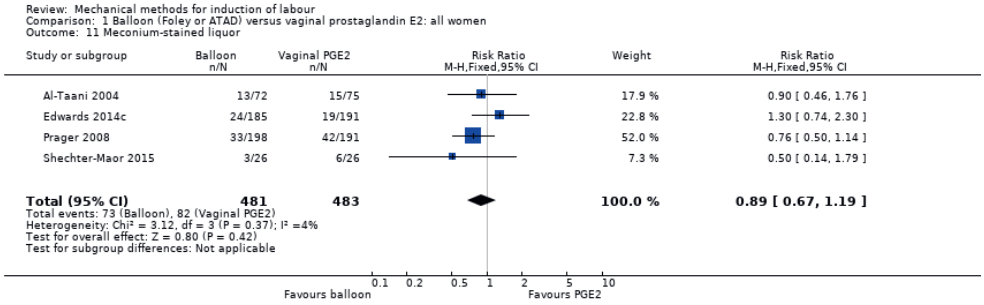
Figure 7: *Funnel plot of comparison: 1 Balloon (Foley or ATAD) versus vaginal Prostaglandin E2: all women, outcome: 1.10 Instrumental vaginal delivery*



***Analysis 1.10**: Comparison 1 Balloon (Foley or ATAD) versus vaginal prostaglandin E2: all women, Outcome 10 Instrumental vaginal delivery.*

Meconium-stained liquor

It is uncertain whether there is a difference in meconium-stained liquor between both induction methods (RR 0.89, 95% CI 0.67 to 1.19; 964 women; 4 studies; Analysis 1.11).



Analysis 1.11: Comparison 1 Balloon (Foley or ATAD) versus vaginal prostaglandin E2: all women, Outcome 11 Meconium-stained liquor.

Apgar score less than seven at five minutes

It is uncertain whether there is a difference in Apgar score less than seven at five minutes between both induction methods (RR 0.74, 95% CI 0.49 to 1.14; 4271 women; 14 studies; low-quality evidence; Analysis 1.12). Visual inspection of the funnel plot associated with this outcome does not suggest any evidence of publication bias (Figure 8).

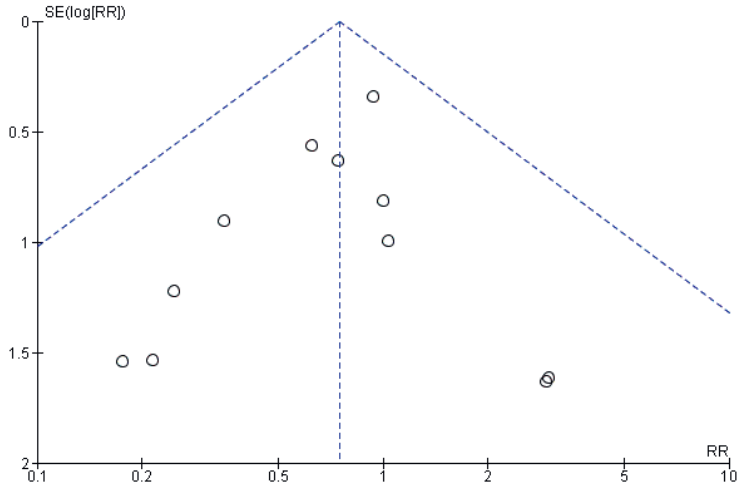
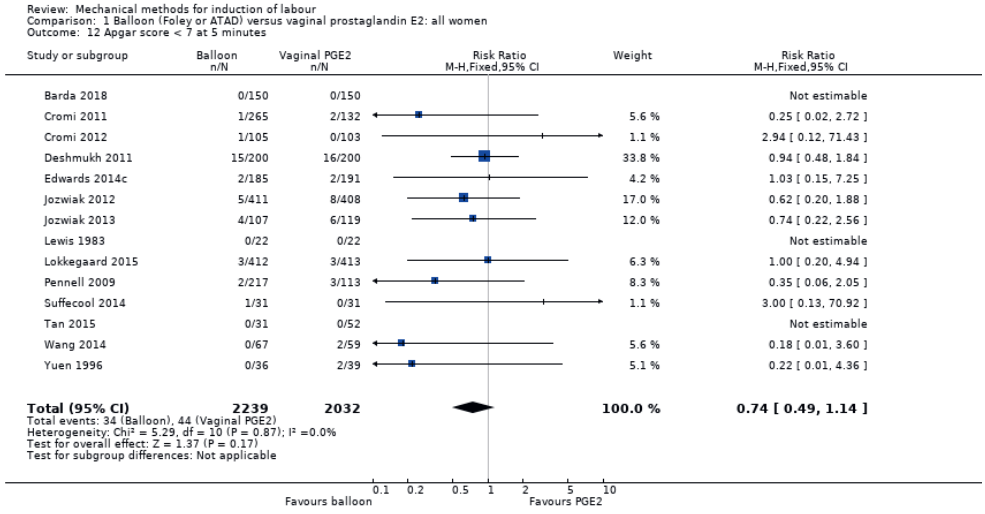


Figure 8: *Funnel plot of comparison: 1 Balloon (Foley or ATAD) versus vaginal Prostaglandin E2: all women, outcome: 1.12 Apgar score < 7 at 5 minutes*



Analysis 1.12: Comparison 1 Balloon (Foley or ATAD) versus vaginal prostaglandin E2: all women, Outcome 12 Apgar score < 7 at 5 minutes.

Neonatal intensive care unit (NICU) admission

A balloon catheter may reduce the risk of a NICU admission when compared to vaginal PGE2 (RR 0.82, 95% CI 0.65 to 1.04; 3647 women; 12 studies; low-quality evidence; Analysis 1.13), the absolute effect being 15 fewer NICU admission per 1000 deliveries. Although it should be noted that there is a wide range of treatment effects that are compatible with the data, from a very small increase in risk to very large decrease. Visual inspection of the funnel plot associated with this outcome does not suggest any evidence of publication bias (Figure 9).

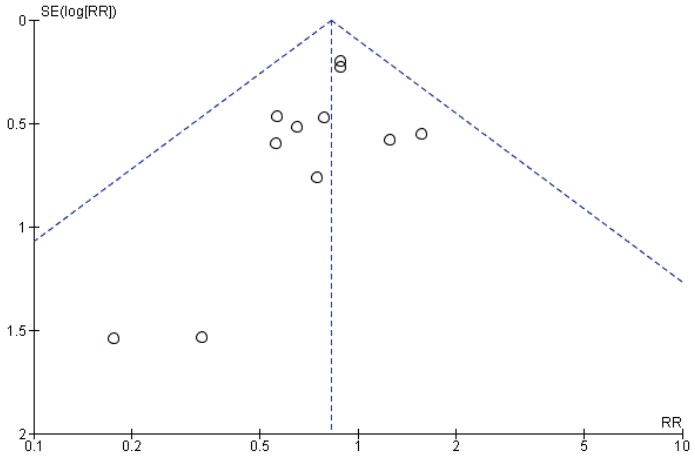
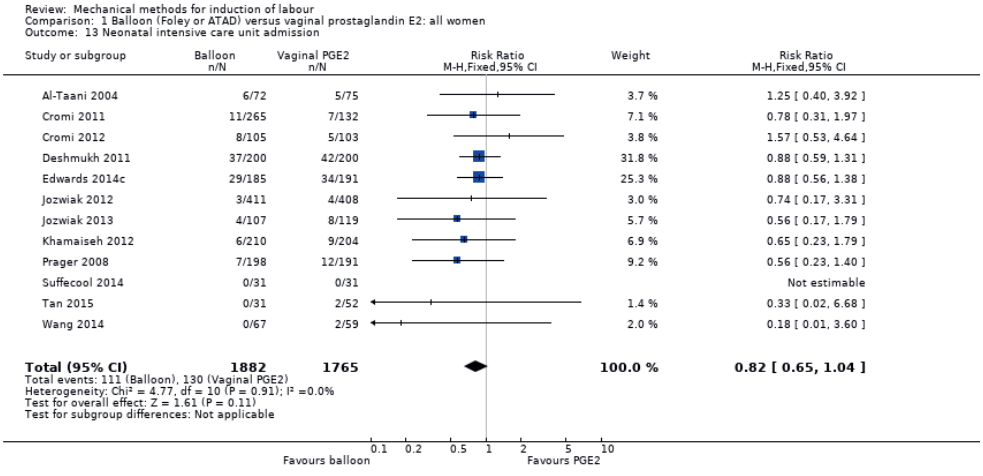


Figure 9: *Funnel plot of comparison: 1 Balloon (Foley or ATAD) versus vaginal Prostaglandin E2: all women, outcome: 1.13 Neonatal intensive care unit admission.*



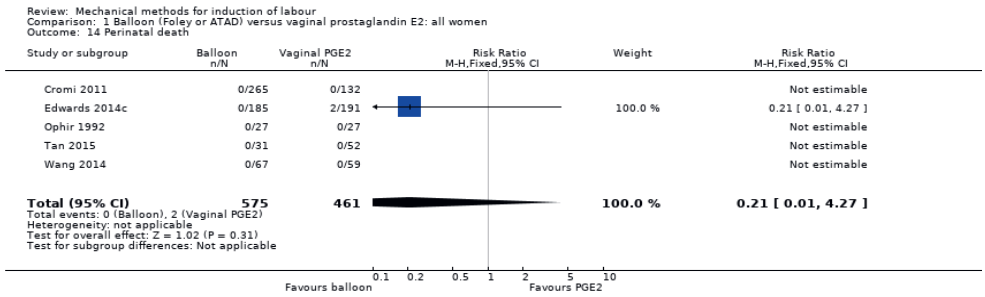
Analysis 1.13*: Comparison 1 Balloon (Foley or ATAD) versus vaginal prostaglandin E2: all women, Outcome 13 Neonatal intensive care unit admission.*

Neonatal encephalopathy

Not reported.

Perinatal death

It is uncertain whether there is a difference in perinatal death between both induction methods (RR 0.21, 95% CI 0.01 to 4.27; 1036 women; 5 studies; Analysis 1.14). Only two cases of perinatal death were reported by Edwards 2014c, both being cases of neonatal death and born to women randomised to vaginal PGE2. The authors describe that in both cases the neonates died as a result of complications related to a congenital diaphragmatic hernia and were unrelated to the induction method.



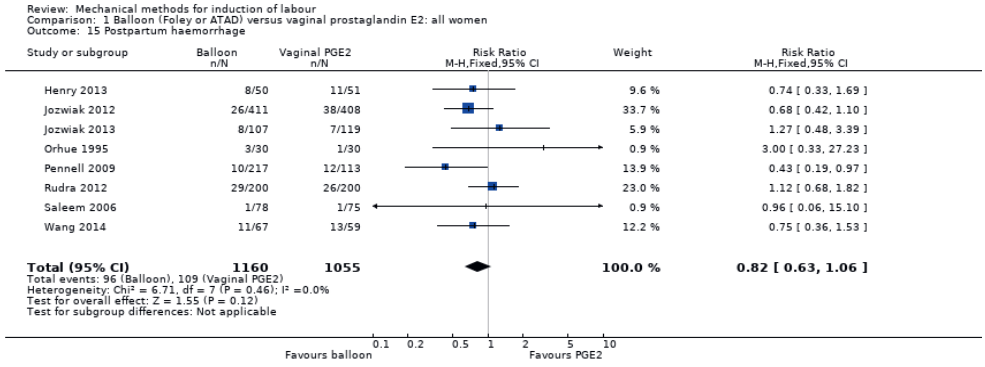
Analysis 1.14*: Comparison 1 Balloon (Foley or ATAD) versus vaginal prostaglandin E2: all women, Outcome 14 Perinatal death.*

Disability in childhood - Maternal side effects (all)- Maternal nausea - Maternal vomiting - Maternal diarrhoea - Other maternal side effects

Not reported

Postpartum haemorrhage

It is uncertain whether there is a difference in postpartum haemorrhage between both induction methods (RR 0.82, 95% CI 0.63 to 1.06; 2215 women; 8 studies; Analysis 1.15).



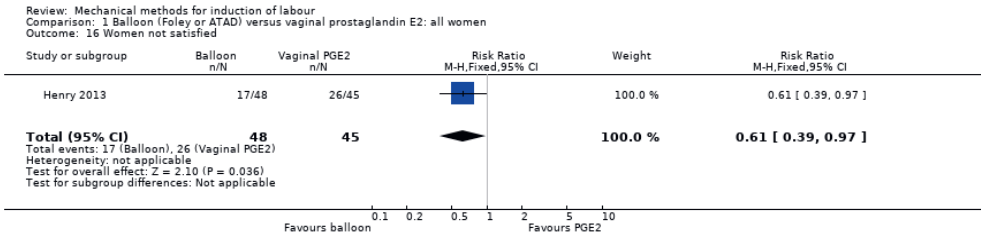
Analysis 1.15*: Comparison 1 Balloon (Foley or ATAD) versus vaginal prostaglandin E2: all women, Outcome 15 Postpartum haemorrhage.*

Serious maternal complications - Maternal death

Not reported.

Woman not satisfied

A balloon catheter may reduce the amount of women not being satisfied with the induction method when compared to prostaglandin E2 (RR 0.61, 95% CI 0.39 to 0.97; 93 women; 1 study; Analysis 1.16), the absolute effect being 224 fewer women not satisfied per 1000 deliveries. This outcome was reported by Henry 2013 by asking the women if they would choose the randomised induction method again. Patient satisfaction was also reported by Shechter-Maor 2015, but could not be included in the meta-analysis. In this study women were asked to score their satisfaction with the induction process on a five-point Likert scale. No difference in satisfaction was seen between both induction methods (3.41 (± 1.3) versus 3.33 (± 1.2), respectively; P = 0.860).



***Analysis 1.16**: Comparison 1 Balloon (Foley or ATAD) versus vaginal prostaglandin E2: all women, Outcome 16 Women not satisfied.*

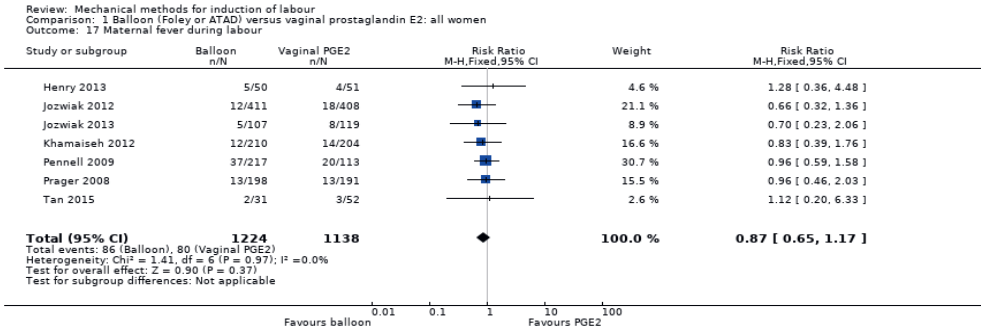
Caregiver not satisfied

Not reported.

Other outcomes (not pre-specified)

Maternal fever during labour

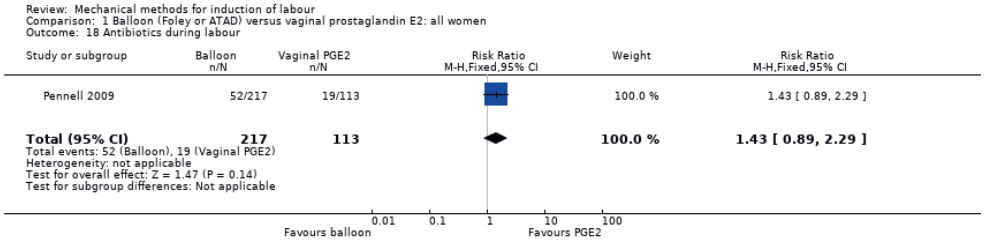
It is uncertain whether there is a difference in maternal fever during labour between both methods (RR 0.87, 95% CI 0.65 to 1.17; 2362 women; 7 studies; Analysis 1.17).



***Analysis 1.17**: Comparison 1 Balloon (Foley or ATAD) versus vaginal prostaglandin E2: all women, Outcome 17 Maternal fever during labour.*

Antibiotics during labour

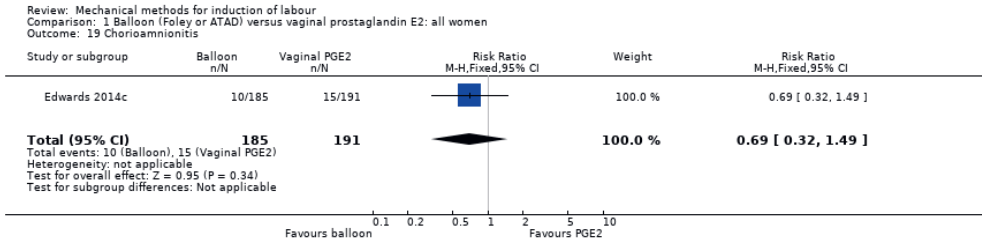
It is uncertain whether there is a difference in antibiotics during labour between both methods (RR 1.43, 95% CI 0.89 to 2.29; 330 women; 1 study; Analysis 1.18).



***Analysis 1.18**: Comparison 1 Balloon (Foley or ATAD) versus vaginal prostaglandin E2: all women, Outcome 18 Antibiotics during labour.*

Chorioamnionitis

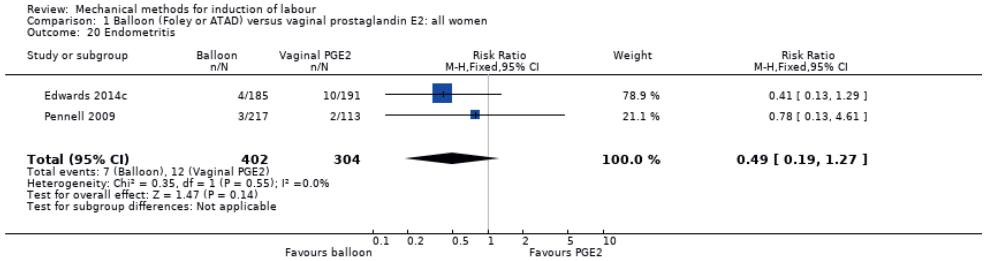
It is uncertain whether there is a difference in chorioamnionitis between both induction methods (RR 0.69, 95% CI 0.32 to 1.49; 376 women; 1 study; Analysis 1.19).



***Analysis 1.19**: Comparison 1 Balloon (Foley or ATAD) versus vaginal prostaglandin E2: all women, Outcome 19 Chorioamnionitis.*

Endometritis

It is uncertain whether there is a difference in endometritis between both induction methods (RR 0.49, 95% CI 0.19 to 1.27; 706 women; 2 studies; Analysis 1.20).



***Analysis 1.20**: Comparison 1 Balloon (Foley or ATAD) versus vaginal prostaglandin E2: all women, Outcome 20 Endometritis.*

Fetal distress

A balloon catheter probably reduces the risk of fetal distress for which a caesarean section is indicated when compared to vaginal PGE2 (RR 0.71, 95% CI 0.60 to 0.83; 4753 women; 20 studies; Analysis 1.21). Visual inspection of the funnel plot associated with this outcome does not suggest any evidence of publication bias (Figure 10).

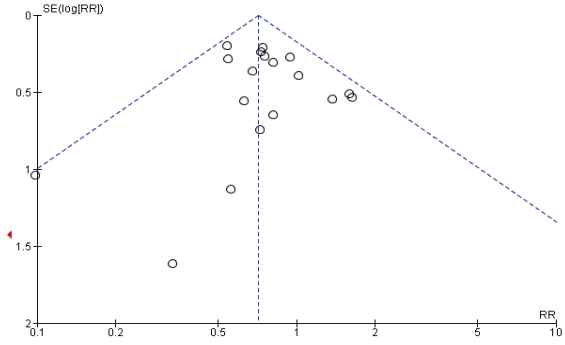
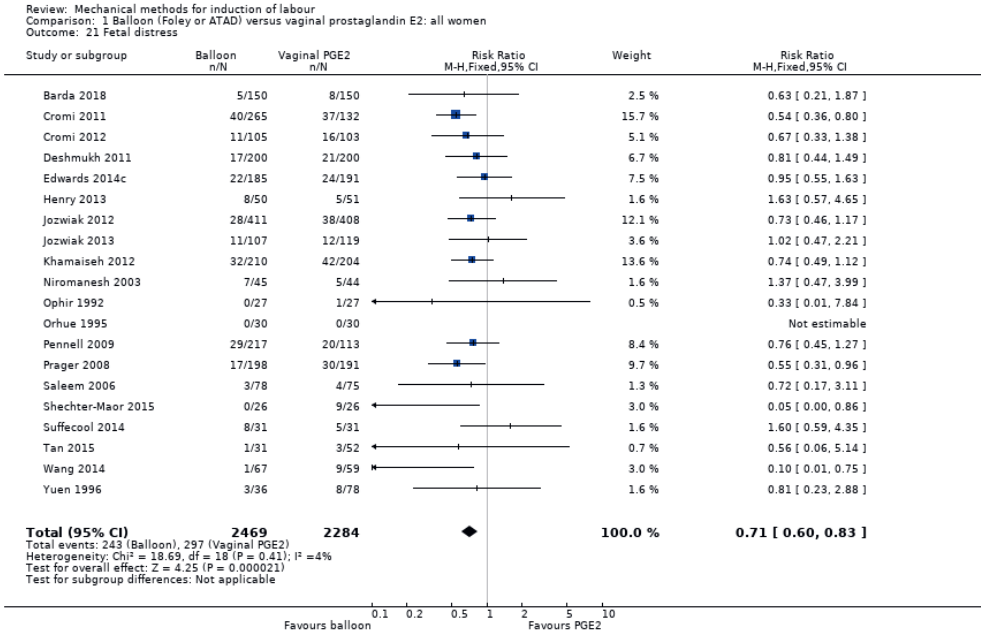


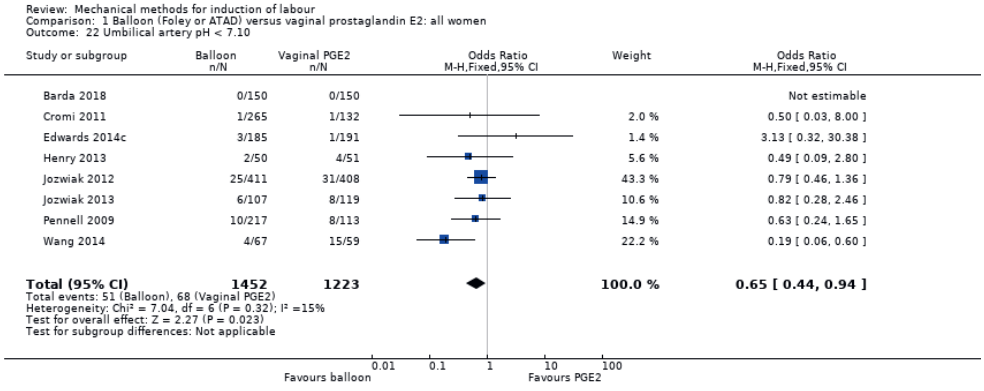
***Figure 10:** Funnel plot of comparison: 1 Balloon (Foley or ATAD) versus vaginal Prostaglandin E2: all women, outcome: 1.21 Fetal distress.*



Analysis 1.21: *Comparison 1 Balloon (Foley or ATAD) versus vaginal prostaglandin E2: all women, Outcome 21 Fetal distress.*

Umbilical artery pH < 7.10

A balloon catheter probably reduces the risk of an umbilical artery pH less than 7.10 directly postpartum when compared to vaginal PGE2 (RR 0.65, 95% CI 0.44 to 0.94; 2675 women, 8 studies; Analysis 1.22). However, numbers occurred infrequently in both groups (35 per 1000 versus 56 per 1000, respectively).



Analysis 1.22*:Comparison 1 Balloon (Foley or ATAD) versus vaginal prostaglandin E2: all women, Outcome 22 Umbilical artery pH < 7.10.*

Balloon (single or double) versus cervical prostaglandin E2 (10 trials involving 1428 women)

Primary outcomes

Vaginal delivery not achieved within 24 hours

It is uncertain whether there is a difference in vaginal deliveries achieved within 24 hours between induction of labour with a balloon catheter and cervical PGE2 (average RR 1.01, 95% CI 0.35 to 2.91; 200 women; 2 studies; Analysis 4.1). There also was substantial heterogeneity for this outcome (Tau^2 = 0.53; Chi^2 = 10.35, df = 1 (P = 0.001); I^2 = 90%). Even though data were pooled, both studies may be incompatible as no overlap of CIs is present. No sensitivity analysis was conducted as no potential high-risk studies were included for this outcome.For the subgroups of primiparous and multiparous women, no outcomes were reported.

Uterine hyperstimulation with FHR changes

It is uncertain whether there is a difference in uterine hyperstimulation with FHR changes between both induction methods (RR 0.37, 95% CI 0.02 to 8.90; 447 women; 4 studies; Analysis 4.2).Only one small study (53 women) reported this outcome for the subgroups of primiparous and multiparous women. No events were reported in primiparous women (Analysis 5.1). For multiparous women, it is uncertain whether there is a difference for this outcome between both induction methods (RR 0.30, 95% CI 0.01 to 7.02; 53 women; 1 study; Analysis 6.1).

Caesarean section

There probably is little or no difference in caesarean sections between both induction methods (RR 0.97, 95% CI 0.81 to 1.15; 1309 women; 9 studies; Analysis 4.3). Visual inspection of the funnel plot associated with this outcome does not suggest any evidence of publication bias (Figure 11).

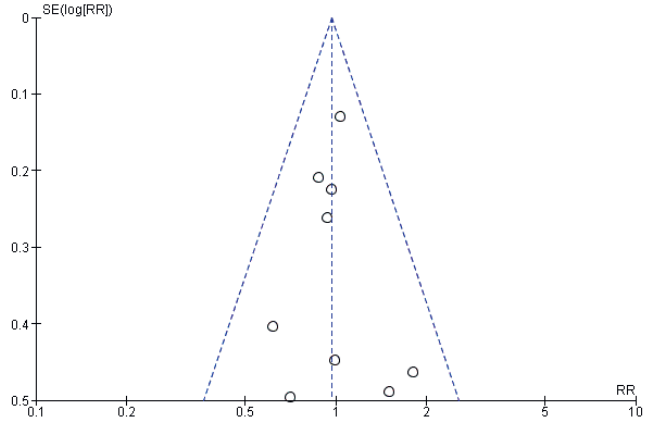


Figure 11: *Funnel plot of comparison: 4 Balloon (Foley or ATAD) versus intracervical Prostaglandin E2: all women, outcome: 4.3 Caesarean section*

It is uncertain whether there is a difference in caesarean sections between both induction methods on subgroup comparisons for both primiparous women (RR 1.30, 95% CI 0.86 to 1.95; 245 women; 3 studies; Analysis 5.2) and multiparous women (average RR 0.66, 95% CI 0.16 to 2.78; 136 women; 3 studies; Analysis 6.2) as the results for both comparisons were imprecise. For the multiparous group, there also was substantial heterogeneity ($Tau^2 = 0.90$; $Chi^2 = 4.78$, df = 2 (P = 0.09); $I^2 = 58\%$).

Serious neonatal morbidity or perinatal death

It is uncertain whether there is a difference in serious neonatal morbidity or perinatal death between both induction methods (RR 0.78, 95% CI 0.29 to 2.05; 500 women; 2 studies; Analysis 4.4). Of the 10 studies included for this comparison, two studies (Benzineb 1996; Laddad 2013) reported on this composite outcome. All reported events in these studies were cases of perinatal death. For the subgroups of primiparous and multiparous women, no outcomes were reported.

Serious maternal morbidity or death

Not reported.

2

Secondary outcomes

Cervix unfavourable/unchanged after 24 hours

It is uncertain whether there is a difference in an unfavourable cervix after 24 hours between both induction methods (RR 0.96, 95% CI 0.70 to 1.34; 219 women; 2 studies; Analysis 4.5).

Oxytocin augmentation

There may be little or no difference in oxytocin augmentation between both induction methods (RR 1.08, 95% CI 0.93 to 1.26; 400 women; 1 study; Analysis 4.6).

Uterine hyperstimulation without FHR changes

It is uncertain whether there is a difference in uterine hyperstimulation without FHR changes between both induction methods (average RR 0.99, 95% CI 0.09 to 10.38; 654 women; 5 studies; Analysis 4.7). Also, there was substantial heterogeneity for this outcome ($Tau^2 = 2.92$; $Chi^2 = 6.33$, df = 2 (P = 0.04); $I^2 = 68\%$). A sensitivity analysis, after eliminating the two trials assessed as having a potentially higher risk of allocation or attrition bias (Sciscione 1999; Yuen 1996) did not alter the result, nor did it lower heterogeneity (average RR 0.56, 95% CI 0.01 to 39.31; 430 women; 3 studies; $I^2 = 76\%$).

Uterine rupture

Not reported.

Epidural analgesia

There may be little or no difference in epidural analgesia during labour between both induction methods (RR 0.91, 95% CI 0.81 to 1.02; 149 women; 1 study; Analysis 4.8).

Instrumental vaginal delivery

It is uncertain whether there is a difference in instrumental vaginal deliveries between both induction methods (RR 1.18, 95% CI 0.68 to 2.05; 337 women; 3 studies; Analysis 4.9).

Meconium-stained liquor
It is uncertain whether there is a difference in meconium-stained liquor between both induction methods (RR 1.17, 95% CI 0.42 to 3.26; 118 women; 1 study; Analysis 4.10).

Apgar score less than seven at five minutes
It is uncertain whether there is a difference in Apgar scores less than seven at five minutes (RR 0.79, 95% CI 0.41 to 1.53; 475 women; 2 studies; Analysis 4.11).

Neonatal intensive care unit admission
It is uncertain whether there is a difference in NICU admissions between both methods (RR 0.88, 95% CI 0.60 to 1.31; 400 women; 1 study; Analysis 4.12).

Neonatal encephalopathy
Not reported.

Perinatal death
It is uncertain whether there is difference in perinatal death between both induction methods (RR 0.78, 95% CI 0.29 to 2.05; 500 women; 2 studies. Analysis 4.13). Noteworthy, there was a relatively high number of neonatal deaths reported in the study of Laddad 2013 for the balloon group (6/200), as well as in the cervical PGE2 group (8/200), for which no explanation was given by the authors.

Disability in childhood
Not reported.

Maternal side effects
It is uncertain whether there is a difference in maternal side effects (RR 0.15, 95% CI 0.02 to 1.24; 211 women; 2 studies; Analysis 4.14). The nature of the side effects was not specified in both included studies.

Maternal nausea - Maternal vomiting - Maternal diarrhoea - Other maternal side effects
Not reported.

Postpartum haemorrhage
It is uncertain whether there is a difference in postpartum haemorrhage between both induction methods (RR 0.20, 95% CI 0.01 to 4.06; 100 women; 1 study; Analysis 4.15).

Serious maternal complications - Maternal death - Woman not satisfied - Caregiver not satisfied
Not Reported

Other outcomes (not pre-specified)
Maternal fever during labour - Antibiotics during labour
Not reported.

Chorioamnionitis

It is uncertain whether there is a difference in chorioamnionitis between both induction methods (RR 1.00, 95% CI 0.21 to 4.75; 118 women; 1 study; Analysis 4.16).

Endometritis

It is uncertain whether there is a difference in endometritis between both induction methods (RR 1.00, 95% CI 0.06 to 15.61; 118 women; 1 study; Analysis 4.17).

Fetal distress

A balloon catheter probably reduces the risk of fetal distress for which a caesarean section is indicated when compared to cervical PGE2 (RR 0.61, 95% CI 0.42 to 0.89; 1023 women; 6 studies; Analysis 4.18).

Umbilical artery pH < 7.10

Not reported.

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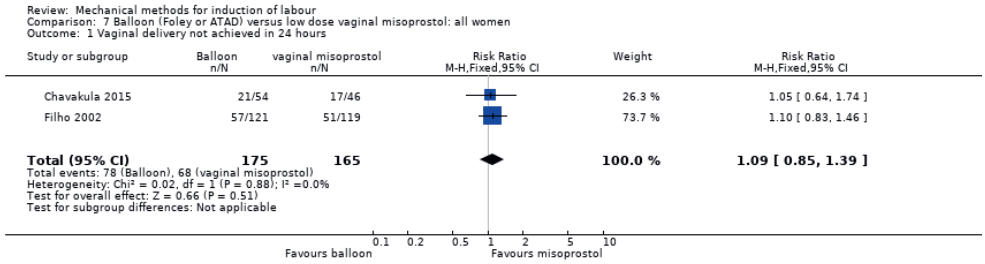
Balloon (single or double) versus low-dose vaginal misoprostol (13 trials involving 1818 women)

Primary outcomes

Vaginal delivery not achieved within 24 hours

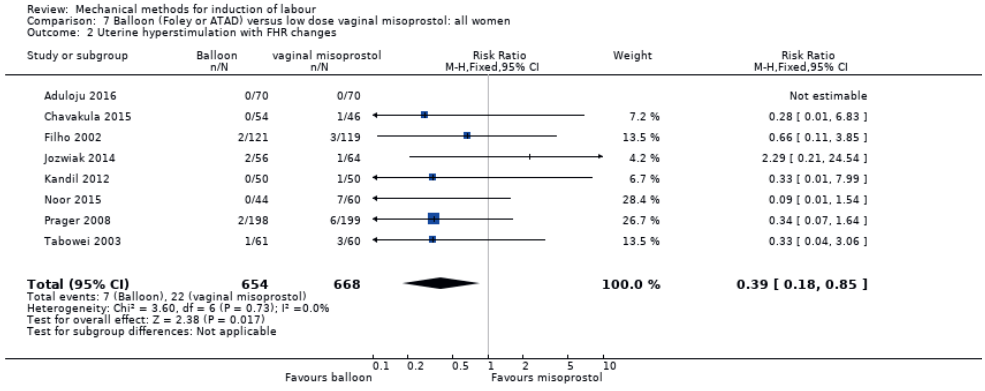
It is uncertain whether there is a difference in vaginal deliveries not achieved within 24 hours between induction of labour with a balloon catheter and vaginal misoprostol (RR 1.09, 95% CI 0.85 to 1.39; 340 women; 2 studies; low-quality evidence; Analysis 7.1). For the subgroups of primiparous and multiparous women, no outcomes were reported.



Analysis 7.1: *Comparison 7 Balloon (Foley or ATAD) versus low dose vaginal misoprostol: all women, Outcome 1 Vaginal delivery not achieved in 24 hours.*

Uterine hyperstimulation with FHR changes

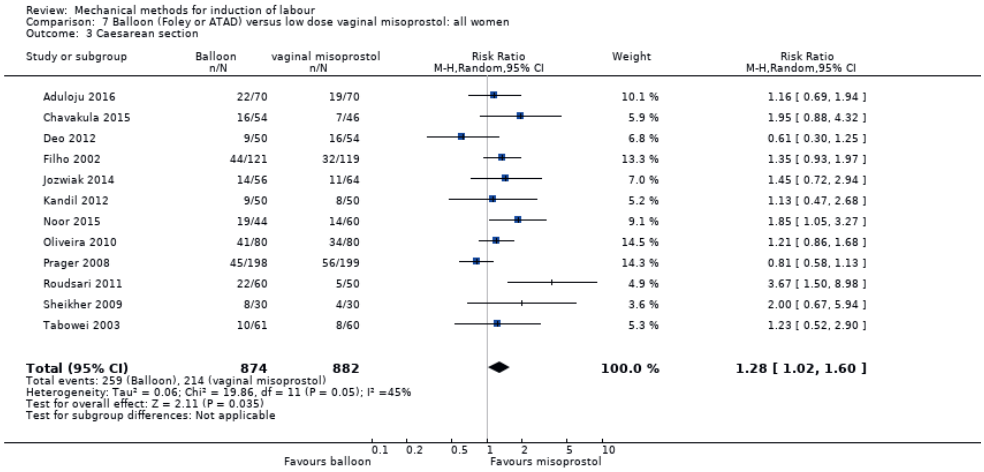
A balloon catheter probably reduces the risk of uterine hyperstimulation with FHR changes when compared to vaginal misoprostol (RR 0.39, 95% CI 0.18 to 0.85; 1322 women; moderate-quality evidence; 8 studies; Analysis 7.2), the absolute effect being 22 fewer cases per 1000 deliveries. For the subgroups of primiparous and multiparous women, no outcomes were reported.



Analysis 7.2: *Comparison 7 Balloon (Foley or ATAD) versus low dose vaginal misoprostol: all women, Outcome 2 Uterine hyperstimulation with FHR changes.*

Caesarean section

A balloon catheter may increase the risk of a caesarean section when compared to vaginal misoprostol (average RR 1.28, 95% CI 1.02 to 1.60; 1756 women; 12 studies; low-quality evidence; Analysis 7.3), the absolute effect being 53 more caesarean sections per 1000 deliveries. However, there was moderate heterogeneity for this outcome ($Tau^2 = 0.06$; $Chi^2 = 19.86$, df = 11 (P = 0.05); $I^2 = 45\%$).



Analysis 7.3: *Comparison 7 Balloon (Foley or ATAD) versus low dose vaginal misoprostol: all women, Outcome 3 Caesarean section.*

A sensitivity analysis, after eliminating the three trials assessed as having a potentially higher risk of allocation or attrition bias (Deo 2012; Kandil 2012; Sheikher 2009), did not alter the result, nor did it lower heterogeneity (average RR 1.34, 95% CI 1.05 to 1.71; 1492 women; 10 studies; $I^2 = 48\%$). Visual inspection of the funnel plot associated with this outcome does not suggest any evidence of publication bias (Figure 12).

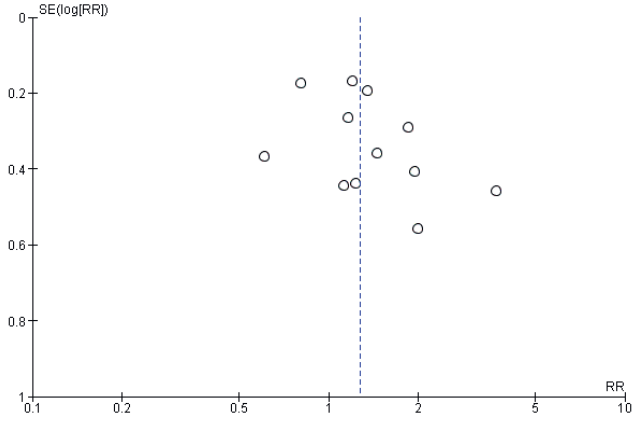
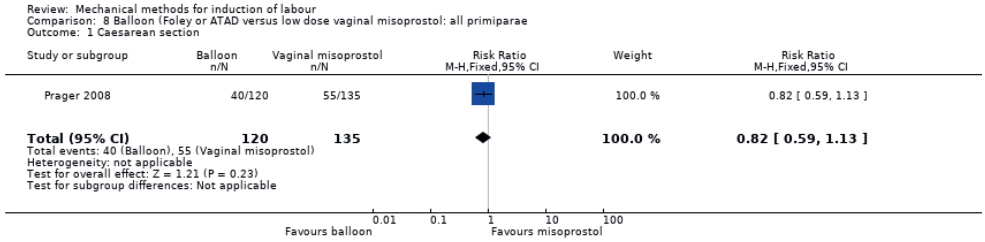


Figure 12: *Funnel plot of comparison: 7 Balloon (Foley or ATAD) versus vaginal misorostol: all women, outcome: 7.3 Caesarean section*

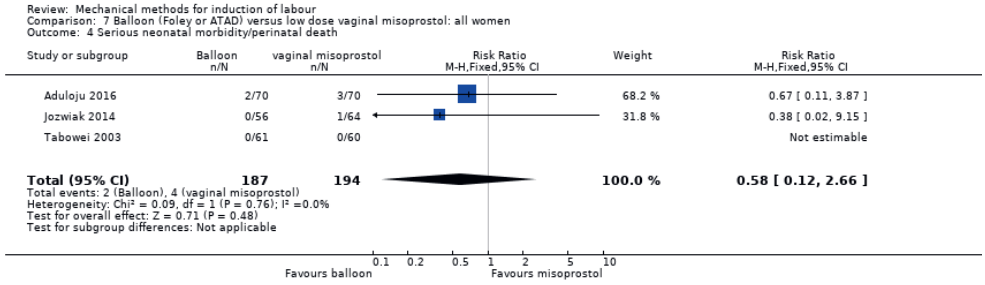
For the subgroup of primiparous women, it is uncertain whether there is a difference in caesarean sections between both induction methods (RR 0.82, 95% CI 0.59 to 1.13; 255 women; 1 study; Analysis 8.1). For multiparous women, no outcomes were reported.



Analysis 8.1: *Comparison 8 Balloon (Foley or ATAD versus low dose vaginal misoprostol: all primiparae, Outcome 1 Caesarean section.*

Serious neonatal morbidity or perinatal death

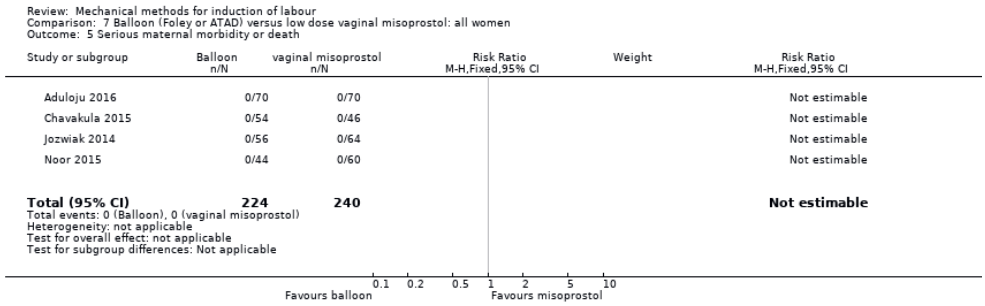
It is uncertain whether there is a difference in serious neonatal morbidity or perinatal death between both induction methods (RR 0.58, 95% CI 0.12 to 2.66; 381 women; 3 studies; very low-quality evidence; Analysis 7.4). All of the cases included for this composite outcome were cases of perinatal asphyxia (2/187 versus 4/194, respectively). For the subgroups of primiparous and multiparous women, no outcomes were reported.



Analysis 7.4: *Comparison 7 Balloon (Foley or ATAD) versus low dose vaginal misoprostol: all women, Outcome 4 Serious neonatal morbidity/perinatal death.*

Serious maternal morbidity or death

It is uncertain whether there is a difference in serious maternal morbidity or death between both induction methods (very low-quality evidence; Analysis 7.5). Of the 13 studies included for this comparison, four studies (464 women) reported on this composite outcome. No events of maternal morbidity or death occurred in one of these studies. For the subgroups of primiparous and multiparous women, no outcomes were reported.

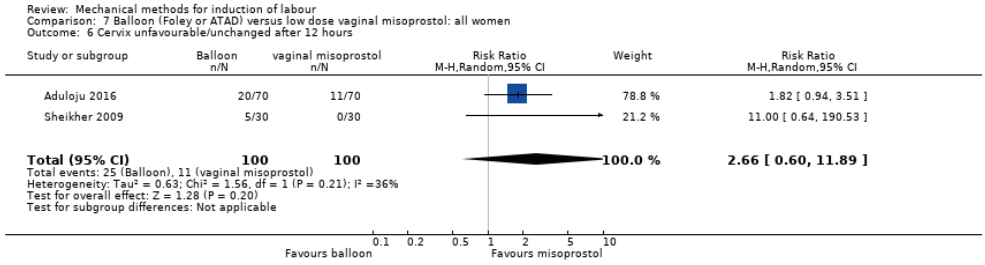


Analysis 7.5: *Comparison 7 Balloon (Foley or ATAD) versus low dose vaginal misoprostol: all women, Outcome 5 Serious maternal morbidity or death.*

Secondary outcomes

Cervix unfavourable/unchanged after 12 hours

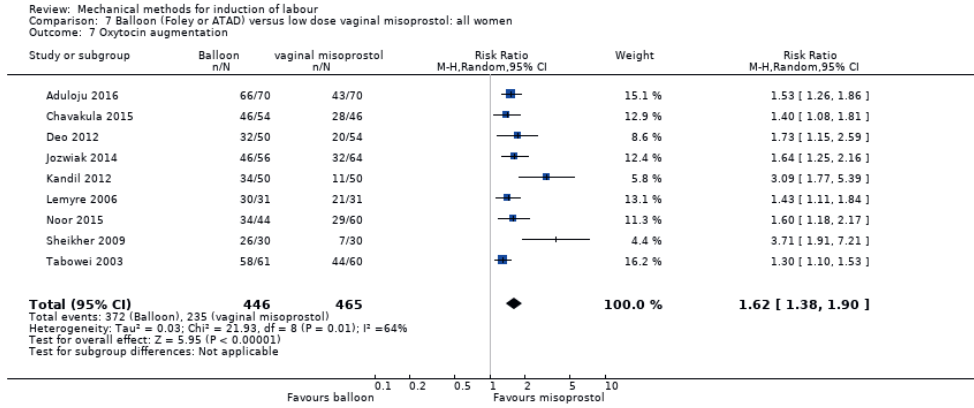
It is uncertain whether there is a difference in an unfavourable cervix after 12 hours between both induction methods (average RR 2.66, 95% CI 0.60 to 11.89; 200 women; 2 studies; Analysis 7.6). Also, there was moderate heterogeneity for this outcome (Tau² = 0.63; Chi² = 1.56, df = 1 (P = 0.21); I² = 36%). No studies reported on a time period of 24 hours. A sensitivity analysis, after eliminating one trial assessed as having a potentially higher risk of allocation or attrition bias (Sheikher 2009), did not change the result, but did narrow the CI (RR 1.82, 95% CI 0.94 to 3.51; 1 study).



Analysis 7.6: *Comparison 7 Balloon (Foley or ATAD) versus low dose vaginal misoprostol: all women, Outcome 6 Cervix unfavourable/unchanged after 12 hours.*

Oxytocin augmentation

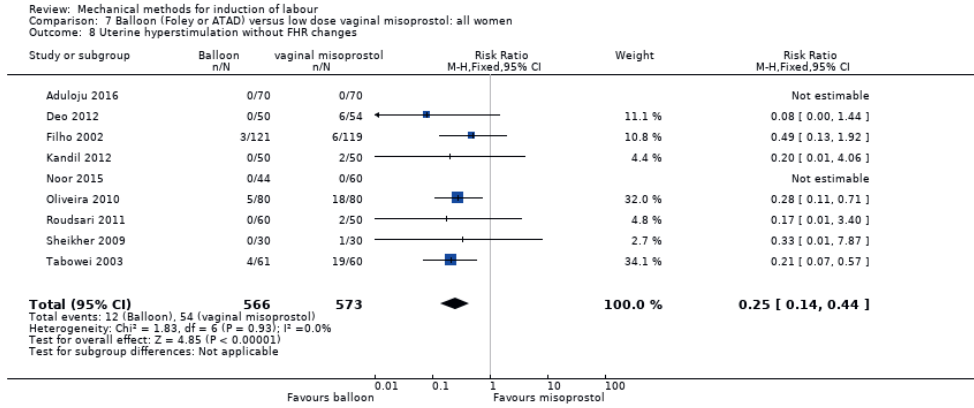
A balloon catheter probably increases the risk of oxytocin augmentation when compared to vaginal misoprostol (average RR 1.62, 95% CI 1.38 to 1.90; 911 women; 9 studies; Analysis 7.7), although there was substantial heterogeneity for this outcome (Tau² = 0.03; Chi² = 21.93, df = 8 (P = 0.005); I² = 64%). In the sensitivity analysis, after eliminating two trial assessed as having a potentially higher risk of allocation or attrition bias (Kandil 2012 and Sheikher 2009), heterogeneity was lost without altering the effect observed (average RR 1.50, 95% CI 1.36 to 1.64; 751 women, 7 studies; I² = 0%).



Analysis 7.7: *Comparison 7 Balloon (Foley or ATAD) versus low dose vaginal misoprostol: all women, Outcome 7 Oxytocin augmentation.*

Uterine hyperstimulation without FHR changes

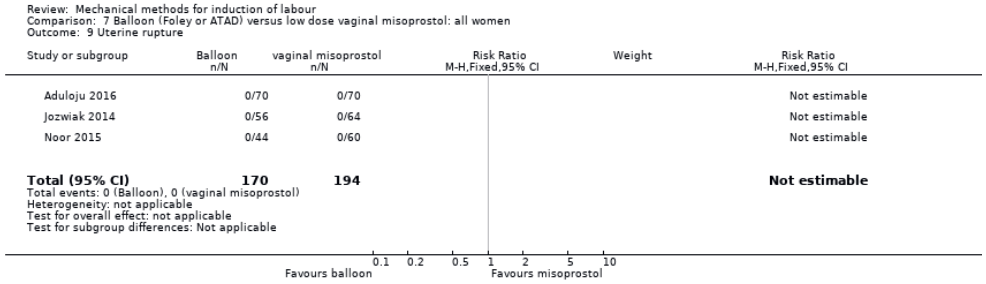
A balloon catheter probably reduces the risk of uterine hyperstimulation without FHR changes when compared to vaginal misoprostol (RR 0.25, 95% CI 0.14 to 0.44; 1139 women; 9 studies; Analysis 7.8).



Analysis 7.8: *Comparison 7 Balloon (Foley or ATAD) versus low dose vaginal misoprostol: all women, Outcome 8 Uterine hyperstimulation without FHR changes.*

Uterine rupture

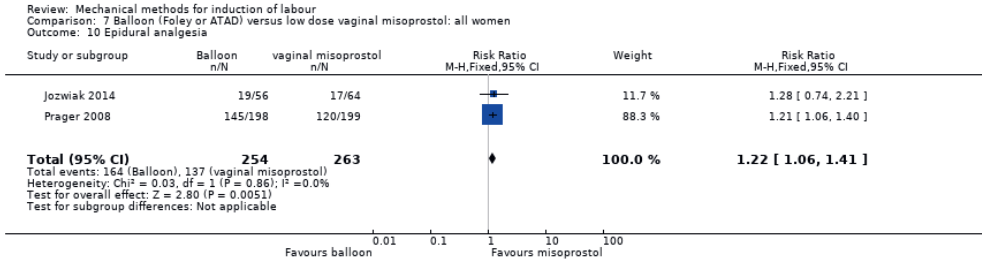
It is uncertain whether there is a difference in uterine rupture between both induction methods (Analysis 7.9). Of the 13 studies included for this comparison, only three studies (364 women) reported on this outcome. No events of uterine rupture occurred in one of these studies.



Analysis 7.9: *Comparison 7 Balloon (Foley or ATAD) versus low dose vaginal misoprostol: all women, Outcome 9 Uterine rupture.*

Epidural analgesia

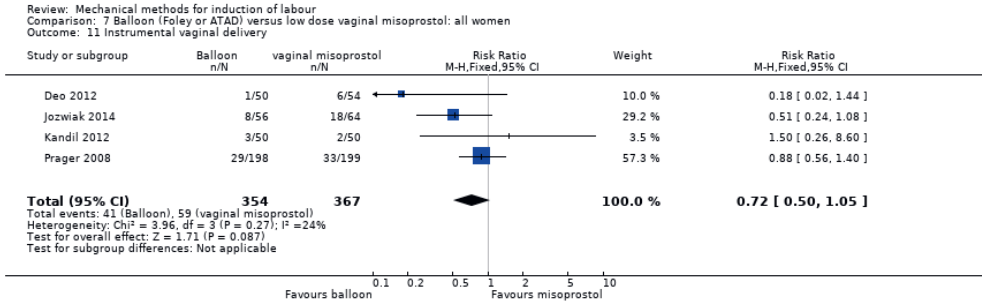
A balloon catheter probably slightly increases the use of epidural analgesia during labour when compared to vaginal misoprostol (RR 1.22, 95% CI 1.06 to 1.41; 517 women; 2 studies; Analysis 7.10).



Analysis 7.10: *Comparison 7 Balloon (Foley or ATAD) versus low dose vaginal misoprostol: all women, Outcome 10 Epidural analgesia.*

Instrumental vaginal delivery

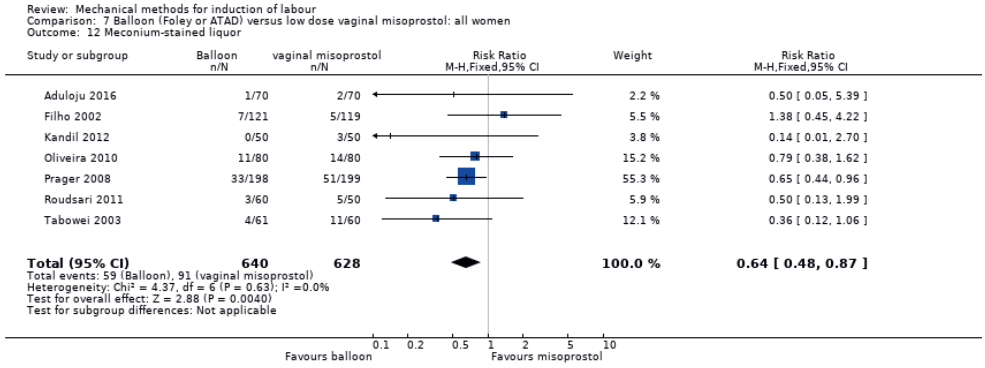
It is uncertain whether there is a difference in instrumental vaginal deliveries between both induction methods (RR 0.72, 95% CI 0.50 to 1.05; 721 women; 4 studies; Analysis 7.11).



Analysis 7.11: *Comparison 7 Balloon (Foley or ATAD) versus low dose vaginal misoprostol: all women, Outcome 11 Instrumental vaginal delivery.*

Meconium-stained liquor

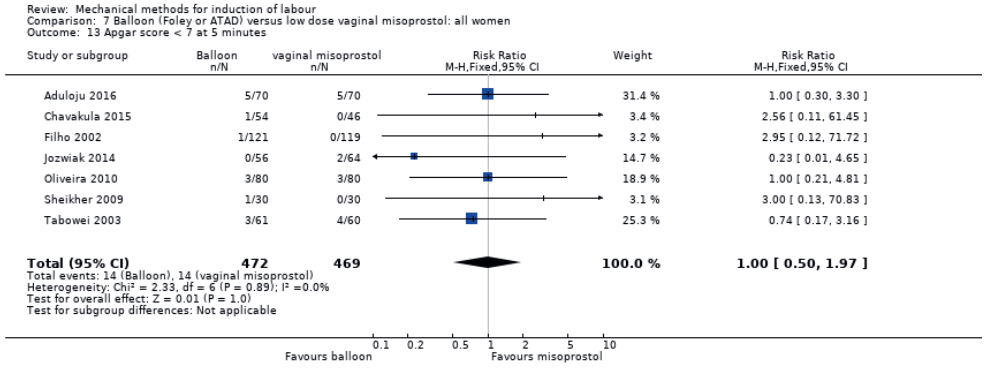
A balloon catheter probably reduces the risk of meconium-stained liquor when compared to vaginal misoprostol (RR 0.64, 95% CI 0.48 to 0.87; 1268 women; 7 studies; Analysis 7.12).



Analysis 7.12: *Comparison 7 Balloon (Foley or ATAD) versus low dose vaginal misoprostol: all women, Outcome 12 Meconium-stained liquor.*

Apgar score less than seven at five minutes

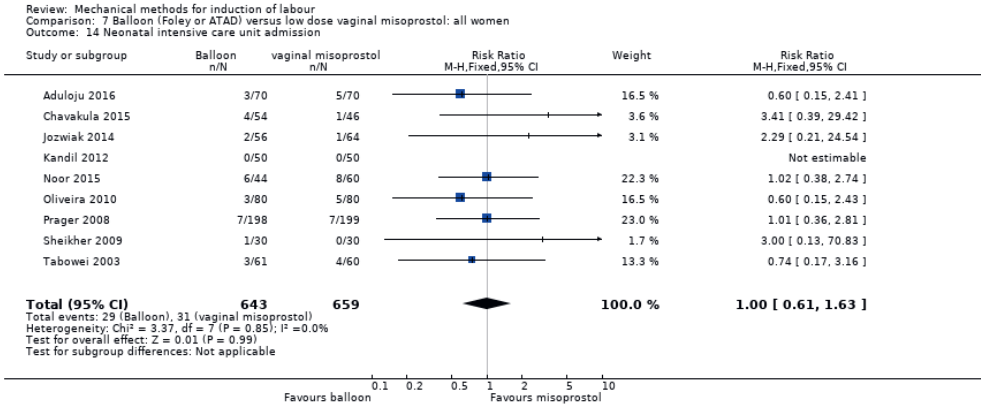
It is uncertain whether there is a difference in Apgar scores less than seven at five minutes between both induction methods (RR 1.00, 95% CI 0.50 to 1.97; 941 women; 7 studies; low-quality evidence; Analysis 7.13).



Analysis 7.13: *Comparison 7 Balloon (Foley or ATAD) versus low dose vaginal misoprostol: all women, Outcome 13 Apgar score < 7 at 5 minutes.*

Neonatal intensive care unit admission

It is uncertain whether there is a difference in NICU admissions between both induction methods (RR 1.00, 95% CI 0.61 to 1.63; 1302 women; 9 studies; low-quality evidence; Analysis 7.14).



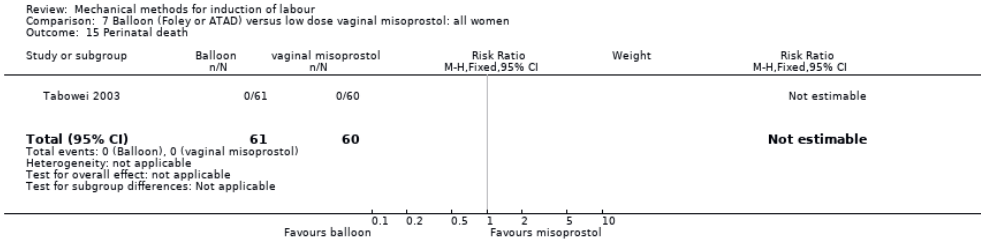
Analysis 7.14: *Comparison 7 Balloon (Foley or ATAD) versus low dose vaginal misoprostol: all women, Outcome 14 Neonatal intensive care unit admission.*

Neonatal encephalopathy

Not reported.

Perinatal death

It is uncertain whether there is difference in perinatal death between both induction methods (Analysis 7.15). Of the 13 studies included for this comparison, only one study (121 women) pre-specified this outcome. No cases of perinatal death were reported in this study.



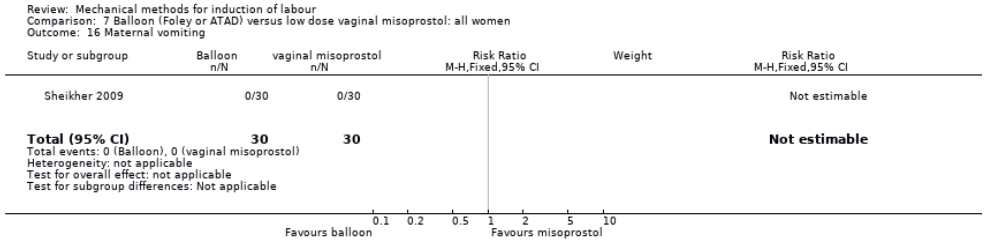
Analysis 7.15: *Comparison 7 Balloon (Foley or ATAD) versus low dose vaginal misoprostol: all women, Outcome 15 Perinatal death.*

Disability in childhood - Maternal side effects (all) - Maternal nausea

Not reported

Maternal vomiting

It is uncertain whether there is difference in maternal vomiting between both induction methods (Analysis 7.16). Of all the 13 studies included for this comparison, only one study (60 women) pre-specified this outcome. No cases of maternal vomiting were reported in this study.



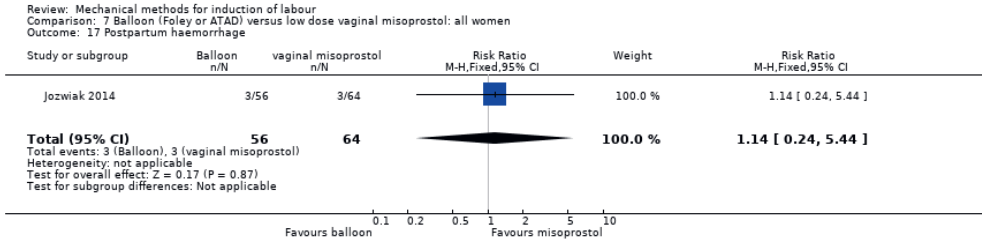
Analysis 7.16: *Comparison 7 Balloon (Foley or ATAD) versus low dose vaginal misoprostol: all women, Outcome 16 Maternal vomiting.*

Maternal diarrhoea - Other maternal side effects

Not reported.

Postpartum haemorrhage

It is uncertain whether there is difference in postpartum haemorrhage between both induction methods (RR 1.14, 95% CI 0.24 to 5.44; 120 women; 1 study; (Analysis 7.17).



Analysis 7.17: *Comparison 7 Balloon (Foley or ATAD) versus low dose vaginal misoprostol: all women, Outcome 17 Postpartum haemorrhage.*

Serious maternal complications - Maternal death

Not reported.

Woman not satisfied

One study (Chavakula 2015) reported on patient satisfaction, but could not be included in the meta-analysis. In this study, satisfaction was assessed by a visual analogue score ranging from zero to five (0 = very poor; 5 = very good), in which no difference between both induction methods was seen (100 women; 4.5 [4-5] versus 4.45 [3-5], respectively; P = 0.488).

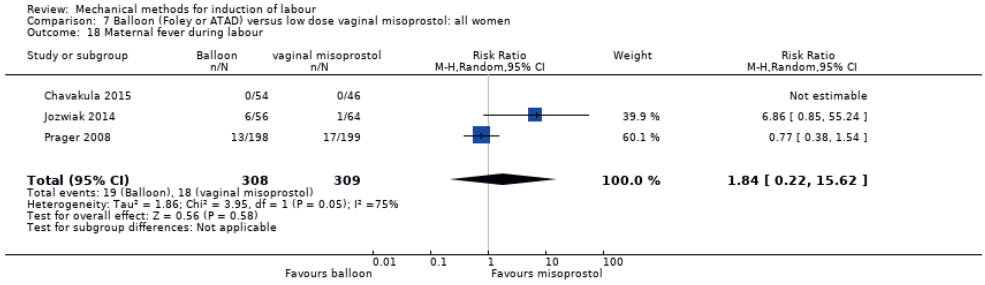
Caregiver not satisfied

Not reported.

Not pre-specified outcomes

Maternal fever during labour

It is uncertain whether there is a difference in maternal fever during labour between both methods (average RR 1.84, 95% CI 0.22 to 15.62; 617 women; 3 studies; Analysis 7.18). Also, there was substantial heterogeneity for this outcome (Tau² = 1.86; Chi² = 3.95, df = 1 (P = 0.05); I² = 75%). No sensitivity analysis was performed as no potential high-risk studies were included for this outcome.



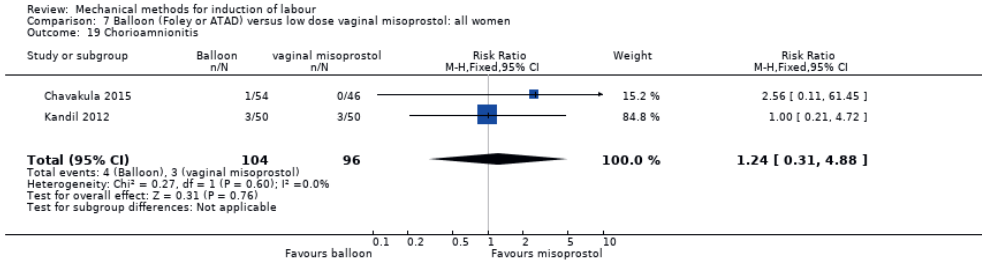
Analysis 7.18: *Comparison 7 Balloon (Foley or ATAD) versus low dose vaginal misoprostol: all women, Outcome 18 Maternal fever during labour.*

Antibiotics during labour

Not reported.

Chorioamnionitis

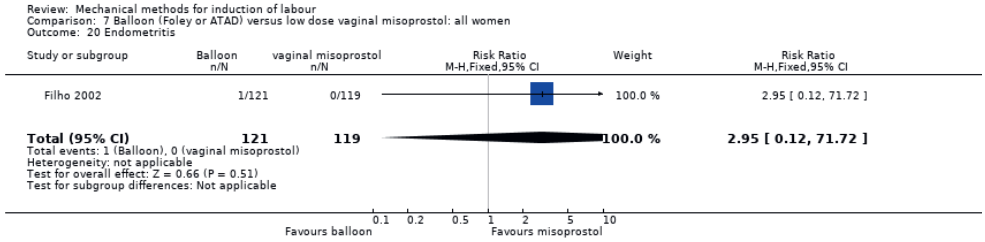
It is uncertain whether there is a difference in chorioamnionitis between both induction methods (RR 1.24, 95% CI 0.31 to 4.88; 200 women; 2 studies; Analysis 7.19).



Analysis 7.19: *Comparison 7 Balloon (Foley or ATAD) versus low dose vaginal misoprostol: all women, Outcome 19 Chorioamnionitis.*

Endometritis

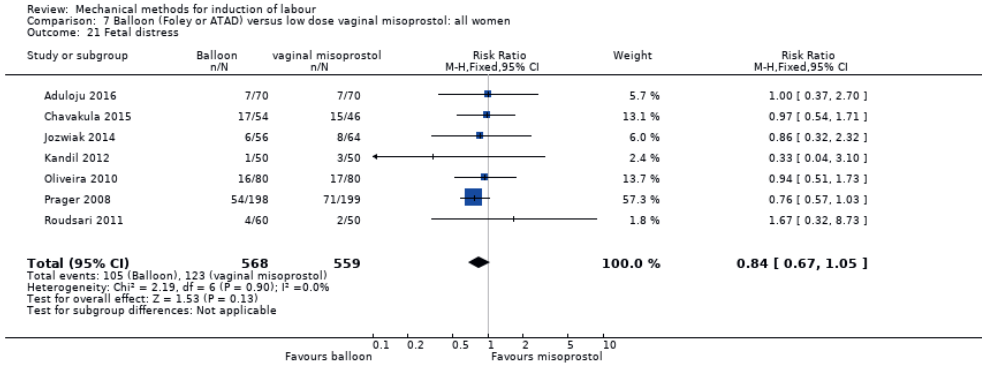
It is uncertain whether there is a difference in endometritis between both induction methods (RR 2.95, 95% CI 0.12 to 71.72; 240 women; 1 study; Analysis 7.20).



Analysis 7.20: *Comparison 7 Balloon (Foley or ATAD) versus low dose vaginal misoprostol: all women, Outcome 20 Endometritis.*

Fetal distress

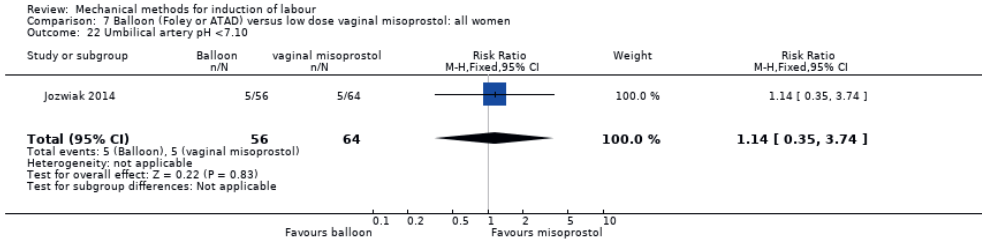
It is uncertain whether there is a difference in fetal distress for which a caesarean section is indicated (RR 0.84, 95% CI 0.67 to 1.05; 1127 women; 7 studies; Analysis 7.21).



Analysis 7.21: *Comparison 7 Balloon (Foley or ATAD) versus low dose vaginal misoprostol: all women, Outcome 21 Fetal distress.*

Umbilical artery pH < 7.10

It is uncertain whether there is a difference in umbilical artery pH less than 7.10 directly postpartum between both induction methods (RR 1.14, 95% CI 0.35 to 3.74; 120 women; 1 study; Analysis 7.22).



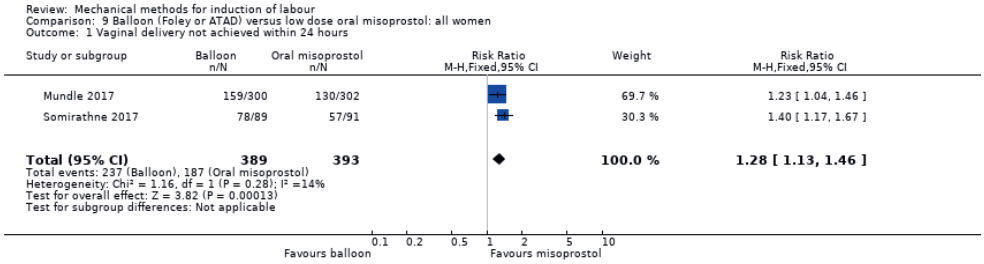
Analysis 7.22*: Comparison 7 Balloon (Foley or ATAD) versus low dose vaginal misoprostol: all women, Outcome 22 Umbilical artery pH <7.10*.

Balloon (single or double) versus low-dose oral misoprostol (seven trials involving 3178 women)

Primary outcomes

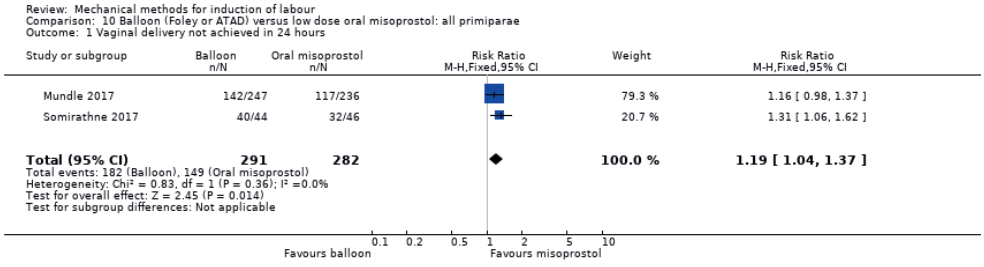
Vaginal delivery not achieved within 24 hours

A balloon catheter probably increases the risk of a vaginal delivery not achieved within 24 hours when compared to oral misoprostol (RR 1.28, 95% CI 1.13 to 1.46; 782 women, 2 studies. moderate-quality evidence, Analysis 9.1), the absolute effect being 133 more per 1000 deliveries.

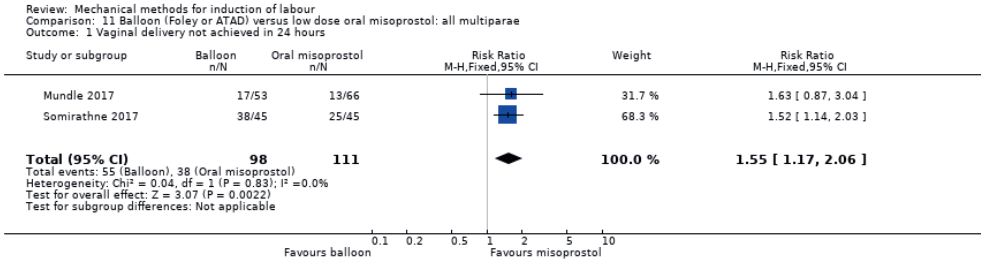


***Analysis 9.1**: Comparison 9 Balloon (Foley or ATAD) versus low dose oral misoprostol: all women, Outcome 1 Vaginal delivery not achieved within 24 hours.*

The same results were seen on parity subgroup comparisons for primiparous women (RR 1.19, 95% CI 1.04 to 1.37; 573 women; 2 studies; Analysis 10.1) and multiparous women (RR 1.55, 95% CI 1.17 to 2.06; 209 women; 2 studies; Analysis 11.1).



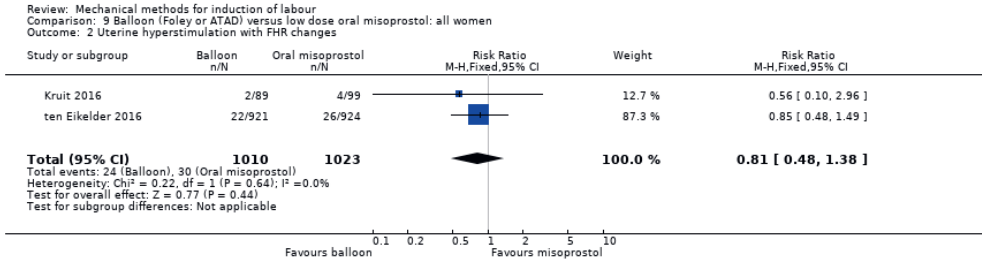
***Analysis 10.1**: Comparison 10 Balloon (Foley or ATAD) versus low dose oral misoprostol: all primiparae, Outcome 1 Vaginal delivery not achieved in 24 hours.*



***Analysis 11.1**: Comparison 11 Balloon (Foley or ATAD) versus low dose oral misoprostol: all multiparae, Outcome 1 Vaginal delivery not achieved in 24 hours.*

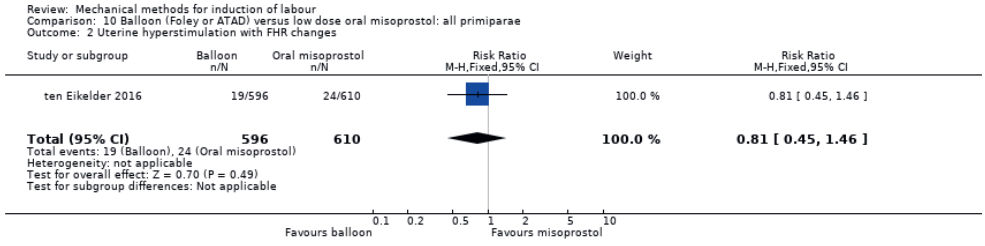
Uterine hyperstimulation with FHR changes

It is uncertain whether there is a difference in uterine hyperstimulation with FHR changes between both induction methods (RR 0.81, 95% CI 0.48 to 1.38; 2033 women; 2 studies; low-quality evidence; Analysis 9.2).

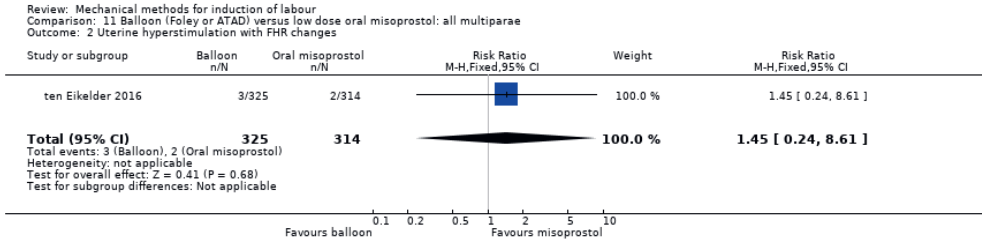


Analysis 9.2: *Comparison 9 Balloon (Foley or ATAD) versus low dose oral misoprostol: all women, Outcome 2 Uterine hyperstimulation with FHR changes.*

The same results were seen on parity subgroup comparisons for primiparous women (RR 0.81, 95% CI 0.45 to 1.46; 1206 women; 1 study; Analysis 10.2 and multiparous women (RR 1.45, 95% CI 0.24 to 8.61; 639 women; 1 study; Analysis 11.2).



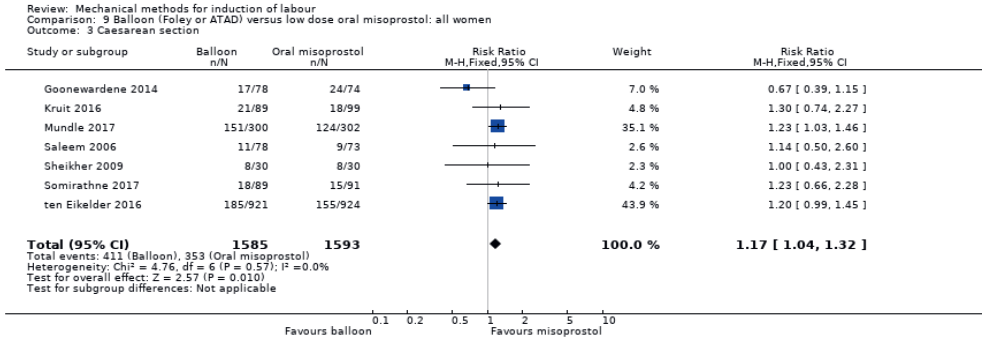
Analysis 10.2: *Comparison 10 Balloon (Foley or ATAD) versus low dose oral misoprostol: all primiparae, Outcome 2 Uterine hyperstimulation with FHR changes.*



Analysis 11.2: *Comparison 11 Balloon (Foley or ATAD) versus low dose oral misoprostol: all multiparae, Outcome 2 Uterine hyperstimulation with FHR changes*

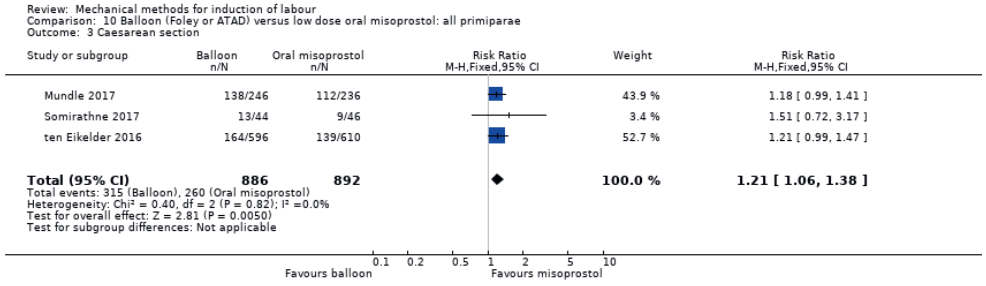
Caesarean section

A balloon catheter probably slightly increases the risk of a caesarean section when compared to oral misoprostol (RR 1.17, 95% CI 1.04 to 1.32; 3178 women; 7 studies; moderate-quality evidence; Analysis 9.3), the absolute effect being 37 more caesarean sections per 1000 deliveries.

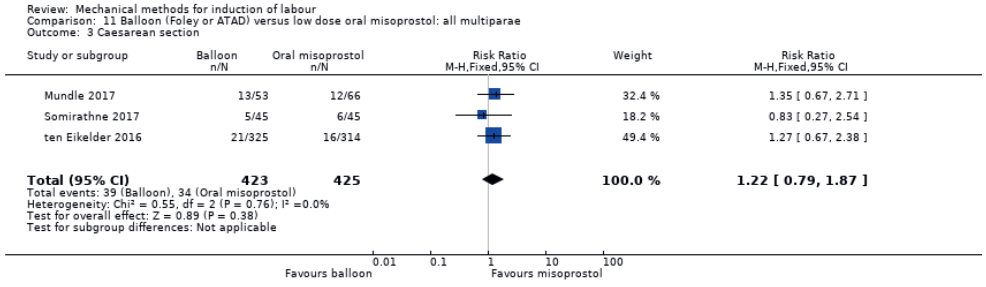


Analysis 9.3: *Comparison 9 Balloon (Foley or ATAD) versus low dose oral misoprostol: all women, Outcome 3 Caesarean section.*

The same result was seen on the subgroup of primiparous women (RR 1.21, 95% CI 1.06 to 1.38; 1778 women; 3 studies; Analysis 10.3). For multiparous women, it is uncertain whether there is a difference in caesarean sections between both methods (RR 1.22, 95% CI 0.79 to 1.87; 848 women; 3 studies; Analysis 11.3).



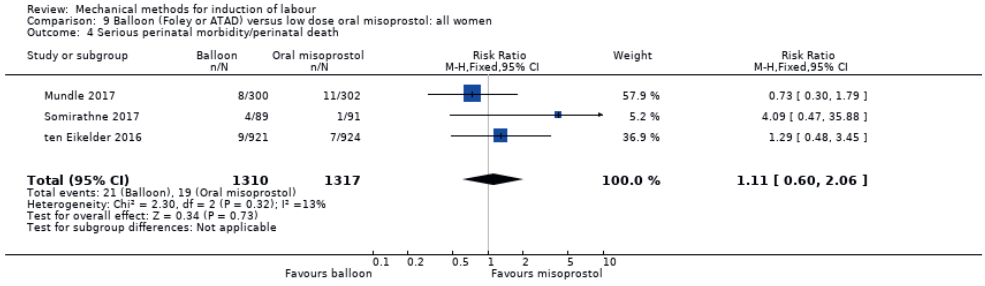
Analysis 10.3: *Comparison 10 Balloon (Foley or ATAD) versus low dose oral misoprostol: all primiparae, Outcome 3 Caesarean section.*



Analysis 11.3: *Comparison 11 Balloon (Foley or ATAD) versus low dose oral misoprostol: all multiparae, Outcome 3 Caesarean section.*

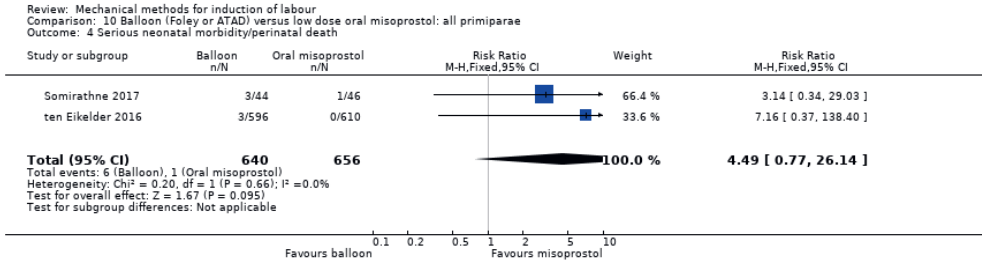
Serious neonatal morbidity or perinatal death

It is uncertain whether there is a difference in serious neonatal morbidity or perinatal death between both induction methods (RR 1.11, 95% CI 0.60 to 2.06; 2627 women; 3 studies; low-quality evidence; Analysis 9.4).

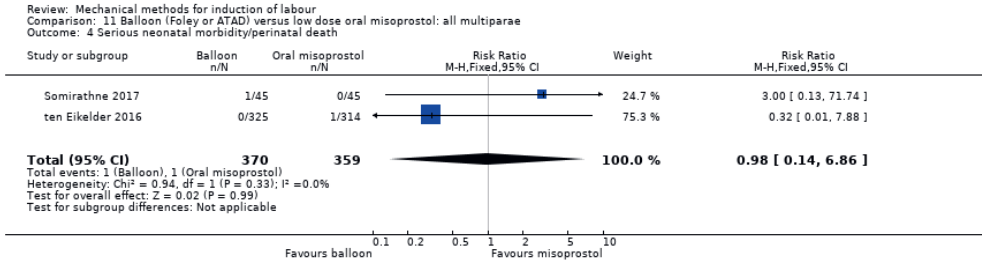


***Analysis 9.4**: Comparison 9 Balloon (Foley or ATAD) versus low dose oral misoprostol: all women, Outcome 4 Serious perinatal morbidity/perinatal death.*

The same results were seen on parity subgroup comparisons for primiparous women (RR 4.49, 95% CI 0.77 to 26.14; 1296 women; 2 studies; Analysis 10.4) and multiparous women (RR 0.98, 95% CI 0.14 to 6.86; 729 women; 2 studies; Analysis 11.4).



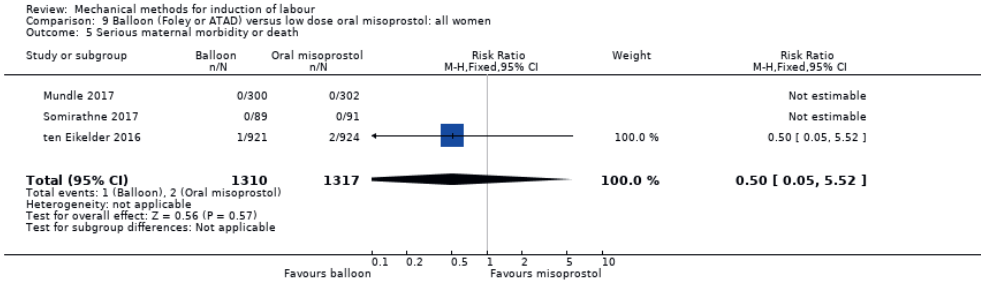
***Analysis 10.4:** Comparison 10 Balloon (Foley or ATAD) versus low dose oral misoprostol: all primiparae, Outcome 4 Serious neonatal morbidity/perinatal death.*



***Analysis 11.4:** Comparison 11 Balloon (Foley or ATAD) versus low dose oral misoprostol: all multiparae, Outcome 4 Serious neonatal morbidity/perinatal death.*

Serious maternal morbidity or death

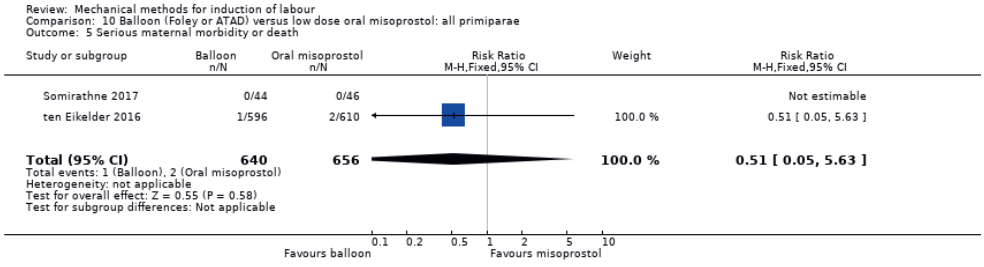
It is uncertain whether there is a difference in serious maternal morbidity or death between both induction methods (RR 0.50, 95% CI 0.05 to 5.52; 2627 women; 3 studies; very low-quality evidence; Analysis 9.5).



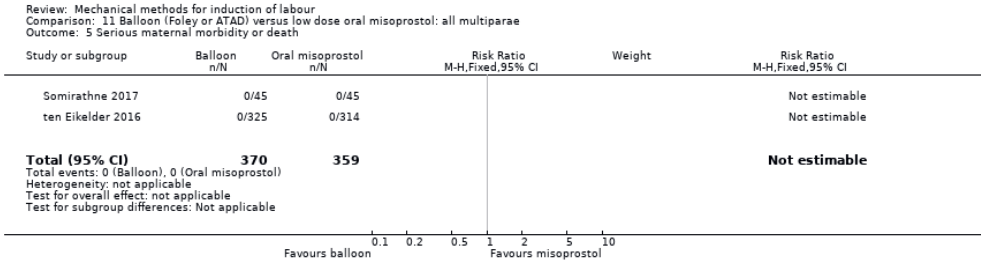
Analysis 9.5: *Comparison 9 Balloon (Foley or ATAD) versus low dose oral misoprostol: all women, Outcome 5 Serious maternal morbidity or death.*

2

The same results were seen on parity subgroup comparisons for primiparous women (RR 0.51, 95% CI 0.05 to 5.63; 1296 women; 2 studies; Analysis 10.5) and multiparous women (Analysis 11.5). In the latter group, no events of maternal morbidity or death were reported (2 studies; 729 women).



Analysis 10.5: *Comparison 10 Balloon (Foley or ATAD) versus low dose oral misoprostol: all primiparae, Outcome 5 Serious maternal morbidity or death.*

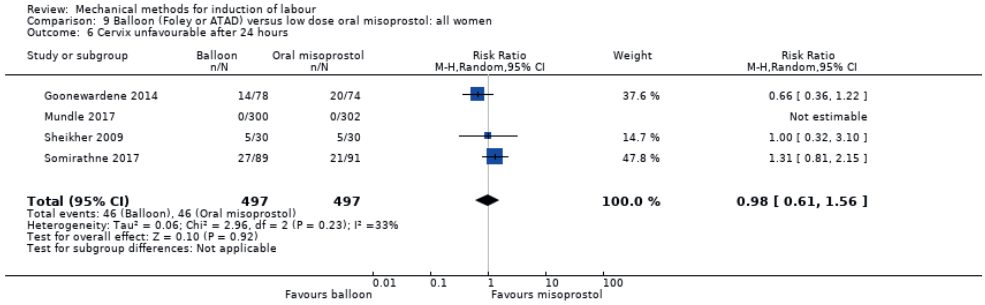


Analysis 11.5: *Comparison 11 Balloon (Foley or ATAD) versus low dose oral misoprostol: all multiparae, Outcome 5 Serious maternal morbidity or death.*

Secondary outcomes

Cervix unfavourable/unchanged after 24 hours

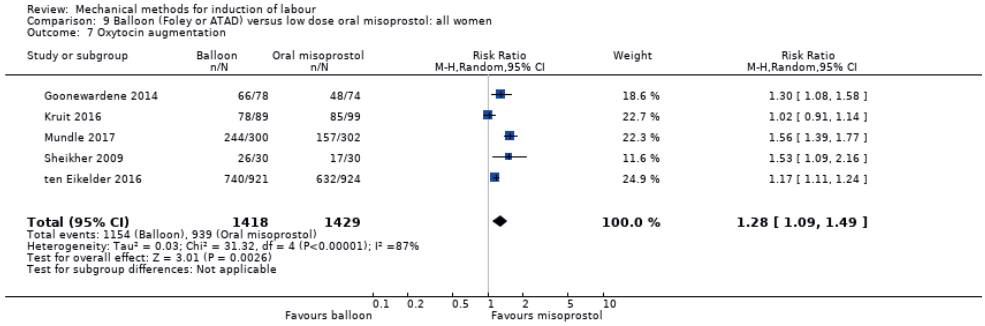
It is uncertain whether there is a difference in an unfavourable cervix after 24 hours between both induction methods (average RR 0.98, 95% CI 0.61 to 1.56; 994 women; 4 studies; Analysis 9.6). Also, there was moderate heterogeneity for this outcome (Tau² = 0.06; Chi² = 2.96, df = 2 (P = 0.23); I² = 33%). A sensitivity analysis, after eliminating the two trials assessed as having a potentially higher risk of allocation or attrition bias (Goonewardene 2014; Sheikher 2009), did not change the result, although heterogeneity was lost (RR 1.31, 95% CI 0.81 to 2.15; 782 women; 2 studies; I² = 0%).



Analysis 9.6*: Comparison 9 Balloon (Foley or ATAD) versus low dose oral misoprostol: all women, Outcome 6 Cervix unfavourable after 24 hours*

Oxytocin augmentation

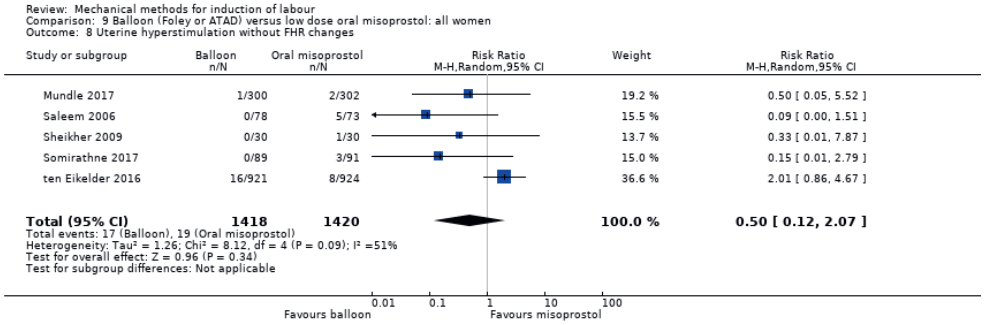
A balloon catheter may increase the risk of oxytocin augmentation when compared to oral misoprostol (average RR 1.28, 95% CI 1.09 to 1.49; 2847 women; 5 studies; Analysis 9.7) although there was substantial heterogeneity for this outcome (Tau² = 0.03; Chi² = 31.32, df = 4 (P < 0.000001); I² = 87%). A sensitivity analysis, after eliminating the three trials assessed as having a potentially higher risk of allocation or attrition bias (Goonewardene 2014; Kruit 2016; Sheikher 2009), did not change this result, nor did it lower heterogeneity (average RR 1.35, 95% CI 1.02 to 1.79; 2447 women; 2 studies; I² = 95%).



Analysis 9.7: Comparison 9 Balloon (Foley or ATAD) versus low dose oral misoprostol: all women, Outcome 7 Oxytocin augmentation.

Uterine hyperstimulation without FHR changes

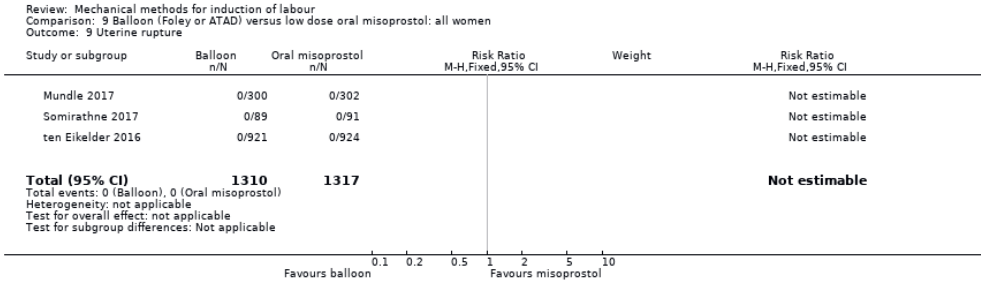
It is uncertain whether there is a difference in uterine hyperstimulation without FHR changes between both induction methods (average RR 0.50, 95% CI 0.12 to 2.07; 2838 women; 5 studies; Analysis 9.8). Also, there was substantial heterogeneity for this outcome ($Tau^2 = 1.26$; $Chi^2 = 8.12$, df = 4 (P = 0.09); $I^2 = 51\%$). A sensitivity analysis, after eliminating the one trial assessed as having a potentially higher risk of allocation or attrition bias (Sheikher 2009), did not change the effect observed, nor did it lower heterogeneity (average RR 0.49, 95% CI 0.09 to 2.64; 2778 women; 4 studies; $I^2 = 60\%$).



Analysis 9.8: *Comparison 9 Balloon (Foley or ATAD) versus low dose oral misoprostol: all women, Outcome 8 Uterine hyperstimulation without FHR changes.*

Uterine rupture

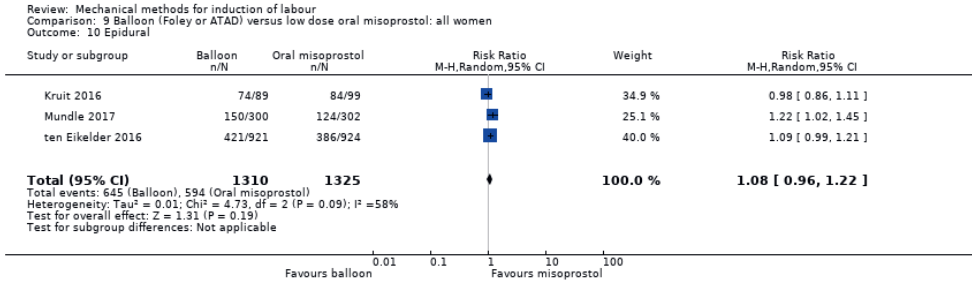
It is uncertain whether there is a difference in uterine rupture between both induction methods (Analysis 9.9). Of the seven studies included for this comparison, three studies (2627 women) pre-specified this outcome. No events of uterine rupture occurred in any of these studies.



Analysis 9.9: *Comparison 9 Balloon (Foley or ATAD) versus low dose oral misoprostol: all women, Outcome 9 Uterine rupture.*

Epidural analgesia

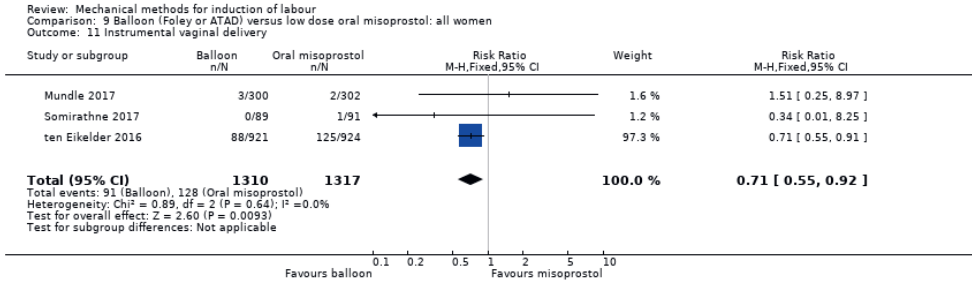
A balloon catheter may slightly increase the risk for epidural analgesia when compared to oral misoprostol (average RR 1.08, 95% CI 0.96 to 1.22; 2635 women; 3 studies; Analysis 9.10). However, the result is still too imprecise to make a valid judgement on this outcome. Also, there was substantial heterogeneity for this outcome ($Chi^2 = 4.73$, df = 2 (P = 0.09); $I^2 = 58\%$). A sensitivity analysis, after eliminating the one trial assessed as having a potentially higher risk of allocation or attrition bias (Kruit 2016), did not change this result, but did lower heterogeneity for this outcome (RR 1.13, 95% CI 1.03 to 1.24; 2447; 2 studies; $I^2 = 5\%$).



Analysis 9.10: *Comparison 9 Balloon (Foley or ATAD) versus low dose oral misoprostol: all women, Outcome 10 Epidural.*

Instrumental vaginal delivery

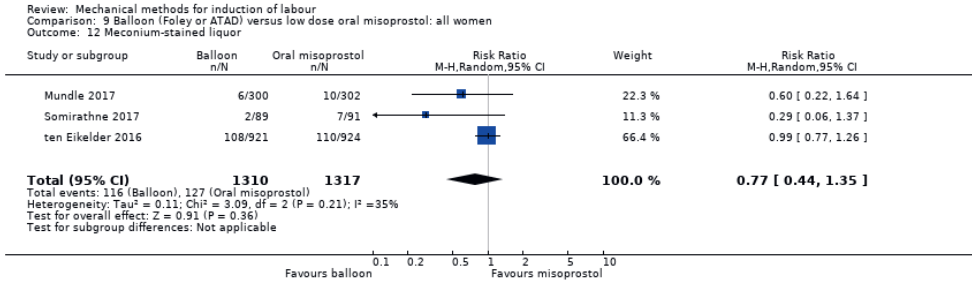
A balloon catheter probably reduces the risk of an instrumental vaginal delivery when compared to oral misoprostol (RR 0.71, 95% CI 0.55 to 0.92; 2627 women; 3 studies; Analysis 9.11).



Analysis 9.11*: Comparison 9 Balloon (Foley or ATAD) versus low dose oral misoprostol: all women, Outcome 11 Instrumental vaginal delivery.*

Meconium-stained liquor

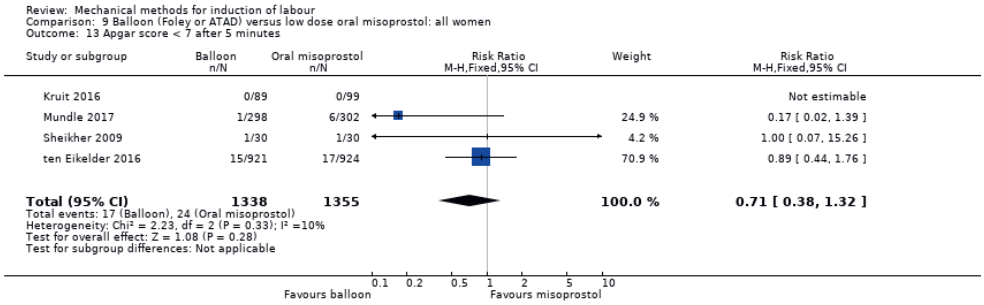
It is uncertain whether there is a difference in meconium-stained liquor between both induction methods (average RR 0.77, 95% CI 0.44 to 1.35; 2627 women; 3 studies; Analysis 9.12). Also, there was moderate heterogeneity for this outcome (Tau² = 0.11; Chi² = 3.09, df = 2 (P = 0.21); I² = 35%). No sensitivity analysis was conducted as no potential high-risk studies were included for this outcome.



Analysis 9.12: Comparison 9 Balloon (Foley or ATAD) versus low dose oral misoprostol: all women, Outcome 12 Meconium-stained liquor.

Apgar score less than seven at five minutes

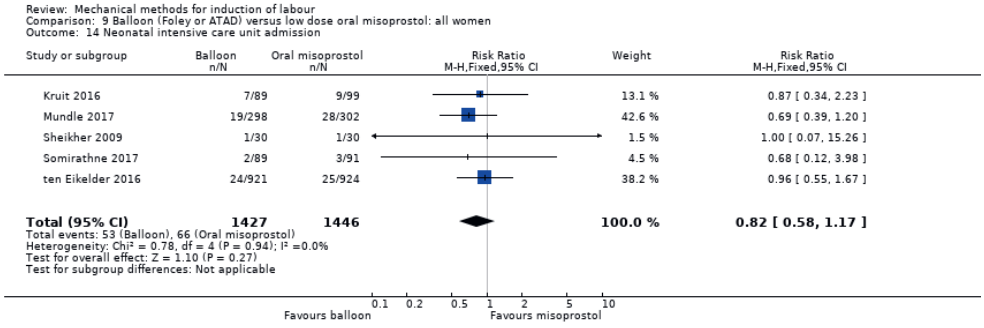
It is uncertain whether there is a difference in Apgar scores less than seven at five minutes between both induction methods (RR 0.71, 95% CI 0.38 to 1.32; 2693 women; 4 studies; low-quality evidence; Analysis 9.13).



Analysis 9.13: *Comparison 9 Balloon (Foley or ATAD) versus low dose oral misoprostol: all women, Outcome 13 Apgar score < 7 after 5 minutes.*

Neonatal intensive care unit admission

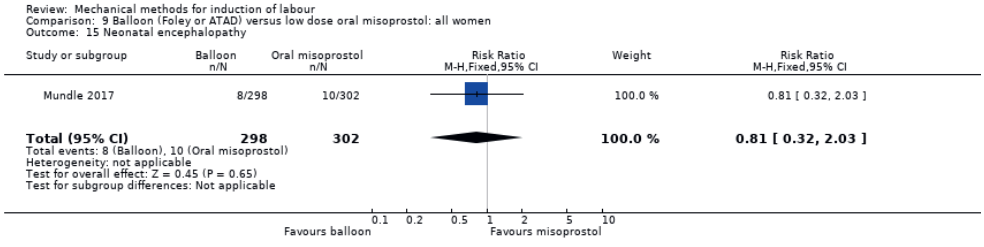
It is uncertain whether there is a difference in NICU admissions between both induction methods (RR 0.82, 95% CI 0.58 to 1.17; 2873 women; 5 studies; low-quality evidence; Analysis 9.14).



Analysis 9.14: *Comparison 9 Balloon (Foley or ATAD) versus low dose oral misoprostol: all women, Outcome 14 Neonatal intensive care unit admission.*

Neonatal encephalopathy

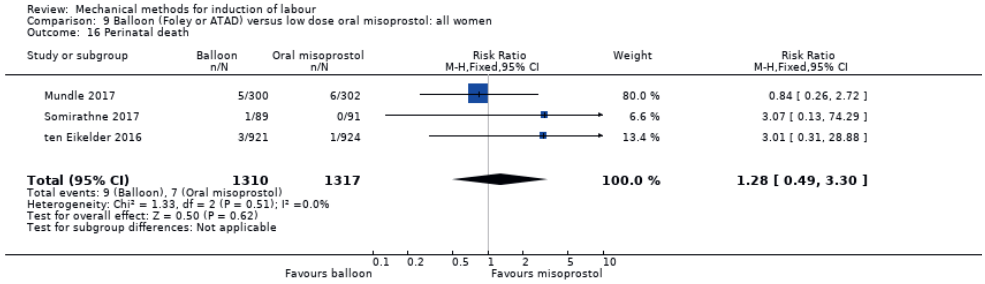
It is uncertain whether there is a difference in neonatal encephalopathy between both induction methods (RR 0.81, 95% CI 0.32 to 2.03; 600 women; 1 study; Analysis 9.15).



Analysis 9.15: *Comparison 9 Balloon (Foley or ATAD) versus low dose oral misoprostol: all women, Outcome 15 Neonatal encephalopathy.*

Perinatal death

It is uncertain whether there is difference in perinatal death between both induction methods (RR 1.28, 95% CI 0.49 to 3.30; 2627 women; 3 studies; Analysis 9.16) as the result was imprecise and events occurred infrequently (9/1310 versus 7/1317, respectively). In the balloon group, two cases of perinatal death were related to asphyxia, compared to one case in the misoprostol group.



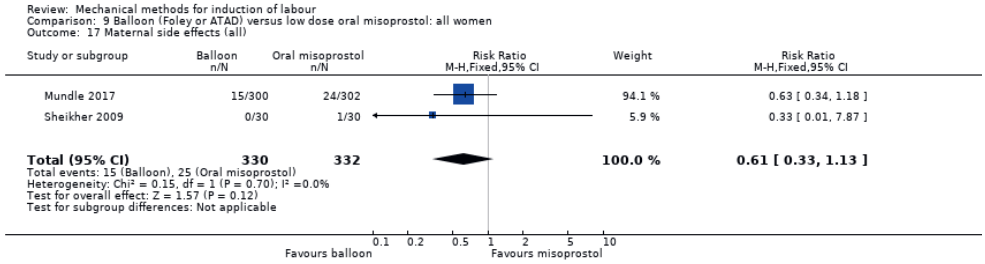
Analysis 9.16: *Comparison 9 Balloon (Foley or ATAD) versus low dose oral misoprostol: all women, Outcome 16 Perinatal death.*

Disability in childhood

Not reported.

Maternal side effects (all)

It is uncertain whether there is a difference in maternal side effects between both induction methods (RR 0.61, 95% CI 0.33 to 1.13; 662 women; 2 studies; Analysis 9.17).



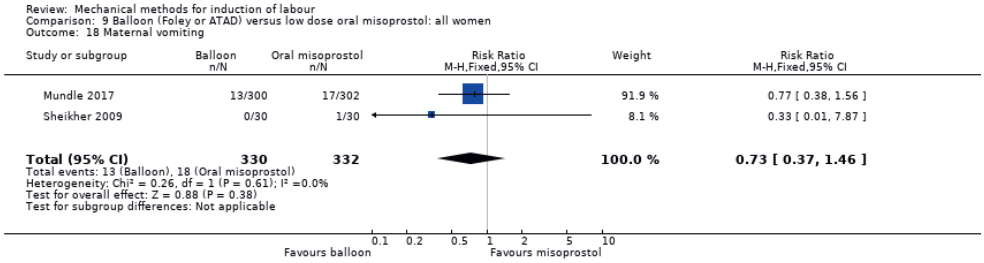
Analysis 9.17*: Comparison 9 Balloon (Foley or ATAD) versus low dose oral misoprostol: all women, Outcome 17 Maternal side effects (all).*

Maternal nausea - Serious maternal complications

Not reported.

Maternal vomiting

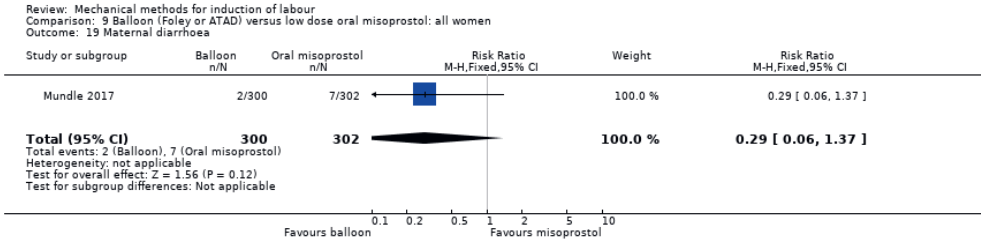
It is uncertain whether there is a difference in maternal vomiting between both induction methods (RR 0.73, 95% CI 0.37 to 1.46; 662 women; 2 studies; Analysis 9.18).



Analysis 9.18: *Comparison 9 Balloon (Foley or ATAD) versus low dose oral misoprostol: all women, Outcome 18 Maternal vomiting.*

Maternal diarrhoea

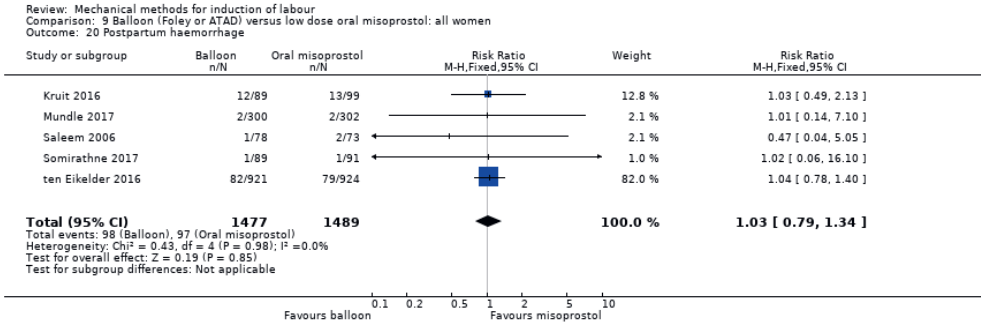
It is uncertain whether there is a difference in maternal diarrhoea between both induction methods (RR 0.29, 95% CI 0.06 to 1.37; 602 women; 1 study; Analysis 9.19).



Analysis 9.19: *Comparison 9 Balloon (Foley or ATAD) versus low dose oral misoprostol: all women, Outcome 19 Maternal diarrhoea.*

Postpartum haemorrhage

It is uncertain whether there is difference in postpartum haemorrhage between both induction methods (RR 1.03, 95% CI 0.79 to 1.34; 2966 women; 5 studies; Analysis 9.20).



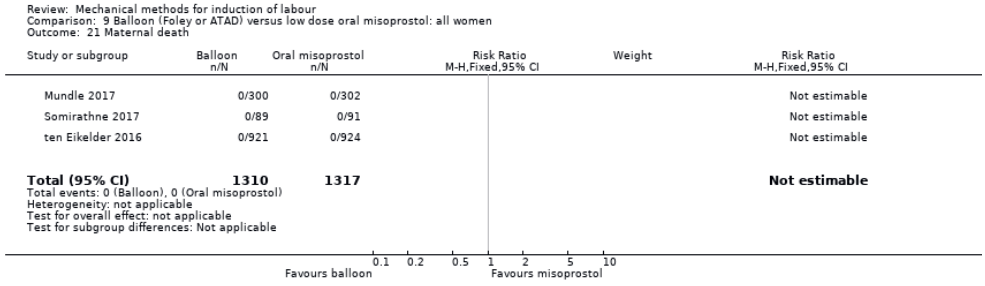
Analysis 9.20: *Comparison 9 Balloon (Foley or ATAD) versus low dose oral misoprostol: all women, Outcome 20 Postpartum haemorrhage.*

Other maternal side effects

Not reported.

Maternal death

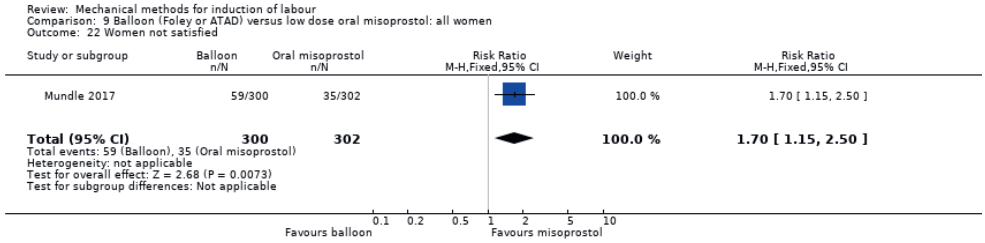
It is uncertain whether there is a difference in maternal death between both induction methods (Analysis 9.21). Of the 13 studies included for this comparison, three studies (2627 women) pre-specified this outcome. No events of maternal death occurred in one of these studies.



Analysis 9.21: *Comparison 9 Balloon (Foley or ATAD) versus low dose oral misoprostol: all women, Outcome 21 Maternal death.*

Woman not satisfied

A balloon catheter may increase the risk of women not being satisfied when compared to oral misoprostol (RR 1.70, 95% CI 1.15 to 2.50; 602 women; 1 study; Analysis 9.22), the absolute effect being 80 more women not satisfied per 1000 deliveries. In the one study included for this outcome, women were asked if they would choose the same induction method again in a future induction of labour.



Analysis 9.22: *Comparison 9 Balloon (Foley or ATAD) versus low dose oral misoprostol: all women, Outcome 22 Women not satisfied.*

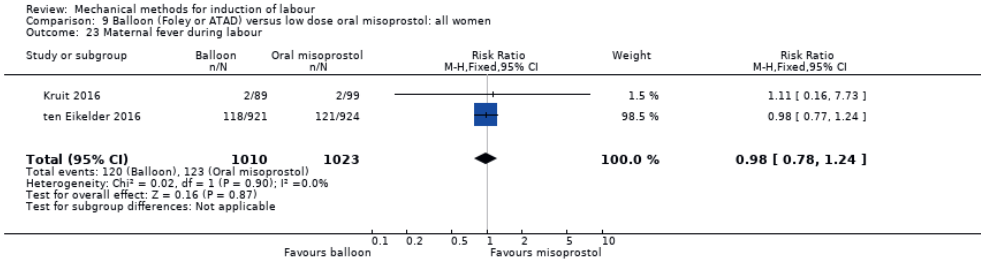
Caregiver not satisfied

Not reported.

Not pre-specified outcomes

Maternal fever during labour

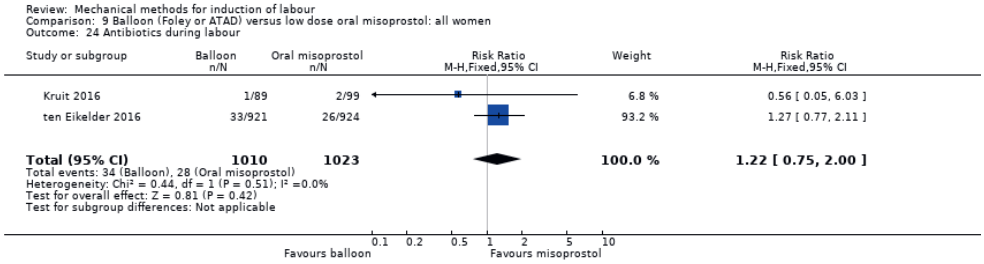
There probably is little or no difference in maternal fever during labour between both induction methods (RR 0.98, 95% CI 0.78 to 1.24; 2033 women; 2 studies; Analysis 9.23).



Analysis 9.23: *Comparison 9 Balloon (Foley or ATAD) versus low dose oral misoprostol: all women, Outcome 23 Maternal fever during labour.*

Antibiotics during labour

It is uncertain whether there is a difference in antibiotics during labour between both induction methods (RR 1.22, 95% CI 0.75 to 2.00; 2033 women; 2 studies; Analysis 9.24).



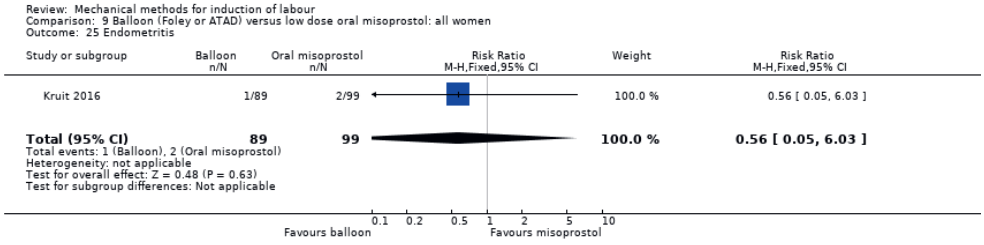
Analysis 9.24*: Comparison 9 Balloon (Foley or ATAD) versus low dose oral misoprostol: all women, Outcome 24 Antibiotics during labour.*

Chorioamnionitis

Not reported.

Endometritis

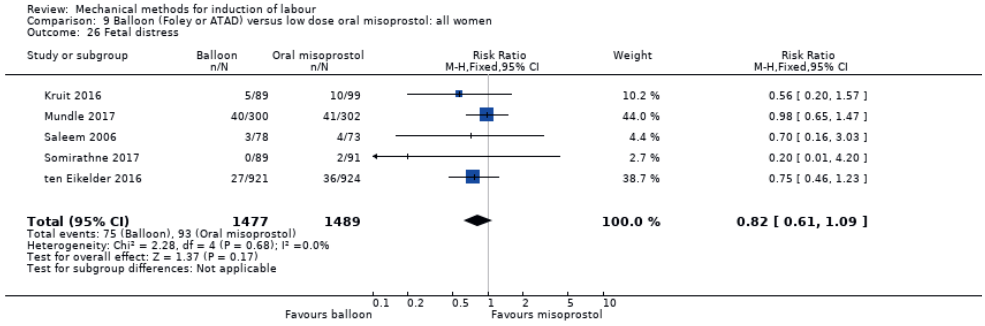
It is uncertain whether there is a difference in endometritis between both induction methods (RR 0.56, 95% CI 0.05 to 6.03; 188 women; 1 study; Analysis 9.25).



Analysis 9.25: *Comparison 9 Balloon (Foley or ATAD) versus low dose oral misoprostol: all women, Outcome 25 Endometritis.*

Fetal distress

It is uncertain whether there is a difference in fetal distress for which a caesarean section is indicated between both induction methods (RR 0.82, 95% CI 0.61 to 1.09; 2966 women; 5 studies; Analysis 9.26).



Analysis 9.26: *Comparison 9 Balloon (Foley or ATAD) versus low dose oral misoprostol: all women, Outcome 26 Fetal distress.*

Umbilical artery pH < 7.10

It is uncertain whether there is a difference in umbilical artery pH less than 7.10 directly postpartum between both induction methods (RR 0.77, 95% CI 0.53 to 1.12; 1535 women; 2 studies; Analysis 9.27).

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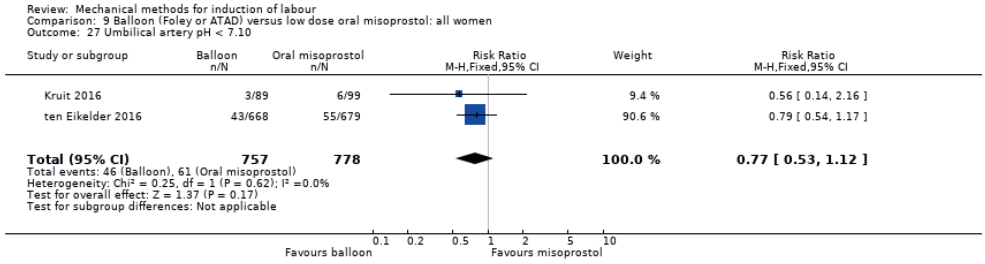

Analysis 9.27*: Comparison 9 Balloon (Foley or ATAD) versus low dose oral misoprostol: all women, Outcome 27 Umbilical artery pH < 7.10.*

Balloon (single or double) versus oxytocin (eight trials involving 781 women)

Primary outcomes

Vaginal delivery not achieved within 24 hours

Not reported.

Uterine hyperstimulation with FHR changes

It is uncertain whether there is a difference in uterine hyperstimulation with FHR changes between induction of labour with a balloon and oxytocin (RR 0.20, 95% CI 0.01 to 4.11; 200 women; 1 study; Analysis 12.1). For the subgroups of primiparous and multiparous women, no outcomes were reported.

Caesarean section

A balloon catheter probably reduces the risk of a caesarean section when compared to oxytocin (RR 0.68, 95% CI 0.56 to 0.83; 781 women; 8 studies; Analysis 12.2), the absolute effect being 126 fewer caesarean sections per 1000 deliveries. For women with a previous caesarean section, a balloon catheter may slightly reduce the risk of a caesarean section when compared to oxytocin (RR 0.80, 95% CI 0.64 to 1.00; 364 women; 3 studies; Analysis 13.1). However, the result is still too imprecise to make a valid judgement on this outcome. For primiparous women, it is uncertain whether there is a difference in effect as the result of this outcome was imprecise (RR 0.43, 95% CI 0.12 to 1.50; 60 women; 1 study; Analysis 14.1). For multiparous women, no outcomes were reported.

Serious neonatal morbidity or perinatal death

It is uncertain whether there is a difference in serious neonatal morbidity or perinatal death between both induction methods (Analysis 12.3). Of the eight studies included for this comparison, one study (100 women) reported on this composite outcome. No events of neonatal morbidity or perinatal death occurred in this study. The same result was seen on a subgroup of women with a previous caesarean section. One study (100 women) reported on this outcome, in which no events of serious neonatal morbidity of perinatal death occurred (Analysis 13.2). For the subgroups of primiparous and multiparous women, no outcomes were reported.

Serious maternal morbidity or death

It is uncertain whether there is a difference in serious maternal morbidity or death between both induction methods (Analysis 12.4). Of the eight studies included for this comparison, two studies (160 women) reported on this composite outcome. No events of serious maternal morbidity or death occurred in these studies. The same result was seen on a subgroup of women with a previous caesarean section. One study (100 women) reported on this outcome, in which no events of serious maternal morbidity of death occurred (Analysis 13.3). On parity subgroup comparisons, one study (60 women) reported on this outcome in primiparous women, in which no events were seen (Analysis 14.2). For multiparous women, no outcomes were reported.

Secondary outcomes

Cervix unfavourable/unchanged after 24 hours

It is uncertain whether there is a difference in an unfavourable cervix after 24 hours between both induction methods (RR 0.56, 95% CI 0.20 to 1.54; 100 women; 1 study; Analysis 12.5).

Oxytocin augmentation
Not a relevant outcome because all women in the comparison group received oxytocin.

Uterine hyperstimulation without FHR changes
It is uncertain whether there is a difference in uterine hyperstimulation without FHR changes between both induction methods (RR 1.00, 95% CI 0.23 to 4.29; 192 women; 3 studies; Analysis 12.6).

Uterine rupture
It is uncertain whether there is a difference in uterine rupture between both induction methods (Analysis 12.7). Of the eight studies included for this comparison, one study (100 women) pre-specified this outcome. No events of uterine rupture occurred in this study.

Epidural analgesia
Not reported.

Instrumental vaginal delivery
It is uncertain whether there is a difference in instrumental vaginal deliveries between both induction methods (RR 1.19, 95% CI 0.55 to 2.57; 220 women; 3 studies; Analysis 12.8).

Meconium-stained liquor
It is uncertain whether there is a difference in meconium-stained liquor between both induction methods (RR 0.53, 95% CI 0.23 to 1.21; 272 women; 2 studies; Analysis 12.9).

Apgar score less than seven at five minutes
It is uncertain whether there is a difference in Apgar scores less than seven at five minutes between both induction methods (RR 0.71, 95% CI 0.14 to 3.53; 300 women; 2 studies; Analysis 12.10).

Neonatal intensive care unit admission
It is uncertain whether there is difference in NICU admissions between both induction methods (RR 0.80, 95% CI 0.32 to 1.98; 372 women; 3 studies; Analysis 12.11).

Neonatal encephalopathy
Not reported.

Perinatal death
It is uncertain whether there is a difference in perinatal death between both induction methods (Analysis 12.12). Of the eight studies included for this comparison, one study (100 women) pre-specified this outcome. No cases of perinatal death occurred in this study.

Disability in childhood - Maternal side effects (all) - Maternal nausea - Maternal vomiting - Maternal diarrhoea - Other maternal side effects
Not reported.

Postpartum haemorrhage
It is uncertain whether there is difference in postpartum haemorrhage between both induction methods (RR 1.26, 95% CI 0.51 to 3.11; 396 women; 4 studies; Analysis 12.13).

Serious maternal complications - Maternal death - Woman not satisfied - Caregiver not satisfied
Not reported

Other outcomes (not pre-specified)
Maternal fever during labour
It is uncertain whether there is difference in maternal fever during labour between both induction methods (RR 0.20, 95% CI 0.01 to 4.00; 60 women; 1 study; Analysis 12.14).

Antibiotics during labour – Chorioamnionitis - Endometritis
Not reported.

Fetal distress
A balloon catheter probably reduces the risk of fetal distress for which a caesarean section is indicated when compared to oxytocin (RR 0.43, 95% CI 0.19 to 0.98; 332 women; 3 studies; Analysis 12.15).

Umbilical artery pH < 7.10
Not reported.

Balloon (single or double) versus amniotomy (one trial involving 20 women)

The only outcome of interest reported for this comparison was caesarean section. Other outcomes were not reported.

Caesarean section
It is uncertain whether there is difference in caesarean sections between induction of labour with a balloon and amniotomy (RR 0.25, 95% CI 0.03 to 1.86; 20 women; 1 study; Analysis 15.1).
For the subgroups of primiparous and multiparous women, no outcomes were reported.

Singe balloon (Foley) versus double balloon (ATAD/Cook) (five trials involving 826 women)

Primary outcomes

Vaginal delivery not achieved within 24 hours

There may be little or no difference in vaginal deliveries not achieved within 24 hours between induction of labour with a single balloon and a double balloon (average RR 0.97, 95% CI 0.75 to 1.25; 608 women; 3 studies; Analysis 16.1), although there was substantial heterogeneity for this outcome (Chi^2 = 5.64, df = 2 (P = 0.06); I^2 = 65%). No sensitivity analysis was performed as no high-risk studies were included for this outcome. It is uncertain whether there is a difference in vaginal deliveries not achieved within 24 hours between both induction methods on subgroups for both primiparous women (RR 1.14, 95% CI 0.95 to 1.38; 50 women; 1 study; Analysis 17.1) and multiparous women (RR 1.24, 95% CI 0.80 to 1.93; 48 women; 1 study; Analysis 18.1) as the results for these outcomes were imprecise.

Uterine hyperstimulation with FHR changes

It is uncertain whether there is a difference in uterine hyperstimulation with FHR changes (Analysis 16.2), as events seem to occur infrequently after the use of both induction methods. Of the five studies included for this comparison, one study (217 women) reported on this outcome. No events of uterine hyperstimulation with FHR occurred in this study.

Caesarean section

It is uncertain whether there is a difference in caesarean sections between both induction methods (average RR 0.97, 95% CI 0.71 to 1.33; 862 women; 5 studies; Analysis 16.3). Also, there was moderate heterogeneity for this outcome (Chi^2 = 6.99, df = 4 (P = 0.14); I^2 = 43%). A sensitivity analysis, after eliminating the one trial assessed as having a potentially higher risk of concealment or attrition bias (Ahmed 2016), did not change the effect observed, nor did it lower heterogeneity (average RR 0.92, 95% CI 0.65 to 1.32; 788 women; 5 studies; I^2 = 50%). The same result was seen on parity subgroup comparisons for primiparous women (average RR 1.30, 95% CI 0.76 to 2.22; 374 women; 4 studies; Analysis 17.2) and multiparous women (RR 0.74, 95% CI 0.30 to 1.84; 186 women; 2 studies; Analysis 18.2). Furthermore, for the primiparous group, there was also substantial heterogeneity (Tau^2 = 0.18; Chi^2 = 7.96, df = 3 (P = 0.05); I^2 = 62%).

Serious neonatal morbidity or perinatal death

Not reported.

Serious maternal morbidity or death

It is uncertain whether there is a difference in serious maternal morbidity or death between both induction methods (Analysis 16.4). Of the five studies included for this comparison, one study (217 women) reported on this composite outcome. No events of serious maternal morbidity or death occurred in this study.

For the subgroups of primiparous and multiparous women, no outcomes were reported.

Secondary outcomes

Cervix unfavourable/unchanged after 24 hours

Not reported.

Oxytocin augmentation

There probably is little or no difference in oxytocin augmentation between both induction methods (RR 0.94, 95% CI 0.82 to 1.08; 278 women; 2 studies; Analysis 16.5).

Uterine hyperstimulation without FHR changes

It is uncertain whether there is a difference in uterine hyperstimulation without FHR changes (Analysis 16.6), although events seem to occur infrequently after the use of both induction methods. Of the five studies included for this comparison, one study (217 women) reported on this outcome. No events of uterine hyperstimulation without FHR occurred in this study.

Uterine rupture

It is uncertain whether there is a difference in uterine rupture between both induction methods (Analysis 16.7). Of the five studies included for this comparison, one study (217 women) reported on this outcome. No events of uterine rupture occurred in this study.

Epidural analgesia

There probably is little or no difference in epidural analgesia between both induction methods (RR 0.93, 95% CI 0.83 to 1.03; 608 women; 3 studies; Analysis 16.8).

Instrumental vaginal delivery

It is uncertain whether there is a difference in instrumental vaginal deliveries between both induction methods (RR 0.86, 95% CI 0.61 to 1.20; 690 women; 3 studies; Analysis 16.9).

Meconium-stained liquor

A single balloon may reduce the risk of meconium-stained liquor when compared to a double balloon (RR 0.40, 95% CI 0.15 to 1.04; 98 women; 1 study; Analysis 16.10). However, the result is still too imprecise to make a valid judgement on this outcome.

Apgar score less than seven at five minutes

It is uncertain whether there is a difference in Apgar scores less than seven at five minutes between both induction methods (RR 0.84, 95% CI 0.25 to 2.79; 608 women; 3 studies; Analysis 16.11).

Neonatal intensive care unit admission

It is uncertain whether there is a difference in NICU admissions between both induction methods (RR 1.67, 95% CI 0.71 to 3.93; 391 women; 2 studies; Analysis 16.12).

Neonatal encephalopathy - Perinatal death - Disability in childhood - Maternal side effects (all) - maternal nausea - Maternal vomiting - Maternal diarrhoea

Not reported.

Other maternal side effects: pain after insertion
It is uncertain whether there is a difference in pain after insertion of the catheter between both induction methods (RR 0.67, 95% CI 0.20 to 2.17; 74 women; 1 study; Analysis 16.13).

Postpartum haemorrhage
It is uncertain whether there is a difference in postpartum haemorrhage between both induction methods (RR 0.83, 95% CI 0.27 to 2.52; 291 women; 2 studies; Analysis 16.14).

Serious maternal complications - Maternal death - Woman not satisfied - Caregiver not satisfied
Not reported.

Other outcomes (not pre-specified)
Maternal fever during labour
It is uncertain whether there is a difference in maternal fever during labour between both induction methods (average RR 0.61, 95% CI 0.16 to 2.34; 584 women; 3 studies; Analysis 16.15). Also, there was substantial heterogeneity for this outcome ($Chi^2 = 2.85$, df = 1 (P = 0.09); $I^2 = 65\%$). A sensitivity analysis, after eliminating the one trial assessed as having a potentially higher risk of allocation or attrition bias (Ahmed 2016), did not alter the result, nor did it lower heterogeneity (average RR 0.61, 95% CI 0.16 to 2.34; 510 women; 2 studies; $I^2 = 65\%$).

Antibiotics during labour
It is uncertain whether there is a difference in antibiotics during labour between both induction methods (RR 0.97, 95% CI 0.61 to 1.56; 217 women; 1 study; Analysis 16.16).

Chorioamnionitis
It is uncertain whether there is a difference in chorioamnionitis between both induction methods (RR 1.56, 95% CI 0.47 to 5.20; 98 women;1 study; Analysis 16.17).

Endometritis
It is uncertain whether there is a difference in endometritis between both induction methods (RR 1.95, 95% CI 0.18 to 21.14; 217 women; 1 study; Analysis 16.18).

Fetal distress
It is uncertain whether there is a difference in fetal distress for which a caesarean section is indicated (RR 0.98, 95% CI 0.70 to 1.36; 682 women; 4 studies; Analysis 16.19).

Umbilical artery pH < 7.10
It is uncertain whether there is a difference in umbilical artery pH less than 7.10 directly postpartum between both induction methods (RR 0.42, 95% CI 0.11 to 1.57; 217 women; 1 study; Analysis 16.20).

Laminaria tent versus vaginal prostaglandin E2 (five trials involving 263 women)

Primary outcomes

Vaginal delivery not achieved within 24 hours

Not reported.

Uterine hyperstimulation with FHR changes

A laminaria tent probably reduces the risk of uterine hyperstimulation with FHR changes when compared to vaginal prostaglandin E2 (RR 0.11, 95% CI 0.02 to 0.60; 188 women; 3 studies; Analysis 19.1), the absolute effect being 118 fewer per 1000 deliveries. For primiparous women, it is uncertain whether there is a difference in effect as the result of this outcome was imprecise (RR 0.33, 95% CI 0.01 to 7.95; 80 women; 1 study; Analysis 20.1). For multiparous women, this outcome was not reported.

Caesarean section

It is uncertain whether there is a difference in caesarean sections between both induction methods (RR 0.91, 95% CI 0.56 to 1.48; 263 women; 5 studies; Analysis 19.2). The same result was seen on parity subgroup comparisons for primiparous women (average RR 1.07, 95% CI 0.24 to 4.89; 90 women; 2 studies; Analysis 20.2) and multiparous women (RR 0.50, 95% CI 0.06 to 3.91; 10 women; 1 study; Analysis 21.1). Furthermore, for the primiparous group, there was also substantial heterogeneity ($Chi^2 = 2.25$, df = 1 (P = 0.13); $I^2 = 56\%$).

Serious neonatal morbidity or perinatal death

It is uncertain whether there is a difference in serious neonatal morbidity or perinatal death between both induction methods (Analysis 19.3). Of the five studies included for this comparison, one study (80 women) reported on this composite outcome. No events of neonatal morbidity or perinatal death occurred in this study. For the subgroups of primiparous and multiparous women, no outcomes were reported.

Serious maternal morbidity or death

It is uncertain whether there is a difference in serious maternal morbidity or death between both induction methods (Analysis 19.4). Of the five studies included for this comparison, one study (28 women) reported on this composite outcome. No events of serious maternal morbidity or death occurred in this study. For the subgroups of primiparous and multiparous women, no outcomes were reported.

Secondary outcomes

Cervix unfavourable/unchanged after 24 hours - Oxytocin augmentation

Not reported.

Uterine hyperstimulation without FHR changes

A laminaria tent may reduce the risk of uterine hyperstimulation without FHR changes when compared to vaginal PGE2 (RR 0.22, 95% CI 0.09 to 0.49; 180 women; 3 studies; Analysis 19.5).

Epidural analgesia
It is uncertain whether there is a difference in epidural analgesia between both induction methods (RR 0.91, 95% CI 0.74 to 1.13; 80 women; 1 study; Analysis 19.6).

Instrumental vaginal delivery
It is uncertain whether there is a difference in instrumental vaginal deliveries between both induction methods (RR 0.71, 95% CI 0.43 to 1.17; 80 women; 1 study; Analysis 19.7).

Meconium-stained liquor
It is uncertain whether there is a difference in meconium-stained liquor between both induction methods (RR 0.14, 95% CI 0.01 to 2.68; 80 women; 1 study; Analysis 19.8).

Apgar score less than seven at five minutes
It is uncertain whether there is a difference in Apgar scores less than seven at five minutes between both induction methods (Analysis 19.9). Of the five studies included for this comparison, two studies (160 women) reported on this outcome. No events of Apgar scores less than seven at five minutes occurred in these studies.

Neonatal intensive care unit admission - Neonatal encephalopathy – uterine rupture
Not reported.

Perinatal death
It is uncertain whether there is a difference in perinatal death between both induction methods (Analysis 19.10). Of the five studies included for this comparison, one study (80 women) reported on this outcome. No events of perinatal deaths occurred in this study.

Maternal side effects (all)
It is uncertain whether there is a difference in maternal side effects between both induction methods (RR 0.29, 95% CI 0.01 to 6.60; 28 women; 1 study; Analysis 19.11).

Maternal nausea
It is uncertain whether there is a difference in maternal nausea between both induction methods (RR 0.29, 95% CI 0.01 to 6.60; 28 women; 1 study; Analysis 19.12).

Maternal vomiting - Maternal diarrhoea - Other maternal side effects – Disabilty in childood - Postpartum haemorrhage -Serious maternal complications - Maternal death - Woman not satisfied - Caregiver not satisfied -Other outcomes (not pre-specified) - Maternal fever during labour - Antibiotics during labour -Chorioamnionitis - Endometritis
Not reported.

Fetal distress
It is uncertain whether there is a difference in fetal distress for which a caesarean section is indicated between both induction methods (RR 0.62, 95% CI 0.34 to 1.15; 188 women; 3 studies; Analysis 19.13).

Laminaria tent versus cervical prostaglandin E2 (five trials involving 920 women)

Primary outcomes

Vaginal delivery not achieved within 24 hours

Not reported.

Uterine hyperstimulation with FHR changes

It is uncertain whether there is a difference in uterine hyperstimulation with FHR changes between induction of labour with a laminaria tent and cervical PGE2 (RR 0.17, 95% CI 0.02 to 1.42; 350 women; 2 studies; Analysis 22.1). For the subgroups of primiparous and multiparous women, no outcomes were reported.

Caesarean section

It is uncertain whether there is a difference in caesarean sections between both induction methods (RR 1.16, 95% CI 0.93 to 1.45; 920 women; 5 studies; Analysis 22.2). The same results were seen on parity subgroup comparisons for primiparous women (RR 1.15, 95% CI 0.62 to 2.13; 116 women; 1 study; Analysis 23.1) and multiparous women (RR 1.28, 95% CI 0.45 to 3.65; 69 women; 1 study; Analysis 24.1).

Serious neonatal morbidity or perinatal death

It is uncertain whether there is a difference in serious neonatal morbidity or perinatal death between both induction methods (RR 3.16, 95% CI 0.13 to 76.70; 185 women; 1 study; Analysis 22.3). One event, a case of perinatal death, was reported in the laminaria group. No events occurred in the cervical PGE2 group. For the subgroups of primiparous and multiparous women, no outcomes were reported.

Serious maternal morbidity or death

It is uncertain whether there is a difference in serious maternal morbidity or death between both induction methods (RR 0.35, 95% CI 0.01 to 8.52; 185 women; 1 study; Analysis 22.4). No events occurred in the laminaria group. One event, a uterine rupture, was reported in the cervical PGE2 group. For the subgroups of primiparous and multiparous women, no outcomes were reported.

Secondary outcomes

Cervix unfavourable/unchanged after 24 hours

It is uncertain whether there is a difference in an unfavourable cervix after 24 hours between both induction methods (average RR 0.46, 95% CI 0.11 to 1.96; 218 women; 2 studies; Analysis 22.5). Also, there was substantial heterogeneity for this outcome ($Tau^2 = 0.62$; $Chi^2 = 1.98$, df = 1 (P = 0.16); $I^2 = 50\%$). A sensitivity analysis, after eliminating the one trial assessed as having a potentially higher risk of allocation or attrition bias (Roztocil 1998), did not alter the result (RR 0.16, 95% CI 0.02 to 1.24; 53 women; 1 study; $I^2 = 0\%$).

Oxytocin augmentation

A laminaria tent probably increases the risk of oxytocin augmentation when compared to cervical PGE2 (RR 1.41, 95% CI 1.21 to 1.64; 185 women; 1 study; Analysis 22.6).

Uterine hyperstimulation without FHR changes
It is uncertain whether there is a difference in uterine hyperstimulation without FHR changes between both induction methods (RR 0.17, 95% CI 0.02 to 1.36; 601 women; 2 studies; Analysis 22.7).

Uterine rupture
It is uncertain whether there is a difference in uterine rupture between both induction methods (RR 0.35, 95% CI 0.01 to 8.52; 185 women; 1 study; Analysis 22.8). One study reported on this outcome in which one uterine rupture occurred in the PGE2 group. No uterine ruptures were seen in the laminaria group.

Epidural analgesia
Not reported.

Instrumental vaginal delivery
It is uncertain whether there is a difference in instrumental vaginal deliveries between both induction methods (RR 1.05, 95% CI 0.65 to 1.69; 424 women; 3 studies; Analysis 22.9).

Meconium-stained liquor
Not reported.

Apgar score less than seven at five minutes
It is uncertain whether there is a difference in Apgar scores less than seven at five minutes between both induction methods (RR 5.28, 95% CI 0.63 to 44.30; 185 women; 1 study; Analysis 22.10).

Neonatal intensive care unit admission
It is uncertain whether there is a difference in NICU admissions between both induction methods (RR 1.58, 95% CI 0.58 to 4.33; 259 women; 2 studies; Analysis 22.11).

Neonatal encephalopathy
Not reported.

Perinatal death
It is uncertain whether there is a difference in perinatal death between both induction methods (RR 3.16, 95% CI 0.13 to 76.70; 185 women; 1 study; Analysis 22.12). One study reported on this outcome, in which one perinatal death occurred in the laminaria group. No perinatal death were seen in the cervical PGE2 group.

Disability in childhood
Not reported.

Maternal side effects (all)
It is uncertain whether there is a difference in maternal side effects between both induction methods (RR 0.20, 95% CI 0.01 to 4.15; 165 women; 1 study; Analysis 22.13). The one study included for this outcome reported on gastro-intestinal symptoms without specifying what the symptoms were.

Maternal nausea - Maternal vomiting - Maternal diarrhoea - Other maternal side effects
Not reported.

Postpartum haemorrhage
It is uncertain whether there is a difference in postpartum haemorrhage between both induction methods (RR 1.14, 95% CI 0.46 to 2.81; 239 women; 2 studies; Analysis 22.14).

Serious maternal complications - Maternal death - Woman not satisfied - Caregiver not satisfied - Other outcomes (not pre-specified) - Maternal fever during labour - Antibiotics during labour
Not reported.

Chorioamnionitis
It is uncertain whether there is a difference in chorioamnionitis between both induction methods (RR 3.17, 95% CI 0.35 to 29.06; 74 women; 1 study; Analysis 22.15).

Endometritis
It is uncertain whether there is a difference in endometritis between both induction methods (average RR 0.30, 95% CI 0.08 to 1.09; 490 women; 2 studies; Analysis 22.16). Also, there was substantial heterogeneity for this outcome (Tau^2 = 0.54; Chi^2 = 2.54, df = 1 (P = 0.11); I^2 = 61%). A sensitivity analysis, after eliminating the one trial assessed as having a potentially higher risk of allocation or attrition bias (Krammer 1995a), did not alter the result (RR 0.63, 95% CI 0.16 to 2.46; 74 women; 1 study; I^2 = 0%).

Fetal distress
It is uncertain whether there is a difference in fetal distress for which a caesarean section is indicated between both induction methods (RR 0.44, 95% CI 0.07 to 2.90; 128 women; 2 studies; Analysis 22.17).

Umbilical artery pH < 7.10
Not reported.

Laminaria tent versus oxytocin (two trials involving 73 women)

The only outcomes of interest reported for this comparison were caesarean section and fetal distress. Other outcomes were not reported.

Caesarean section
It is uncertain whether there is a difference in caesarean sections between induction of labour with a laminaria tent and oxytocin (RR 0.83, 95% CI 0.36 to 1.89; 73 women; 2 studies; Analysis 25.1).
For the subgroups of primiparous and multiparous women, no outcomes were reported.

Fetal distress
It is uncertain whether there is a difference in fetal distress for which a caesarean section is indicated between both induction methods (RR 2.69, 95% CI 0.11 to 63.18; 53 women; 1 study; Analysis 25.2).

Laminaria tent versus amniotomy (one trial involving 20 women)

The only outcome of interest reported for this comparison was caesarean section. Other outcomes were not reported.

Caesarean section

It is uncertain whether there is a difference in caesarean sections between induction of labour with a laminaria tent compared to amniotomy (RR 0.75, 95% CI 0.22 to 2.52; 20 women; 1 study; Analysis 26.1). For the subgroups of primiparous and multiparous women, no outcomes were reported.

Laminaria tent versus other hygroscopic dilators (one trial involving 41 women)

The only outcome of interest reported for this comparison was caesarean section. Other outcomes were not reported.

Caesarean section

It is uncertain whether there is a difference in caesarean sections between induction of labour with a laminaria tent and other hygroscopic dilators (RR 1.70, 95% CI 0.44 to 6.66; 41 women; 1 study; Analysis 27.1).

For the subgroups of primiparous and multiparous women, no outcomes were reported.

Extra amniotic saline infusion (EASI) versus vaginal prostaglandin E2 (two trials involving 221 women)

Primary outcomes

Vaginal delivery not achieved within 24 hours

EASI probably increases the risk of a vaginal delivery not achieved within 24 hours when compared to vaginal PGE2 (RR 1.74, 95% CI 1.21 to 2.49; 109 women; 1 study; Analysis 28.1).

Uterine hyperstimulation with FHR changes

It is uncertain whether there is a difference in uterine hyperstimulation with FHR changes between both induction methods (RR 0.23, 95% CI 0.03 to 2.07; 221 women; 2 studies; Analysis 28.2). For the subgroups of primiparous and multiparous women, no outcomes were reported.

Caesarean section

It is uncertain whether there is a difference in caesarean sections between both induction methods (average RR 1.35, 95% CI 0.94 to 1.96; 221 women; 2 studies; Analysis 28.3). Also, there was substantial heterogeneity for this outcome ($Chi^2 = 5.24$, df = 1 (P = 0.02); $I^2 = 81\%$). No sensitivity analysis could be done as both included studies were assessed as having a potentially higher risk of allocation or attrition bias. For the subgroups of primiparous and multiparous women, no outcomes were reported.

Serious neonatal morbidity or perinatal death - Serious maternal morbidity or death

Not reported.

Secondary outcomes

Cervix unfavourable/unchanged after 24 hours

Not reported.

Oxytocin augmentation

EASI may increase the risk of oxytocin augmentation when compared to vaginal PGE2 (RR 12.71, 95% CI 3.20 to 50.57; 109 women; 1 study; Analysis 28.4).

Uterine hyperstimulation without FHR changes

It is uncertain whether there is a difference in uterine hyperstimulation without FHR changes between both induction methods (RR 0.23, 95% CI 0.03 to 2.07; 221 women; 2 studies; Analysis 28.5).

Uterine rupture

Not reported.

Epidural analgesia

There may be little or no difference in epidural analgesia between both induction methods (RR 1.00, 95% CI 0.97 to 1.04; 112 women; 1 study; Analysis 28.6).

Instrumental vaginal delivery

It is uncertain whether there is a difference in instrumental vaginal deliveries between both induction methods (RR 0.58, 95% CI 0.30 to 1.14; 109 women; 1 study; Analysis 28.7).

Meconium-stained liquor

It is uncertain whether there is a difference in meconium-stained liquor between both induction methods (RR 3.00, 95% CI 0.12 to 72.10; 112 women; 1 study; Analysis 28.8).

Apgar score less than seven at five minutes

It is uncertain whether there is a difference in Apgar scores less than seven at five minutes between both induction methods (RR 4.25, 95% CI 0.21 to 86.51; 109 women; 1 study; Analysis 28.9).

Neonatal intensive care unit admission

It is uncertain whether there is a difference in NICU admissions between both induction methods (RR 1.50, 95% CI 0.45 to 5.03; 112 women; 1 study; Analysis 28.10).

Neonatal encephalopathy - Perinatal death - Disability in childhood - Maternal side effects (all) - Maternal nausea - Maternal vomiting - Maternal diarrhoea - Other maternal side effects - Postpartum haemorrhage - Serious maternal complications - Maternal death

Not reported.

Woman not satisfied

It is uncertain whether there is a difference in women not being satisfied between both induction methods (RR 0.56, 95% CI 0.10 to 3.25; 109 women; 1 study; Analysis 28.11). For this outcome, women in the included study were asked to comment on the induction method, for which they could choose between recommendable, satisfactory and unsatisfactory.

Caregiver not satisfied - Maternal fever during labour - Antibiotics during labour – Chorioamnionitis – Endometritis
Not reported

Fetal distress
It is uncertain whether there is a difference in fetal distress for which a caesarean section is indicated between both induction methods (RR 1.20, 95% CI 0.39 to 3.71; 112 women; 1 study; Analysis 28.12).

Umbilical artery pH < 7.10
Not reported.

Extra amniotic saline infusion versus cervical prostaglandin E2 (two trials involving 155 women)

Primary outcomes

Vaginal delivery not achieved within 24 hours - Uterine hyperstimulation with FHR changes
Not reported.

Caesarean section
It is uncertain whether there is a difference in caesarean sections between both induction methods (average RR 0.73, 95% CI 0.10 to 5.12; 155 women; 2 studies; Analysis 29.1). Also, there was substantial heterogeneity for this outcome ($Tau^2 = 1.60$; $Chi^2 = 5.11$, df = 1 (P = 0.02); $I^2 = 80\%$). As the results for both included studies show no overlap of CI, this makes the pooled result for this outcome less meaningful. No sensitivity analysis was performed as no potential high-risk studies were included for this outcome. The same result was seen on a subgroup comparison for primiparous women (RR 0.25, 95% CI 0.06 to 1.09; 70 women; 1 study; Analysis 30.1). For multiparous women, no outcomes were reported.

Serious neonatal morbidity or perinatal death - Serious maternal morbidity or death
Not reported.

Secondary outcomes

Cervix unfavourable/unchanged after 24 hours
EASI may reduce the risk of an unfavourable cervix after 24 hours when compared to cervical PGE2 (RR 0.06, 95% CI 0.00 to 0.97; 85 women; 1 study; Analysis 29.2).

Oxytocin augmentation
It is uncertain whether there is a difference in oxytocin augmentation between both induction methods (RR 1.10, 95% CI 0.54 to 2.25; 70 women; 1 study; Analysis 29.3).

Uterine hyperstimulation without FHR changes - Uterine rupture - Epidural analgesia
Not reported.

Instrumental vaginal delivery
It is uncertain whether there is a difference in instrumental vaginal deliveries between both induction methods (RR 0.33, 95% CI 0.04 to 3.01; 85 women; 1 study; Analysis 29.4).

Meconium-stained liquor
Not reported.

Apgar score less than seven at five minutes
It is uncertain whether there is a difference in Apgar scores less than seven at five minutes between both induction methods (Analysis 29.5). One study (85 women) pre-specified this outcome in which no Apgar scores less than seven after five minutes were reported.

Neonatal intensive care unit admission - Neonatal encephalopathy - Perinatal death - Disability in childhood - Maternal side effects (all) - Maternal nausea - Maternal vomiting - Maternal diarrhoea - Other maternal side effects - Postpartum haemorrhage - Serious maternal complications - Maternal death - Woman not satisfied - Caregiver not satisfied
Not reported

Other outcomes (not pre-specified) - Maternal fever during labour - Antibiotics during labour - Chorioamnionitis
Not reported.

Endometritis
It is uncertain whether there is a difference in endometritis between both induction methods (Analysis 29.6). One study (85 women) pre-specified this outcome in which no cases of endometritis were reported.

Fetal distress
It is uncertain whether there is a difference in fetal distress for which a caesarean section is indicated between both induction methods (RR 0.29, 95% CI 0.06 to 1.28; 70 women; 1 study; Analysis 29.7).

Umbilical artery pH < 7.10
Not reported.

Any mechanical method and prostaglandin E2 versus prostaglandin E2 alone (eight trials involving 639 women)

Primary outcomes

Vaginal delivery not achieved within 24 hours

It is uncertain whether there is a difference in vaginal deliveries not achieved within 24 hours between induction of labour with a mechanical method combined with PGE2 and PGE2 alone (RR 0.84, 95% CI 0.53 to 1.33; 39 women; 1 study; Analysis 31.1). For the subgroups of primiparous and multiparous women, no outcomes were reported.

Uterine hyperstimulation with FHR changes

It is uncertain whether there is a difference in uterine hyperstimulation with FHR changes between both induction methods (RR 0.26, 95% CI 0.01 to 5.12; 122 women; 2 studies; Analysis 31.2). For the subgroups of primiparous and multiparous women, no outcomes were reported.

Caesarean section

It is uncertain whether there is a difference in caesarean sections between both induction methods (average RR 0.96, 95% CI 0.66 to 1.40; 517 women; 7 studies; Analysis 31.3). Also, there was moderate heterogeneity for this outcome ($Tau^2 = 0.11$; $Chi^2 = 11.16$, df = 6 (P = 0.08); $I^2 = 46\%$). A sensitivity analysis, after eliminating three trials assessed as having a potentially higher risk of allocation or attrition bias (Browne 2011; Lyndrup 1989; Turnquest 1997), did not alter the result nor did it lower heterogeneity (average RR 1.02, 95% CI 0.56 to 1.84; 364 women; 4 studies; $I^2 = 70\%$). For the subgroups of primiparous and multiparous women, no outcomes were reported.

Serious neonatal morbidity or perinatal death - Serious maternal morbidity or death

Not reported.

Secondary outcomes

Cervix unfavourable/unchanged after 24 hours

A mechanical method combined with PGE2 may reduce the risk of an unfavourable cervix after 24 hours when compared to PGE2 alone (RR 0.52, 95% CI 0.31 to 0.85; 122 women; 1 study; Analysis 31.4).

Oxytocin augmentation

It is uncertain whether there is a difference in oxytocin augmentation between both induction methods (RR 0.95, 95% CI 0.64 to 1.41; 44 women; 1 study; Analysis 31.5).

Uterine hyperstimulation without FHR changes

It is uncertain whether there is a difference in uterine hyperstimulation without FHR changes between both induction methods (Analysis 31.6). Of the eight studies included for this comparison, three studies (239 women) pre-specified this outcome. No events of uterine hyperstimulation without FHR changes occurred in these studies.

Uterine rupture

Not reported.

Epidural analgesia
There may be little or no difference in epidural analgesia during labour between both induction methods (RR 0.98, 95% CI 0.77 to 1.24; 39 women; 1 study; Analysis 31.7).

Instrumental vaginal delivery
It is uncertain whether there is a difference in instrumental vaginal deliveries between both induction methods (RR 0.56, 95% CI 0.22 to 1.45; 78 women; 2 studies; Analysis 31.8).

Meconium-stained liquor
It is uncertain whether there is a difference in meconium-stained liquor between both induction methods (RR 0.97, 95% CI 0.33 to 2.83; 120 women; 1 study; Analysis 31.9).

Neonatal intensive care unit admission
It is uncertain whether there is a difference in NICU admissions between both methods (RR 0.26, 95% CI 0.01 to 5.12; 44 women; 1 study; Analysis 31.10).

Apgar score less than seven at five minutes - Neonatal encephalopathy - Perinatal death - Disability in childhood - Maternal side effects - Maternal nausea - Maternal vomiting - Maternal diarrhoea - Other maternal side effects
Not reported.

Postpartum haemorrhage
It is uncertain whether there is a difference in postpartum haemorrhage between both induction methods (Analysis 31.11). Of the eight studies included for this comparison, one study (39 women) pre-specified this outcome. No events of postpartum haemorrhage occurred in this study.

Serious maternal complications - Maternal death - Woman not satisfied - Caregiver not satisfied
Not reported.

Maternal fever during labour - Antibiotics during labour
Not reported.

Chorioamnionitis
It is uncertain whether there is a difference in chorioamnionitis between both induction methods (RR 1.56, 95% CI 0.45 to 5.45; 122 women; 2 studies; Analysis 31.12).

Endometritis
It is uncertain whether there is a difference in endometritis between both induction methods (RR 1.07, 95% CI 0.41 to 2.78; 237 women; 3 studies; Analysis 31.13).

Fetal distress
It is uncertain whether there is a difference fetal distress for which a caesarean section is indicated between both induction methods (RR 2.28, 95% CI 0.54 to 9.69; 140 women; 2 studies; Analysis 31.14).

Umbilical artery pH < 7.10
Not reported.

Any mechanical method and prostaglandin E2 versus low-dose misoprostol alone (one trial involving 127 women)

Primary outcomes

Vaginal delivery not achieved within 24 hours

A mechanical method combined with PGE2 probably reduces the risk of a vaginal delivery not achieved within 24 hours when compared to misoprostol (RR 0.32, 95% CI 0.12 to 0.82; 127 women; 1 study; Analysis 32.1). the absolute effect being 165 less per 1000 deliveries. For the subgroups of primiparous and multiparous women, no outcomes were reported.

Uterine hyperstimulation with FHR changes

Not reported.

Caesarean section

It is uncertain whether there is a difference in caesarean sections between both induction methods (RR 1.09, 95% CI 0.58 to 2.04; 127 women; 1 study; Analysis 32.2). For the subgroups of primiparous and multiparous women, no outcomes were reported.

Serious neonatal morbidity or perinatal death

It is uncertain whether there is a difference in serious neonatal morbidity or perinatal death between both induction methods (RR 0.19, 95% CI 0.01 to 3.90; 127 women; 1 study; Analysis 32.3). Two events occurred in the misoprostol group, both being cases of perinatal death. For the subgroups of primiparous and multiparous women, no outcomes were reported.

Serious maternal morbidity or death

Not reported.

Secondary outcomes

Cervix unfavourable/unchanged after 24 hours

A mechanical method combined with PGE2 probably reduces the risk of an unfavourable cervix after 24 hours when compared to misoprostol (RR 0.41, 95% CI 0.25 to 0.67; 127 women; 1 study; Analysis 32.4).

Oxytocin augmentation

A mechanical method combined with PGE2 probably slightly increases the risk of oxytocin augmentation when compared to misoprostol (RR 1.21, 95% CI 1.01 to 1.46; 127; 1 study; Analysis 32.5).

Uterine hyperstimulation without FHR changes

A mechanical method combined with PGE2 probably increases the risk of uterine hyperstimulation without FHR changes when compared to misoprostol (RR 4.05, 95% CI 1.44 to 11.38; 127; 1 study; Analysis 32.6).

Uterine rupture - Epidural analgesia

Not reported.

Instrumental vaginal delivery
It is uncertain whether there is a difference in instrumental vaginal deliveries between both induction methods (RR 1.26, 95% CI 0.77 to 2.04; 127 women; 1 study; Analysis 32.7).

Meconium-stained liquor
It is uncertain whether there is a difference in meconium-stained liquor between both induction methods (RR 0.56, 95% CI 0.23 to 1.32; 127 women; 1 study; Analysis 32.8).

Apgar score less than seven at five minutes
It is uncertain whether there is a difference in Apgar scores less than seven at five minutes between both induction methods (RR 1.91, 95% CI 0.18 to 20.51; 127 women; 1 study; Analysis 32.9).

Neonatal intensive care unit admission
It is uncertain whether there is a difference in NICU admissions between both methods (RR 0.64, 95% CI 0.31 to 1.31; 127 women; 1 study; Analysis 32.10).

Neonatal encephalopathy
Not reported.

Perinatal death
It is uncertain whether there is a difference in perinatal death between both methods (RR 0.19, 95% CI 0.01 to 3.90; 127 women; 1 study; Analysis 32.11). Two cases of neonatal death were reported by Perry 1998, both were born to women randomised to misoprostol. The authors describe that in both cases the neonates died as a result of complications of congenital malformations and were unrelated to the induction method.

Disability in childhood - Maternal side effects - Maternal nausea - Maternal vomiting - Maternal diarrhoea - Other maternal side effects - Postpartum haemorrhage - Serious maternal complications - Maternal death - Woman not satisfied - Caregiver not satisfied
Not reported.

Other outcomes (not pre-specified)

Maternal fever during labour - Antibiotics during labour
Not reported.

Chorioamnionitis
It is uncertain whether there is a difference in chorioamnionitis between both induction methods (RR 1.91, 95% CI 0.18 to 20.51; 127 women; 1 study; Analysis 32.12).

Endometritis
It is uncertain whether there is a difference in endometritis between both induction methods (RR 1.91, 95% CI 0.36 to 10.05; 127 women; 1 study; Analysis 32.13).

Fetal distress - Umbilical artery pH < 7.10
Not reported.

Any mechanical method and prostaglandin E2 versus oxytocin alone (one trial involving 44 women)

The only outcomes of interest reported for this comparison were caesarean section, instrumental vaginal delivery and endometritis. Other outcomes were not reported.

Caesarean section
It is uncertain whether there is a difference in caesarean sections between induction of labour with a mechanical method combined with PGE2 versus oxytocin (RR 0.30, 95% CI 0.04 to 2.47; 44 women; 1 study; Analysis 33.1). For the subgroups of primiparous and multiparous women, no outcomes were reported.

Instrumental vaginal delivery
It is uncertain whether there is a difference in instrumental vaginal deliveries between both induction methods (RR 0.60, 95% CI 0.12 to 2.94; 44 women; 1 study; Analysis 33.2).

Endometritis
It is uncertain whether there is a difference in endometritis between both induction methods (RR 3.57, 95% CI 0.15 to 83.14; 44 women; 1 study; Analysis 33.3).

Any mechanical method and low-dose misoprostol versus prostaglandin E2 alone (one trial involving 350 women)

Primary outcomes

Vaginal delivery not achieved within 24 hours
It is uncertain whether there is a difference in vaginal deliveries not achieved within 24 hours between induction of labour with a mechanical method combined with misoprostol and prostaglandin E2 (RR 1.14, 95% CI 0.89 to 1.46; 350 women; 1 study; Analysis 34.1). For the subgroups of primiparous and multiparous women, no outcomes were reported.

Uterine hyperstimulation with FHR changes
It is uncertain whether there is a difference in uterine hyperstimulation with FHR changes between both induction methods (RR 0.75, 95% CI 0.27 to 2.13; 327 women; 1 study; Analysis 34.2). For the subgroups of primiparous and multiparous women, no outcomes were reported.

Caesarean section
It is uncertain whether there is a difference in caesarean sections between both induction methods (RR 0.85, 95% CI 0.57 to 1.25; 350 women; 1 study; Analysis 34.3). For the subgroups of primiparous and multiparous women, no outcomes were reported.

Serious neonatal morbidity or perinatal death
It is uncertain whether there is a difference in serious neonatal morbidity or perinatal death between both induction methods (RR 2.04, 95% CI 0.19 to 22.24; 345 women; 1 study; Analysis 34.4). For the subgroups of primiparous and multiparous women, no outcomes were reported.

Serious maternal morbidity or death

It is uncertain whether there is a difference in serious maternal morbidity or death between both induction methods (Analysis 34.5). No events of maternal morbidity or death occurred in the one included study (350 women). For the subgroups of primiparous and multiparous women, no outcomes were reported.

Secondary outcomes

Cervix unfavourable/unchanged after 24 hours

Not reported.

Oxytocin augmentation

A mechanical method combined with misoprostol probably reduces the risk of oxytocin augmentation when compared to PGE2 (RR 0.54, 95% CI 0.34 to 0.86; 350 women; 1 study; Analysis 34.6).

Uterine hyperstimulation without FHR changes

It is uncertain whether there is a difference in uterine hyperstimulation without FHR changes between both induction methods (RR 0.54, 95% CI 0.22 to 1.32; 327 women; 1 study; Analysis 34.7).

Uterine rupture

It is uncertain whether there is a difference in uterine rupture between both induction methods (Analysis 34.8). No events of uterine rupture occurred in the one included study (350 women).

Epidural analgesia

Not reported.

Instrumental vaginal delivery

It is uncertain whether there is a difference in instrumental vaginal deliveries between both induction methods (RR 1.01, 95% CI 0.26 to 3.98; 350 women; 1 study; Analysis 34.9).

Meconium-stained liquor

It is uncertain whether there is a difference in meconium-stained liquor between both induction methods (RR 1.15, 95% CI 0.60 to 2.23; 339 women; 1 study; Analysis 34.10).

Apgar score less than seven at five minutes

It is uncertain whether there is a difference in Apgar scores less than seven at five minutes between both induction methods (RR 0.68, 95% CI 0.25 to 1.88; 346 women; 1 study; Analysis 34.11).

Neonatal intensive care unit admission

It is uncertain whether there is a difference in NICU admissions between both methods (RR 0.68, 95% CI 0.12 to 4.03; 346 women; 1 study; Analysis 34.12).

Neonatal encephalopathy

Not reported.

Perinatal death
It is uncertain whether there is a difference in perinatal death between both induction methods (RR 1.02, 95% CI 0.06 to 16.14; 345 women; 1 study; Analysis 34.13). Two cases of perinatal death were reported by Matonhodze 2003, one in each group. No further information was given on timing or cause of the demise.

Disability in childhood
Not reported.

Maternal side effects
It is uncertain whether there is a difference in maternal side effects between both induction methods (RR 1.16, 95% CI 0.95 to 1.43; 314 women; 1 study; Analysis 34.14).

Maternal nausea
A mechanical method combined with misoprostol may increase the risk of maternal nausea when compared to PGE2 (RR 1.65, 95% CI 0.98 to 2.79; 300 women; 1 study; Analysis 34.15). However, the result is still too imprecise to make a valid judgement on this outcome.

Maternal diarrhoea
A mechanical method combined with misoprostol probably increases the risk of maternal diarrhoea when compared to PGE2 (RR 3.72, 95% CI 1.53 to 9.00; 313 women; 1 study; Analysis 34.16).

Maternal vomiting - Other maternal side effects
Not reported.

Postpartum haemorrhage
It is uncertain whether there is a difference in postpartum haemorrhage between both induction methods (RR 0.98, 95% CI 0.67 to 1.41; 348 women; 1 study; Analysis 34.17).

Serious maternal complications
It is uncertain whether there is a difference in serious maternal complications between both induction methods (Analysis 34.18). One study (350 women) was included for this outcome in which no cases of septicaemia or intensive care unit admission were reported.

Maternal death - Woman not satisfied - Caregiver not satisfied
Not reported.

Other outcomes (not pre-specified)

Maternal fever during labour
It is uncertain whether there is a difference in maternal fever during labour between both induction methods (RR 1.53, 95% CI 0.26 to 9.02; 347 women; 1 study; Analysis 34.19).

Antibiotics during labour – Chorioamnionitis – Endometritis - Fetal distress - Umbilical artery pH < 7.10
Not reported

Any mechanical method and low dose misoprostol versus misoprostol alone (seven trials involving 1422 women)

Primary outcomes

Vaginal delivery not achieved within 24 hours

It is uncertain whether there is a difference in vaginal deliveries not achieved within 24 hours between any mechanical method combined with misoprostol and misoprostol alone (RR 1.14 95% CI 0.89 to 1.46; 350 women; 1 study; Analysis 35.1).

For the subgroups of primiparous and multiparous women, no outcomes were reported

Uterine hyperstimulation with FHR changes

It is uncertain whether there is a difference in uterine hyperstimulation with FHR changes between both induction methods (average RR 0.54, 95% CI 0.20 to 1.45; 707 women; 4 studies; Analysis 35.2). Also, there was substantial heterogeneity for this outcome ($Tau^2 = 0.57$; $Chi^2 = 7.40$, df = 2 (P = 0.02); $I^2 = 73\%$). No sensitivity analysis was performed as no potential high-risk studies were included for this outcome. For the subgroups of primiparous and multiparous women, no outcomes were reported.

Caesarean section

There probably is little or no difference in caesarean sections between both induction methods (RR 0.96, 95% CI 0.79 to 1.17; 1104 women; 6 studies; Analysis 35.3).

For the subgroups of primiparous and multiparous women, no outcomes were reported

Serious neonatal morbidity or perinatal death

It is uncertain whether there is a difference in serious neonatal morbidity or perinatal death between both induction methods (RR 1.25, 95% CI 0.34 to 4.55; 487 women; 2 studies; Analysis 35.4). For the subgroups of primiparous and multiparous women, no outcomes were reported.

Serious maternal morbidity or death

It is uncertain whether there is a difference in serious maternal morbidity or death between both induction methods (Analysis 35.5). Of the six studies included for this comparison, two studies (490 women) reported on this composite outcome. No events of serious maternal morbidity or death occurred in these studies. For the subgroups of primiparous and multiparous women, no outcomes were reported.

Secondary outcomes

Cervix unfavourable/unchanged after 24 hours

A mechanical method combined with misoprostol probably reduces the risk of an unfavourable cervix after 24 hours when compared to misoprostol alone (RR 0.27, 95% CI 0.08 to 0.94; 140 women; 1 study; Analysis 35.6).

Oxytocin augmentation

It is uncertain whether there is a difference in oxytocin augmentation between both induction methods (average RR 0.98, 95% CI 0.66 to 1.48; 733 women; 4 studies; Analysis 35.7). Also, there was substantial heterogeneity for this outcome ($Tau^2 = 0.13$; $Chi^2 = 16.69$, df = 3 (P = 0.0008); $I^2 = 82\%$).

Uterine hyperstimulation without FHR changes
A mechanical method combined with misoprostol probably reduces the risk of uterine hyperstimulation without FHR changes when compared to misoprostol alone (RR 0.50, 95% CI 0.26 to 0.94; 664 women; 3 studies; Analysis 35.8)

Uterine rupture
It is uncertain whether there is a difference in uterine rupture between both induction methods (Analysis 35.9). Of the six studies included for this comparison, two studies (490 women) reported on this outcome. No events of uterine rupture occurred in one of these studies.

Epidural analgesia
There may be little or no difference in epidural analgesia between both induction methods (average RR 1.00, 95% CI 0.91 to 1.10; 443 women; 3 studies; Analysis 35.10), although there was moderate heterogeneity for this outcome ($Tau^2 = 0.00$; $Chi^2 = 3.52$, df = 2 (P = 0.17); 43%).
No sensitivity analysis was performed as no potential high-risk studies were included for this outcome.

Instrumental vaginal delivery
It is uncertain whether there is a difference in instrumental vaginal deliveries between both induction methods (RR 0.93, 95% CI 0.58 to 1.51; 676 women; 3 studies; Analysis 35.11).

Meconium-stained liquor
it is uncertain whether there is difference in meconium-stained liquor between both induction methods (average RR 0.55, 95% CI 0.26 to 1.14; 925 women; 5 studies Analysis 35.12). Also, there was substantial heterogeneity for this outcome ($Tau^2 = 0.43$; $Chi^2 = 11.06$, df = 4 (P = 0.03); $I^2 = 64\%$).

Apgar score less than seven at five minutes
It is uncertain whether there is a difference in Apgar score less than seven at five minutes between both induction methods (RR 1.10, 95% CI 0.50 to 2.43; 484 women; 2 studies; Analysis 35.13).

Neonatal intensive care unit admission
It is uncertain whether there is a difference in NICU admission between both methods (RR 0.79, 95% CI 0.41 to 1.55; 928 women; 5 studies; Analysis 35.14).

Neonatal encephalopathy
Not reported.

Perinatal death
It is uncertain whether there is difference in perinatal death between both induction methods (RR 3.09, 95% CI 0.13 to 75.26; 347 women; 1 study; Analysis 35.15). One case of perinatal death was reported by Matonhodze 2003, which occurred in the combined method group. No further information was given on timing or cause of the demise.

Disability in childhood
Not reported.

Maternal side effects (all)
It is uncertain whether there is a difference in maternal side effects between both induction methods (RR 1.06, 95% CI 0.87 to 1.30; 300 women; 1 study; Analysis 35.16).

Maternal nausea
It is uncertain whether there is a difference in maternal nausea between both induction methods (RR 1.37, 95% CI 0.84 to 2.23; 300 women; study; Analysis 35.17).

Maternal vomiting
Not reported.

Maternal diarrhoea
A mechanical method combined with misoprostol probably increases the risk of maternal diarrhoea when compared to misoprostol alone (RR 3.38, 95% CI 1.40 to 8.17; 298 women; 1 study; Analysis 35.18).

Other maternal side effects
Not reported.

Postpartum haemorrhage
It is uncertain whether there is difference in postpartum haemorrhage between both induction methods (RR 0.93, 95% CI 0.65 to 1.33; 466 women; 2 studies; Analysis 35.19).

Serious maternal complications
It is uncertain whether there is a difference in serious maternal complications between both induction methods (Analysis 35.20). One study (350 women) was included for this outcome in which no cases of septicaemia or intensive care unit admissions were seen.

Maternal death - Woman not satisfied - Caregiver not satisfied
Not reported.

Other outcomes (not pre-specified)
Maternal fever during labour - Antibiotics during labour
Not reported.

Chorioamnionitis
It is uncertain whether there is a difference in chorioamnionitis between both induction methods (RR 0.63, 95% CI 0.28 to 1.38; 443 women; 3 studies; Analysis 35.21).

Endometritis
It is uncertain whether there is a difference in endometritis between both induction methods (RR 0.54, 95% CI 0.05 to 5.84; 117 women; 1 study; Analysis 35.22).

Fetal distress
It is uncertain whether there is a difference in fetal distress for which a caesarean section is indicated between both induction methods (RR 0.94, 95% CI 0.61 to 1.46; 466 women; 3 studies; Analysis 35.23).

Umbilical artery pH < 7.10
Not reported.

Any mechanical method and oxytocin versus prostaglandin E2 alone (four trials involving 713 women)

Primary outcomes

Vaginal delivery not achieved within 24 hours
Not reported.

Uterine hyperstimulation with FHR changes
It is uncertain whether there is a difference in uterine hyperstimulation with FHR changes between a mechanical method combined with oxytocin and PGE2 (RR 1.48, 95% CI 0.55 to 3.95; 151 women; 1 study; Analysis 38.1).
For the subgroups of primiparous and multiparous women, no outcomes were reported.

Caesarean section
It is uncertain whether there is a difference in caesarean sections between both induction methods (RR 0.93, 95% CI 0.72 to 1.20; 713 women; 4 studies; Analysis 38.2).
For the subgroups of primiparous and multiparous women, no outcomes were reported.

Serious neonatal morbidity or perinatal death
Not reported.

Serious maternal morbidity or death
It is uncertain whether there is a difference in serious maternal morbidity or death between both induction methods (Analysis 38.3). One study (200 women) was included for this composite outcome in which no events of maternal morbidity or death occurred.
For the subgroups of primiparous and multiparous women, no outcomes were reported.

Secondary outcomes

Cervix unfavourable/unchanged after 24 hours
Not reported.

Oxytocin augmentation
A mechanical method combined with oxytocin probably increases the risk of oxytocin augmentation when compared to PGE2 (RR 2.48, 95% CI 1.95 to 3.15; 200 women; 1 study; Analysis 38.4).

Uterine hyperstimulation without FHR changes
A mechanical method combined with oxytocin probably increases the risk of uterine hyperstimulation without FHR changes when compared to PGE2 (RR 2.19, 95% CI 1.39 to 3.46; 151 women; 1 study; Analysis 38.5).

Uterine rupture - Epidural analgesia
Not reported.

Instrumental vaginal delivery
It is uncertain whether there is a difference in instrumental vaginal deliveries between both induction methods (RR 0.35, 95% CI 0.08 to 1.58; 41 women; 1 study; Analysis 38.6).

Meconium-stained liquor
It is uncertain whether there is a difference in meconium-stained liquor between both induction methods (RR 1.13, 95% CI 0.43 to 2.95; 151 women; 1 study; Analysis 38.7).

Apgar score less than seven at five minutes
It is uncertain whether there is a difference in Apgar scores less than seven at five minutes between both induction methods (RR 2.96, 95% CI 0.12 to 71.55; 151 women; 1 study; Analysis 38.8).

Neonatal intensive care unit admission
It is uncertain whether there is a difference in NICU admissions between both methods (RR 0.85, 95% CI 0.30 to 2.40; 151 women; 1 study; Analysis 38.9).

Neonatal encephalopathy - Perinatal death - Disability in childhood - Maternal side effects - Maternal nausea - Maternal vomiting - Maternal diarrhoea - Other maternal side effects
Not reported.

Postpartum haemorrhage
It is uncertain whether there is a difference in postpartum haemorrhage between both induction methods (RR 0.14, 95% CI 0.01 to 2.68; 151 women; 1 study; Analysis 38.10).

Serious maternal complications - Maternal death - Woman not satisfied - Caregiver not satisfied
Not reported.

Other outcomes (not pre-specified)

Maternal fever during labour - Antibiotics during labour - Chorioamnionitis
Not reported.

Endometritis
It is uncertain whether there is a difference in endometritis between both induction methods (Analysis 38.11). One study (41 women) reported on this outcome. No events of endometritis occurred in this study.

Fetal distress
It is uncertain whether there is a difference in fetal distress for which a caesarean section is indicated between both induction methods (average RR 0.97, 95% CI 0.61 to 1.56; 498 women; 3 studies; Analysis 38.12). Also, there was moderate heterogeneity for this outcome ($Tau^2 = 0.06$; $Chi^2 = 2.93$, df = 2 (P = 0.23); $I^2 = 32\%$). No sensitivity analysis was performed as no potential high-risk studies were included for this outcome.

Umbilical artery pH < 7.10
Not reported.

Any mechanical method and oxytocin versus misoprostol alone (six trials involving 1779 women)

Primary outcomes

Vaginal delivery not achieved within 24 hours
A mechanical method combined with oxytocin probably reduces the risk of a vaginal delivery not being achieved within 24 hours when compared to misoprostol (RR 0.48, 95% CI 0.37 to 0.63; 362 women; 2 studies; Analysis 39.1), the absolute effect being 285 fewer per 1000 deliveries. For the subgroups of primiparous and multiparous women, no outcomes were reported.

Uterine hyperstimulation with FHR changes
It is uncertain whether there is a difference in uterine hyperstimulation with FHR changes between both induction methods (RR 0.43, 95% CI 0.17 to 1.11; 1463 women; 3 studies; Analysis 39.2). For the subgroups of primiparous and multiparous women, no outcomes were reported.

Caesarean section
There probably is little or difference in caesarean sections between both induction methods (RR 0.95, 95% CI 0.80 to 1.12; 1779 women; 5 studies; Analysis 39.3). For the subgroup of primiparous women, no outcomes were reported. For multiparous women, it is uncertain whether there is a difference in caesarean sections between both induction methods (RR 0.45, 95% CI 0.19 to 1.11; 136 women; 1 study; Analysis 40.1).

Serious neonatal morbidity or perinatal death
It is uncertain whether there is a difference in serious neonatal morbidity or perinatal death between both induction methods (RR 0.82, 95% CI 0.18 to 3.65;1263 women; 2 studies; Analysis 39.4). All the events included for this composite outcome were cases of neonatal death. For the subgroups of primiparous and multiparous women, no outcomes were reported.

Serious maternal morbidity or death
Not reported.

Secondary outcomes

Cervix unfavourable/unchanged after 24 hours
Not reported.

Oxytocin augmentation

It is uncertain whether there is a difference in oxytocin augmentation between both induction methods (average RR 3.89, 95% CI 0.70 to 21.72; 336 women; 2 studies; Analysis 39.5). Also, there was substantial heterogeneity for this outcome ($Tau^2 = 1.46$; $Chi^2 = 18.47$, df = 1 ($P < 0.0001$); $I^2 = 95\%$).

A sensitivity analysis, after eliminating the one trial assessed as having a potentially higher risk of allocation or attrition bias (Garba 2016), changed the result in favour of misoprostol as it showed a mechanical method combined with oxytocin may increase the risk of oxytocin augmentation (RR 1.91, 95% CI 1.59 to 2.31; 200 women; 1 study).

Uterine hyperstimulation without FHR changes

A mechanical method combined with oxytocin probably reduces the risk of uterine hyperstimulation without FHR changes when compared to misoprostol (RR 0.52, 95% CI 0.30 to 0.92; 498 women; 3 studies; Analysis 39.6).

Uterine rupture

Not reported.

Epidural analgesia

It is uncertain whether there is a difference in epidural analgesia between both induction methods (RR 1.07, 95% CI 0.90 to 1.27; 162 women; 1 study; Analysis 39.7).

Instrumental vaginal delivery

Not reported.

Meconium-stained liquor

It is uncertain whether there is a difference in meconium-stained liquor between both induction methods (RR 0.72, 95% CI 0.43 to 1.19; 362 women; 2 studies; Analysis 39.8).

Apgar score less than seven at five minutes

It is uncertain whether there is a difference in Apgar scores less than seven at five minutes between both induction methods (RR 0.95, 95% CI 0.20 to 4.58; 162 women; 1 study; Analysis 39.9).

Neonatal intensive care unit admission

A mechanical method combined with oxytocin probably reduces the risk of a NICU admission when compared to misoprostol (RR 0.66, 95% CI 0.49 to 0.90; 1599 women; 4 studies; Analysis 39.10), the absolute effect being 37 fewer NICU admissions per 1000 deliveries.

Neonatal encephalopathy

Not reported.

Perinatal death

It is uncertain whether there is a difference in perinatal death between both induction methods (RR 0.82, 95% CI 0.18 to 3.65; 1263 women; 2 studies; Analysis 39.11). Perinatal death occurred in one of the included studies (Gilson 2017). All were cases of neonatal death. No further information was given on cause of the demise.

Disability in childhood - Maternal side effects- Maternal nausea - Maternal vomiting - Maternal diarrhoea - Other maternal side effects - Postpartum haemorrhage - Serious maternal complications - Maternal death
Not reported.

Woman not satisfied
A mechanical method combined with oxytocin may increase the risk of women not being satisfied when compared to misoprostol (RR 1.68, 95% CI 1.47 to 1.93; 866 women; 1 study; Analysis 39.12), the absolute effect being 260 more women not satisfied per 1000 deliveries. For this outcome, women in the study of Gilson 2017 were asked if they would choose the same method again if induction of labour was needed in a future pregnancy.

Caregiver not satisfied
Not reported.

Other outcomes (not pre-specified)
Maternal fever during labour
A mechanical method combined with oxytocin may reduce the risk of maternal fever during labour when compared to misoprostol (RR 0.13, 95% CI 0.04 to 0.50; 298 women; 2 studies; Analysis 39.13).

Antibiotics during labour
Not reported.

Chorioamnionitis
It is uncertain whether there is a difference in chorioamnionitis between both induction methods (RR 0.65, 95% CI 0.32 to 1.31; 200 women; 1 study; Analysis 39.14).

Endometritis
Not reported.

Fetal distress
It is uncertain whether there is a difference in fetal distress for which a caesarean section is indicated between both induction methods (RR 0.55, 95% CI 0.25 to 1.21; 362 women; 2 studies; Analysis 39.15).

Umbilical artery pH < 7.10
Not reported.

Any mechanical method and oxytocin versus oxytocin alone (six trials involving 718 women)

Primary outcomes

Vaginal delivery not achieved within 24 hours

It is uncertain whether there is a difference in a vaginal delivery not being achieved within 24 hours between induction of labour with a mechanical method combined with oxytocin and oxytocin alone (average RR 0.71, 95% CI 0.21 to 2.40; 321 women; 2 studies; Analysis 41.1). Also, there was substantial heterogeneity for this outcome (Tau^2 = 0.72; Chi^2 = 19.17, df = 1 (P,0.0001); I^2 = 95%). A sensitivity analysis, after eliminating the one trial assessed as having a potentially higher risk of allocation or attrition bias (Mackeen 2018), changed the result in favour of a mechanical method combined with oxytocin as it showed it may reduce the risk of vaginal delivery not being achieved within 24 hours (RR 0.39, 95% CI 0.27 to 0.55; 120 women; 1 study), the absolute effect being 550 fewer per 1000 deliveries. For the subgroups of primiparous and multiparous women, no outcomes were reported.

Uterine hyperstimulation with FHR changes

Not reported.

Caesarean section

It is uncertain whether there is a difference in caesarean sections between both induction methods (average RR 0.68, 95% CI 0.39 to 1.20; 718 women; 6 studies; Analysis 41.2). Also, there was substantial heterogeneity for this outcome (Tau^2 = 0.32; Chi^2 = 17.15, df = 5 (P = 0.004); I^2 = 71%). A sensitivity analysis, after eliminating the three trials assessed as having a potentially higher risk of allocation or attrition bias (Lyndrup 1989; Mackeen 2018; Tita 2006), did not alter the result nor did it lower heterogeneity (average RR 0.57, 95% CI 0.21 to 1.52; 319 women; 3 studies; I^2 = 82%).

Serious neonatal morbidity or perinatal death

It is uncertain whether there is a difference in serious neonatal morbidity or perinatal death between both induction methods (RR 0.71, 95% CI 0.12 to 4.13; 321 women; 2 studies; Analysis 41.3). All the events included for this composite outcome were cases of asphyxia. For the subgroups of primiparous and multiparous women, no outcomes were reported.

Serious maternal morbidity or death

It is uncertain whether there is a difference in serious maternal morbidity or death between both induction methods (Analysis 41.4). Of the six included studies for this comparison, two studies (321 women) reported on this composite outcome. No events of maternal morbidity or death occurred in these studies. For the subgroups of primiparous and multiparous women, no outcomes were reported.

Secondary outcomes

Cervix unfavourable/unchanged after 24 hours - Oxytocin augmentation

Not reported.

Uterine hyperstimulation without FHR changes

It is uncertain whether there is a difference in uterine hyperstimulation without FHR changes between both induction methods (RR 0.85, 95% CI 0.34 to 2.09; 199 women; 2 studies; Analysis 41.5).

Uterine rupture
It is uncertain whether there is a difference in uterine rupture between both induction methods (Analysis 41.6). Of the six included studies for this comparison, one study (120 women) reported on this outcome. No events of uterine rupture occurred in this study.

Epidural analgesia
There probably is little or no difference in epidural analgesia between both induction methods (RR 1.03, 95% CI 0.98 to 1.09; 127 women; 1 study; Analysis 41.7).

Instrumental vaginal delivery
It is uncertain whether there is a difference in instrumental vaginal deliveries between both induction methods (RR 0.99, 95% CI 0.48 to 2.02; 293 women; 3 studies; Analysis 41.8).

Meconium-stained liquor
It is uncertain whether there is a difference in meconium-stained liquor between both induction methods (RR 0.72, 95% CI 0.32 to 1.63; 319 women; 3 studies; Analysis 41.9).

Apgar score less than seven at five minutes
Not reported.

Neonatal intensive care unit admission
It is uncertain whether there is a difference in NICU admissions between both induction methods (RR 0.98, 95% CI 0.61 to 1.58; 400 women; 3 studies; Analysis 41.10).

Neonatal encephalopathy - Perinatal death - Disability in childhood - Maternal side effects - Maternal nausea - Maternal vomiting - Maternal diarrhoea - Other maternal side effects
Not reported.

Postpartum haemorrhage
It is uncertain whether there is a difference in postpartum haemorrhage between both induction methods (RR 1.18, 95% CI 0.44 to 3.18; 319 women; 3 studies; Analysis 41.11).

Serious maternal complications
It is uncertain whether there is a difference in serious maternal complications between both induction methods (Analysis 41.12). Of the six included studies for this comparison, one study (201 women) reported on maternal sepsis. No events occurred in this study.

Maternal death - Woman not satisfied - Caregiver not satisfied
Other outcomes (not pre-specified)
Not reported.

Maternal fever during labour
Not reported.

Antibiotics during labour

It is uncertain whether there is a difference in antibiotics during labour between both induction methods (RR 2.32, 95% CI 0.82 to 6.55; 201 women; 1 study; Analysis 41.13).

Chorioamnionitis

It is uncertain whether there is a difference in chorioamnionitis between both induction methods (average RR 4.34, 95% CI 0.55 to 34.01; 328 women; 2 studies; Analysis 41.14). Also, there was moderate heterogeneity for this outcome ($Tau^2 = 1.19$; $Chi^2 = 1.92$, df = 1 (P = 0.17); $I^2 = 48\%$).

A sensitivity analysis, after eliminating the one trial assessed as having a potentially higher risk of allocation or attrition bias (Mackeen 2018), did not alter the result (RR 2.16, 95% CI 0.57 to 8.28; 127 women; 1 study).

Endometritis

It is uncertain whether there is a difference in endometritis between both induction methods (RR 1.08, 95% CI 0.16 to 7.45; 374 women; 3 studies; Analysis 41.15).

Fetal distress

It is uncertain whether there is a difference in fetal distress for which a caesarean section is indicated between both induction methods (RR 1.37, 95% CI 0.68 to 2.77; 400 women; 3 studies; Analysis 41.16).

Umbilical artery pH < 7.10

Not reported.

Discussion

We set out to explore the effectiveness of mechanical methods for labour induction and their adverse effects for women and their babies in comparison to different pharmacological methods. We included a total of 112 studies, with 104 studies contributing data involving 22,055 women. This updated review now consists of 21 different comparisons (and 20 subgroup comparisons), where in most of the comparisons a mechanical method (balloon, laminaria or extra-amniotic space infusion (EASI)) was compared with prostaglandin E2 (PGE2), misoprostol or oxytocin. We explored the combination of a mechanical method combined with a pharmacological method, as well as a single versus a double balloon.

Summary of main results

Balloon

Balloon versus PGE2

A balloon catheter is probably as effective for inducing labour as vaginal PGE2, as there was little or no difference in a vaginal delivery not achieved within 24 hours (low-quality evidence) and caesarean sections (moderate-quality evidence) between both induction methods. However, oxytocin augmentation is probably more often required when labour is induced with a balloon catheter. As for perinatal outcomes, a balloon catheter appears to have a more favourable safety profile compared to vaginal PGE2, as it probably reduces the risk of uterine hyperstimulation with and without fetal heart rate (FHR) changes (moderate-quality evidence), fetal distress for which a caesarean section is required and an umbilical artery pH less than 7.10. Also, a balloon catheter may slightly reduce the risk of a neonatal intensive care unit (NICU) admission (low-quality evidence), although conventional statistical significance was not reached as the result was still too imprecise to make a valid judgement. Of note, a balloon catheter probably reduces the risk of serious neonatal morbidity or perinatal death (moderate-risk evidence). However, this outcome should be interpreted with caution as only a few studies (eight out of 28 studies), reported on this composite outcome and therefore a bias for this result could exist. Most of the serious perinatal adverse events in this composite outcome were cases of perinatal asphyxia. Regarding our other main outcomes for this comparison, it was unclear if there is a difference in five-minute Apgar score less than seven (low-quality evidence) or serious maternal morbidity or death (very low-quality evidence).

There was no evidence of a difference in outcomes between induction of labour with a balloon compared to cervical PGE2, although the risk of fetal distress for which a caesarean section is indicated is probably reduced when a balloon is used.

Balloon versus misoprostol

A balloon catheter may be less effective for induction of labour when compared to low-dose oral misoprostol, as a balloon probably increases the risk of a vaginal delivery not achieved within 24 hours (moderate-quality evidence), oxytocin augmentation and probably slightly increases the risk of a caesarean section (moderate-quality evidence). Regarding safety outcomes for the neonate, which are hyperstimulation with (low-quality evidence) and without FHR changes, serious neonatal morbidity or perinatal death (low-quality evidence), NICU admission (low-quality evidence), five-minute Apgar score less than seven (low-quality evidence), fetal distress and umbilical artery pH less than 7.10, it is unclear if there is a difference between both methods as results were too imprecise to make a valid judgement. This was also the case for the composite outcome serious maternal morbidity or death (very low-quality evidence).

When compared to low-dose vaginal misoprostol, a balloon catheter may increase the risk of a caesarean section and oxytocin augmentation (low-quality evidence). However, there was substantial heterogeneity for both outcomes. For the outcome caesarean section, heterogeneity was not reduced after sensitivity analysis. The risk of hyperstimulation, with and without FHR changes, is probably reduced when a balloon catheter is used, as well as the risk of meconium-stained liquor (moderate-quality evidence). Regarding our other main outcomes for this comparison, it was unclear if there was a difference between serious neonatal morbidity or perinatal death (very low-quality evidence), serious maternal morbidity or death (very low-quality evidence), NICU admission (low-quality evidence) and five-minute Apgar score less than seven (low-quality evidence) as these results were too imprecise to make a valid judgement.
Epidural analgesia is probably used slightly more after induction of labour with a balloon compared to low-dose oral misoprostol, as well as vaginal misoprostol.

Balloon versus oxytocin
In women with an unfavourable cervix, cervical ripening with a balloon seems to be more effective than induction with oxytocin as it probably reduces the risk of caesarean section and the risk of fetal distress for which a caesarean section is indicated. For women with a previous caesarean section, a balloon catheter may slightly reduce the risk of a caesarean section when compared to oxytocin. However, the result is too imprecise to make a valid judgement on this outcome.

Single balloon versus double balloon
There is no evidence of benefit of a double balloon over a single balloon. There is little or no difference in vaginal deliveries not achieved within 24 hours and in oxytocin augmentation. No clear difference in caesarean section rate was seen between these induction methods. However, the result was still too imprecise to make a valid judgement. Hyperstimulation seems to occur infrequently with either balloons, as no events of uterine hyperstimulation with or without FHR changes were reported in the one study (217 women) which reported on these outcomes.

Laminaria tent
There was no evidence of a difference in outcomes between a laminaria tent compared to vaginal PGE2. However, results were too imprecise to make a valid judgement. Compared to cervical PGE2, a laminaria tent probably reduces the risk uterine hyperstimulation both with and without FHR changes.

EASI
Only a few small studies compared EASI with other methods. When compared to vaginal PGE2, EASI may increase the risk of a vaginal delivery not achieved within 24 hours and oxytocin augmentation.

Mechanical method combined with a pharmacological method
There was no evidence of clear benefit for a mechanical method combined with PGE2 compared to PGE2 alone or to oxytocin. When compared to low-dose misoprostol, a mechanical method combined with PGE2 may reduce the risk of a vaginal delivery not achieved within 24 hours. However, only one study (127 women) reported on this comparison. When a mechanical method is combined with misoprostol or with oxytocin, it may reduce the risk of a NICU admission when compared to misoprostol alone. However, regarding other perinatal outcomes for both comparisons, there was no

evidence for a difference in serious neonatal morbidity or perinatal death, Apgar scores less than seven at five minutes or fetal distress.

Infection

Risk of infection may theoretically be associated with the insertion of foreign material in the cervix. Most studies did not report on this outcome, resulting in limited data, reported as various outcomes (maternal fever during labour, antibiotic use during labour, chorioamnionitis and endometritis). According to the limited data available, there is no evidence of an increased risk of infectious morbidity with mechanical methods. These data should however be cautiously interpreted as results were imprecise.

Women's view

Data on patient satisfaction or patient preferences are sparse and not all data could be included in the meta-analyses. When a balloon catheter was compared to vaginal PGE2, more women who were randomised to a balloon would choose the allocated induction method again in a subsequent pregnancy, as compared to women who were randomised to PGE2. However, when a balloon catheter was compared to oral misoprostol, more women would choose misoprostol in a subsequent pregnancy. For both outcomes, only one study was included.

Overall completeness and applicability of evidence

This review was previously one of a series of Cochrane Reviews examining various methods for induction of labour and now serves as a stand-alone review. Other reviews have examined pharmacological and non-pharmacological methods including vaginal prostaglandins (Thomas 2014); intracervical prostaglandins (Boulvain 2008); intravenous oxytocin (Alferivic 2009); amniotomy (Bricker 2000); intravenous oxytocin with amniotomy (Howarth 2001); vaginal misoprostol (Hofmeyr 2010); oral misoprostol (Alfirevic 2014), and other methods.

Despite including 112 studies and including data from 104 studies, there were relatively few clear results. Only for the comparison of a balloon versus vaginal prostaglandin E2, including 28 studies involving 6619 women, were there enough data to make a valid judgement on effectiveness and adverse events between these methods.

Most of the outcomes of interest were poorly reported in the included studies, especially serious maternal or perinatal morbidity or death. Also, for some outcomes such as duration from start of induction to vaginal delivery, Apgar score or umbilical cord pH, only continuous data were reported and therefore were not included in this review. Outcomes should therefore be interpreted with caution. Caesarean section on the other hand, was reported in almost every study. Therefore, caesarean section may be the most reliable outcome by which to assess the effectiveness of mechanical methods for cervical ripening and induction of labour.

The external validity of our results can be questioned as the policy of labour induction varies across the different settings in which trials took place. There was a difference seen in maximum ripening time (e.g. the maximum time cervical ripening was awaited, ranging from six hours to 96 hours) and for when induction of labour was declared as failed. As it may take longer to achieve successful cervical ripening when a balloon is used, this could influence the outcome measures of effectiveness used, such as caesarean section. Also, the caesarean rate differs according to the setting in which trials took place, ranging from 9% (Deshmukh 2011) to 70% (Hudon 1999).

Studies ranged in date of publication from 1982 to 2018. While we did not consider the potential influence of date on our results, it is possible that changes in management of labour can mean that for some comparisons, in which relatively older studies were included, may not be generalisable to the current clinical context.

Quality of the evidence

Risk of bias varied throughout the included trials (see Figure 2 and Figure 3). A great proportion of the trial methods were not well reported and were assessed to be at unclear risk of bias in many domains. Three trials were assessed as using inadequate random sequence generation, and in five trials no measures were taken to conceal allocation. In almost all studies, no blinding was done due to the nature of the intervention. However, blinding of the research personnel would have been possible, but was only described in four studies. Two studies reported to have performed a double-blind study, but did not describe how this was achieved. We rated many trials at unclear risk of attrition bias, mainly because it was not clear if intention-to-treat was performed. Although we did attempt to assess reporting bias, lack of trial protocols for most of the older studies, meant this assessment relied on information available in the published trial report.

The outcomes were assessed using the GRADE approach. We determined the evidence to be moderate-quality, low-quality or very low-quality. All evidence was downgraded for lack of blinding. Other reasons for downgrading were predominately for imprecision (uncertain effect estimates, small sample sizes and low event rates) and inconsistencies (heterogeneity). For our three main comparisons (balloon versus vaginal PGE2; balloon versus vaginal misoprostol; balloon versus oral misoprostol), a 'Summary of findings' table was produced (summary of findings Table for the main comparison; summary of findings Table 2; summary of findings Table 3).

Although no publication bias was detected for our main outcomes, there is still a possibility of publication bias. Most comparisons had less than 10 studies included and therefore, a funnel plot could not be produced. Also, for 11 trial registrations the anticipated end date was overdue by two years and it was not clear if the trials had started, were ongoing or finished recruiting (Baacke 2006; Behrashi 2013; Cullimore 2009; Dias 2008; EUCTR 2012; Kamilya 2011; Park 2011; Pathiraja 2014; Reif 2012; Yazdani 2011; Zhang 2014). Therefore, a potential risk exists as results from these studies were not published. We acknowledge that with so many comparisons within the review, there is also a risk of statistical type 1 error, meaning a false-positive result. The results where there are very few studies included, moderate or substantial heterogeneity, or those where the meta-analysis result is of borderline statistical significance must therefore be treated with caution.

Potential biases in the review process

We are aware that the possibility of introducing bias was present at every stage of the reviewing process. We attempted to minimise bias in a number of ways; two review authors assessed studies for eligibility, assessed risk of bias and carried out data extraction. Each review author worked independently. We resolved discrepancies through discussion, or if required we consulted a third review author. Nevertheless, the process of assessing risk of bias, for example, is not an exact science and includes many personal judgements. Four review authors, Mieke ten Eikelder, Marta Jozwiak , Kitty Bloemenkamp and Ben Willem Mol are also trial authors for the following included studies: Jozwiak 2012; Jozwiak 2013; Jozwiak 2014; ten Eikelder 2016. Data extraction and risk of bias assessments were conducted by other review authors for these studies (Marieke de Vaan; Kirsten Palmer).

Agreements and disagreements with other studies or reviews

This review is one the most extensive reviews on mechanical methods of labour induction as most reviews on this subject only contain one or two of the comparisons included in this review. We found eight recent systematic reviews covering one or more of our main comparisons, being balloon versus vaginal PGE2, balloon versus vaginal misoprostol or balloon versus oral misoprostol.

Our review was in line with other systematic reviews on induction of labour with a balloon versus vaginal PGE2. Liu 2018 compared a double balloon with a vaginal PGE2 insert and they found no difference in vaginal deliveries achieved within 24 hours or caesarean section rate. They also found a reduction in uterine hyperstimulation and umbilical artery pH < 7.10 when a balloon was used. All of the five studies included in the review of Liu 2018, were also included in our review. Du 2017 compared a double balloon with PGE2 (vaginal as well as cervical) and produced the same results as described in our review and the review of Liu 2018. However, they found no difference in fetal distress for which a caesarean section was indicated. All eight studies were also included in this review. Zhu 2018 compared a Foley catheter with a vaginal PGE2 and included eight studies of which one (Ghanaie 2013) was excluded in our review because oxytocin was administered concurrent to both induction methods. Just as the other reviews, Zhu 2018 found no difference in caesarean section rate. They also looked at the induction to delivery interval on a continuous level and found no difference between both induction methods. Wang 2016 however, found a longer induction to delivery interval when a Foley catheter was used in comparison to PGE2 vaginal insert. The authors did not compare vaginal delivery rates within 24 hours.

Chen 2016 performed a network meta-analysis in which direct and indirect comparisons between different induction agents, including Foley catheter, vaginal PGE2, vaginal misoprostol and oral misoprostol were made. Studies with high-dose misoprostol were included in the review of Chen 2016 as opposed to our review and only indirect comparisons could be made between a Foley catheter and oral misoprostol in the review of Chen 2016. The outcomes of interest were vaginal delivery not achieved within 24 hours, uterine hyperstimulation with FHR changes and caesarean section. Not all results were in line with our results. In the network meta-analysis, a Foley catheter increased the risk of vaginal delivery not achieved within 24 hours compared to vaginal misoprostol, where in our review the outcome was uncertain. When compared to oral misoprostol, no clear difference in vaginal deliveries within 24 hours was seen by Chen 2016 compared to an increased risk in our review. In our review no clear difference was seen in uterine hyperstimulation with FHR changes, but in the network analysis of Chen 2016, a reduced risk was seen when a Foley catheter was used compared to oral misoprostol. For the outcome of caesarean section, the network meta-analyses of Chen 2016 showed the same results as our review. They found that a Foley catheter may slightly increase the risk of a caesarean section when compared to vaginal or oral misoprostol, with moderate heterogeneity for the comparison with vaginal misoprostol.

Alfirevic 2016 performed a extensive systematic review on induction of labour. The authors included 34 active treatment types/regimens including different dose regimens and routes of administration, and performed a network meta-analysis in which all different treatments were ranked in relation to each other, including direct as well as indirect comparisons. Ranking was done on absolute risks for all pre specified outcomes. Mechanical induction with a balloon was divided in a single or double balloon. Alfirevic 2016 used other cut-off points in dividing oral and vaginal tablets in dose regimens. In our review low dose was defined as ≤ 50 mcg every ≥ four hours, opposed to the cut-of point of ≥ 50 mcg in the review of Alfirevic 2016. Vaginal PGE2 was divided into tablets, gel, slow-release and normal-release inserts. For the outcome of a vaginal delivery not achieved within 24 hours, low-dose

vaginal misoprostol scored better, as well as all different regimens of vaginal PGE2 compared to induction with a balloon (single as well as double). For the outcome caesarean section, a single balloon and vaginal PGE2 gel had a similar mean ranking in the mid regions. Noteworthy is that low-dose titrated oral misoprostol had one of the lowest mean rankings, as compared to oral misoprostol < 50 mcg, which was ranked relatively high. The same high ranking for this outcome was seen for a double balloon. In line with our review, all mechanical methods had a low ranking regarding uterine hyperstimulation with FHR changes. Alfirevic 2016 also looked at neonatal and maternal mortality and severe morbidity, but for these composite outcomes no network meta-analysis was possible as events were rare and poorly reported in studies. For the outcomes of NICU-admission as well as five-minute Apgar score less than seven, there was considerable uncertainty on the probability of the mean ranking as the 95% confidence intervals (CIs) for these rankings were relatively broad.

Ten Eikelder 2016 looked at safety outcomes between induction of labour with a Foley catheter and misoprostol (any route, any dose) and found less uterine hyperstimulation with FHR changes and less fetal distress for which a caesarean section was indicated when a Foley was used. They found that a Foley catheter may slightly increase the caesarean section rate, although conventional statistical significance was not reached and there was moderate heterogeneity for this outcome. Studies with high-dose misoprostol were not excluded in the review of Ten Eikelder 2016. In subgroup analyses for 25 mcg and 50 mcg vaginal misoprostol, no evidence for a difference in safety outcomes were found.

In our review, there was no evidence for a difference in outcomes related to infection between mechanical induction and other methods for induction of labour. However, the results of outcomes covering infection were still too imprecise to make a valid judgement. McMaster 2015 addressed this question by comparing induction of labour with a balloon versus locally-applied prostaglandin and included 26 trials. Their results were in line with our results and found no evidence for a difference in chorioamnionitis, endometritis and neonatal infection. When infection outcomes were pooled, little or no difference was seen, suggesting a Foley catheter does not increase the risk of infection compared to locally-applied prostaglandin.

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Chapter 3

The influence of various induction methods on adverse outcomes in small for gestational age neonates: A secondary analysis of the PROBAAT 1 and 2 trials

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Abstract

Objective

To evaluate the safety aspects of different induction methods in pregnancies with small-for-gestational-age neonates.

Study design

This was a secondary analysis of two previously reported multicenter, randomized controlled trials conducted in the Netherlands. In the original trials, women were randomized to either a 30cc Foley catheter, vaginal prostaglandin E2 (PROBAAT-1) or oral misoprostol (PROBAAT-2). A total of 425 patients with a term, singleton pregnancy in cephalic presentation with an indication for labor induction and a small-for-gestational-age neonate were included in this secondary analysis. Our primary outcome was a composed adverse neonatal outcome of Apgar score <7 after 5 minutes and/or a pH in the umbilical artery <7.05 and/or NICU admission. Secondary outcomes were mode of birth, operative birth for fetal distress and pH <7.10 in the umbilical artery. For these outcome measures, multivariate as well as bivariate analyses were performed.

Results:

An adverse neonatal outcome occurred in 4.7 % (10/214) induction with a Foley catheter, versus 12.8 % (19/149) after misoprostol (RR 0.36; 95 % CI 0.17–0.76) and 4.7 % (3/64) after Prostaglandin E2 (RR 0.98; 95 % CI 0.28–3.51). For individual components of the composed outcome of adverse events, a difference was found between a Foley catheter and misoprostol for Apgar score < 7 at 5 min (0.5 % versus 3.4; RR 0.14; 95 %CI 0.02–1.16) and NICU admission (1.9 % versus 6.1 %; RR 0.31; 0.10–0.97). No differences were found for mode of birth.

Conclusions:

For women who gave birth to a small-for-gestational-age neonate, a Foley catheter is probably a safer induction method compared to oral misoprostol.

Introduction

Induction of labor has become a common procedure and numbers have increased steadily over the last two decades. In developed countries up to 30% of all births are induced [1,2]. In case of an unfavorable cervix, induction starts with ripening of the cervix for which a variety of methods can be used. Approaches to cervical ripening can be pharmacologically (Prostaglandin E1 or Prostaglandin E2) or mechanically (Foley catheter). The mechanism of cervical ripening is different between both methods. Where synthetic prostaglandins imitate physiological cervical ripening and increases the sensitivity of the uterine wall to oxytocin, a foley catheter induces labor by direct mechanical pressure and stimulating endogenous release of prostaglandins [3,4].

Until a decade ago, the most preferred method for induction was vaginal applied Prostaglandin E2 (PGE_2) [5,6]. This tendency changed after publications of the PROBAAT-1 and 2 trials, two multicenter randomized controlled trials, evaluating the safety and effectivity of the transcervical placed Foley catheter compared to PGE_2 and oral misoprostol, respectively [7-9]. Although the CS rate between a Foley catheter and PGE^2 did not differ, fewer CS were performed for fetal distress when a Foley catheter was used [8]. When compared to oral misoprostol, non-inferiority was found between both methods regarding a composite outcome of neonatal asphyxia and post-partum hemorrhage [9].

A Foley catheter, as well as oral misoprostol are now recommended methods for induction of labor [4,10]. A recent Cochrane review on mechanical methods for induction of labor showed a better neonatal safety profile for induction with a foley catheter, with a 50% reduction in severe neonatal adverse events when compared to PGE2 [4].

In current clinical practice, a Foley catheter is more often used in pregnancies with an increased risk of fetal distress, which is the case in pregnancies with an estimated fetal weight $<10^{th}$ percentile. Although small-for-gestational-age neonates (SGA; neonates with a birthweight $<10^{th}$ percentile) are at risk of fetal distress when labor is induced compared to non-SGA neonates, studies on the effect of different induction methods on neonatal outcome in these pregnancies are limited [11-13].

The aim of this study is to evaluate the effect of different induction methods on obstetric and perinatal outcomes in SGA pregnancies.

Material and Methods

This is a post hoc exploratory analysis of the PROBAAT-1 and PROBAAT-2 trials. Both studies were multicenter randomized controlled trials for which the full-scale methods and results were published elsewhere [8,9]. In brief, the PROBAAT-1 trial randomized women to induction of labor with a 30cc Foley catheter or vaginal Prostaglandin E2 gel. The PROBAAT-2 trial randomized women to a 30cc Foley catheter or oral misoprostol.

In total, 29 hospitals collaborating in the Dutch Consortium for Healthcare Evaluation and Research in Obstetrics and Gynaecology (NVOG Consortium 2.0) participated in one or both PROBAAT trials. Both trials were approved by the Central Committee on Research Involving Human Subjects, by the ethics committee of the Academic Medical Center, Amsterdam and by the board of directors of each participating hospital and registered with the Dutch Trial Registry (NTR 1646 and NTR3466). No further approval was required due to the nature of this study.

Both PROBAAT trials studied pregnant women scheduled for induction of labor beyond 37 weeks of gestation with a vital singleton pregnancy in cephalic presentation, intact membranes, and an unfavorable cervix (Bishop score <6). Women younger than 18 years, with a previous caesarean section, placenta previa, lethal fetal congenital anomalies, or known hypersensitivity for one of the products used for induction were ineligible. For this secondary analysis, we only included women who gave birth to a SGA neonate (birthweight <10th percentile) based on the Hoftiezer curve, further described as SGA-pregnancies [14]. For all pregnancies, the gestational age was determined by first trimester measurement of the crown-rump length.

Details on randomization and interventions in each trial have been described previously [7,8]. In short, after written informed consent, women were randomly allocated to induction of labor with either a Foley catheter or prostaglandin by their attending physician, in a 1:1 ratio, using an online program. In both studies, women allocated to induction with a Foley catheter had a 16F or 18F Foley catheter introduced through the cervix either digitally or using a vaginal speculum and was filled with 30 mL 0·9% sodium chloride or sterile water. If the Bishop score remained less than 6 after 24 hours, the location of the Foley catheter was checked. When still in correct position, the Foley catheter was either left in place or replaced with a new one after 24 hours.

Women allocated to prostaglandin E2 (PROBAAT-1) were treated mostly with a starting dose of 1 mg prostaglandin E2 gel, followed by 1 mg after 6 hours, with a maximum of two doses per 24 hours inserted into the posterior vaginal fornix. An initial dose of 2 mg was allowed in nulliparous women, as prescribed by the manufacturer (Pfizer, New York, NY, USA). Women allocated to oral misoprostol (PROBAAT-2) received 50 mcg capsules once every 4 hours with a maximum of three times daily. In both trials, if the cervix was still unfavorable for amniotomy after 48 hours of treatment, women were generally assigned a day of rest followed by another 48 hours of induction.

The main outcome of the current study was a composed outcome of adverse neonatal events being Apgar score <7 after 5 minutes and/or a pH in the umbilical artery <7.05 and/or NICU admission. Other outcomes were uterine hyperstimulation, meconium-stained amnion fluid, oxytocin use, time from start induction to vaginal birth (hours), mode of birth (spontaneous, assisted vaginal birth or CS), assisted birth for fetal distress, pH <7.10 in the umbilical artery, and birthweight.

Data were analyzed on an intention-to-treat basis. Numerical variables were summarized as means with standard deviations if the distribution was normal and analyzed with a one-way ANOVA. When distributions were skewed, they were summarized as medians with interquartile ranges (IQR) and analyzed with a Kruskal-Wallis-test. The X^2 test was used to compare categorical variables. A *p*-value of <0.05 was considered to indicate statistical significance. For the direct comparisons (foley catheter versus misoprostol or Foley catheter versus PGE2) relative risk (RR) and 95% confidence intervals (95%CI) were reported. For the primary outcome of this study, a multivariate logistic regression analysis was performed for study (PROBAAT 1 or 2) and other detected cofounders. Statistical analyses were performed with SPSS version 25.0 (IBM corp, Armonk, NY, USA).

Results

During the original trial periods, 819 and 1845 eligible women were randomized in the PROBAAT 1 and PROBAAT 2 trials, respectively. Of these 2664 women, 1332 (411 and 921, respectively) were allocated to induction with a Foley catheter, 408 women to PGE2 and 924 women to oral misoprostol. In the Foley catheter group, 214 (16.0%) women gave birth to an SGA neonate, in the PGE2 group 64 (15.7%) women, and in the misoprostol group 147 (15.9%) women (see Figure 1).

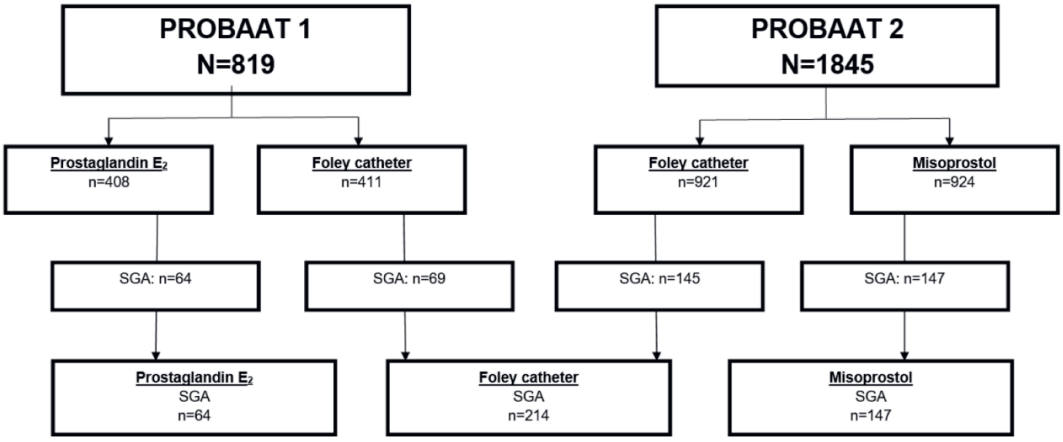

Fig. 1. Flow chart of inclusions.

Baseline characteristics of the included women are presented in Table 1. The groups were comparable with respect to age, BMI at booking, ethnicity, parity, and gestational age. The indication fetal growth restriction was not equal distributed between the women allocated to a Foley catheter (79/214; 36.9%), misoprostol (48/147; 32.7%) and PGE2 (13/64; 20.3%; *p*=0.046). Also, more women in the misoprostol group were induced for decreased fetal movements (18/147; 12.2%), compared to the Foley catheter group (10/214; 4.7%) and the PGE2-group (1/64; 1.6%; *p*=0.004).

Table 1
Baseline characteristics of the study population.

	Foley catheter n = 214	Misoprostol n = 147	PGE_2 n = 64	*p*-value
Gestational age (weeks + days)	39 + 6 [38 + 2–41 + 1]	39 + 2 [38 + 2–41 + 1]	39 + 5 [38 + 1–41 + 2]	0.600†
Parity				0.727
Nulliparity	161 (75.2 %)	108 (73.5 %)	45 (70.3 %)	
multiparity	53 (24.8 %)	39 (26.5 %)	19 (29.7 %)	
Body Mass Index	23.81 [21.3–27.5]	23.92 [21.4–27.4]	23.03 [21.2–26.2]	0.688†
Ethnic origin				0.073
Caucasian	151 (70.6 %)	106 (72.1 %)	55 (85.9 %)	
Non-Caucasian	51 (23.8 %)	30 (20.4 %)	9 (14.1 %)	
Unknown	12 (5.6 %)	11 (7.5 %)	0	
Maternal age (years)	30 (±5.1)	31 (±5.1)	30 (±5.4)	0.158‡

Baseline characteristics of the study population.

	Foley catheter n = 214	Misoprostol n = 147	PGE_2 n = 64	*p*-value
Indication for induction				
Fetal growth restriction	79 (36.9 %)*	48 (32.7 %)	13 (20.3 %)*	0.046
Oligohydramnios	27 (12.6 %)	13 (8.8 %)	8 (12.5 %)	0.51
Hypertensive disorder	64 (29.9 %)	36 (24.5 %)	25 (39.1 %)	0.1
Post term (≥41 weeks)	61(28.5 %)	44 (29.9 %)	17 (26.6 %)	0.88
Insulin dependent diabetes	7 (3.3 %)	3 (2.0 %)	1 (1.6 %)	0.658
Cholestasis	0	2 (1.4 %)	0	0.15
Decreased fetal movements	10 (4.7 %)*	18 (12.2 %)*^	1 (1.6 %)^	0.004
Elective	25 (11.7 %)	13 (8.8 %)	4 (6.3 %)	0.386
Other	10 (4.7 %)	11 (7.5 %)	4 (6.3 %)	0.532
Bishop Score				
0–2	110/176 (62.5 %)	57/105 (54.3 %)	38/64 (59.4 %)	0.398
3–5	64/176 (36.4 %)	47/105 (44.8 %)	26/64 (40.6 %)	0.374

Values are given as numbers (%), mean (±SD) or median [IQR]. †Kruskal-Wallis-test, ‡ one-way ANOVA.
Data missing: [1] 30 (16%) [2] 13 (9%) [3] 8 (9%).
* or ^: statistically significant in bivariate analysis using (X^2 test or Fisher's exact test when appropriate).

An adverse neonatal outcome occurred less often when a Foley catheter (10/214; 4.7%) or PGE2 (3/64; 4.7%) was used compared to oral misoprostol (19/147; 12.9%; *p*=0.009; Table 2). In the bivariate analyses, statistical significance was only present in the direct comparison between a Foley catheter and oral misoprostol (RR 0.36; 95%CI 0.17-0.76; *p*=0.005). A multivariate analysis, in which there was controlled for study (PROBAAT 1 or 2) and indication for induction of labor did not change the result (adjusted odds ratio (aOR) 0.35; 95%CI 0.14-0.87).

Table 2
Perinatal outcomes.

	Foley catheter n = 214	Misoprostol n = 147	PGE_2 n = 64	*p*-value	*Foley vs misoprostol RR (95 %CI; p-value)*	*Foley vs PGE2 RR(95 %CI; p-value)*
Composed adverse neonatal outcome (%)	10 (4.7 %)*	19 (12.9 %)*	3 (4.7 %)	0.009	0.36 (0.17–0.76; *0.005*)	0.98 (0.28–3.51; *0.996*)
Apgar < 7 after 5 min (%)	1 (0.5 %)*	5 (3.4 %)*	0	0.039	0.14 (0.02–1.16; *0.043*)	NA
pH in umbilical artery						
pH ≤ 7.10	18/166 (10.8 %)	19/108 (17.6 %)	5/56 (8.9 %)	0.169	0.62 (0.34–1.12; *0.110*)	1.21 (0.47–3.12; *0.684*)
pH ≤ 7.05	7/166 (4.2 %)	8/108 (7.4 %)	3/56 (5.5 %)	0.524	0.57 (0.21–1.52; *0.257*)	0.79 (0.21–2.94; *0.722*)
NICU admission (%)	4 (1.9 %)*	9 (6.1 %)*	0	0.021	0.31 (0.10–0.97; *0.330*)	NA
Birthweight (gram)	2675 [2439–2950]	2652 [2370–2955]	2720 [2435–2965]	0.839[‡]	NA	NA
Birthweight < p5	137 (64.0 %)	94 (63.9 %)	39 (60.9 %)	0.896	1.00 (0.86–1.17; *0.989*)	1.05 (0.84–1.31; *0.654*)
Birthweight < p3	85 (39.7 %)	62 (42.2 %)	27 (42.2 %)	0.913	0.94 (0.73–1.21; *0.641*)	0.94 (0.68–1.31; *0.724*)
Meconium (%)	15 (7.0 %)*	15 (10.2 %)	12 (18.8 %)*	0.022	0.69 (0.35–1.36; *0.280*)	0.37 (0.19–0.76; *0.005*)
Neonatal mortality	0	0	0	NA	NA	NA

Composed adverse neonatal outcome: Apgar < 7 after 5 min and/or pH in umbilical artery ≤ 7.05 and/or NICU admission.
Values are given as numbers (%) or median [IQR]. NA = not applicable.
†Kruskal-Wallis-test.
*statistical significant in bivariate analysis using (X^2 test or fisher's exact test when appropriate).

When the individual components of the composed adverse neonatal outcome between a Foley catheter, misoprostol and PGE2 were analyzed, there was a statistical difference found for Apgar score <7 at 5 minutes (1/214; 0.5% versus 5/147; 3.4% versus 0/64; 0%, respectively; *p*=0.039) as well as NICU admission (4/214; 1.9% versus 9/147; 6.1% versus 0/64; 0%, respectively; *p*=0.021). In the bivariate analyses, a statistical difference was only present between a Foley catheter compared to oral misoprostol for AS <7 after 5 minutes (RR 0.14; 95%CI 0.02-1.16; *p*=0.043) as well as NICU admission (RR 0.31; 0.10-0.97; *p*=0.033).

No differences were found for mode of birth between induction with a Foley catheter, oral misoprostol or PGE2 (Table 3).The caesarean section rate was 39/214 (18.2%) versus 28/147 (19.0%) versus 12/64 (18.8%), respectively (*p*=0.980). Also, no statistical difference was found for caesarean section for fetal distress (21/214; 9.8% versus 22/147; 15.0% versus 10/64; 15.6%; *p*=0.246) or operative birth for fetal distress (35/214; 16.4% versus 37/147; 25.2% versus 14/64; 21.9%; *p*=0.115). Time from start induction to vaginal birth was longer when a Foley catheter was used compared to misoprostol or PGE2 (29 hours versus 26 hours versus 16 hours; *p*=0.003).

Table 3
Obstetric outcomes.

	Foley catheter n = 214	Misoprostol n = 147	PGE_2 n = 64	*p*-value	*Foley vs misoprostol RR (95 %CI; p-value)*	*Foley vs PGE2 RR(95 %CI; p-value)*
Time from start induction to vaginal birth (hours)	29 [16–37]^	26 [16–46]#	16 [11–29]^#	0.003†	NA	NA
Uterine hyperstimulation	9 (4.2 %)	8 (5.4 %)	2 (3.1 %)	0.642	0.77 (0.31–1.96; *0.586*)	1.35 (0.30–6.07; *0.697*)
Oxytocin (%)	179 (79.4 %)*	87 (59.2 %)*	39 (60.9 %)	<0.001	1.34 (1.15–1.56; *<0.001*)	1.30 (1.06–1.60; *0.003*)
Epidural (%)	87 (40.7 %)	53 (36.1 %)	22 (34.4 %)	0.541	1.13 (0.86–1.48; *0.378*)	1.18–0.81–1.72; *0.367*)
Mode of birth						
Spontaneous	154 (72.0 %)	102 (69.4 %)	45 (70.3 %)	0.865	1.04 (0.91–1.19; *0.597*)	1.02 (0.86–1.23; *0.797*)
Vaginal assisted	21 (9.8 %)	17 (11.6 %)	7 (10.9 %)	0.864	0.85 (0.46–1.55; *0.594*)	0.90 (0.40–2.01; *0793*)
Caesarean section	39 (18.2 %)	28 (19.0 %)	12 (18.8 %)	0.98	0.96 (0.62–1.48; *0.843*)	0.97 (0.54–1.74; *0.924*)
Assisted birth for fetal distress	35 (16.4 %)	37 (25.2 %)	14 (21.9 %)	0.115	0.65 (0.43–0.98; *0.039*)	0.75 (0.43–1.30; *0.309*)
Caesarean section for fetal distress	21 (9.8 %)	22 (15.0 %)	10 (15.6 %)	0.246	0.66 (0.38–1.15; *0.138*)	0.63 (0.31–1.26; *0.195*)
Vaginal assisted for fetal distress	14 (6.5 %)	15 (10.2 %)	4 (6.3 %)	0.392	0.64 (0.3201.28; *0.209*)	1.05 (0.56–3.07; *0.934*)

Values are given as numbers (%) or median [IQR].
†Kruskal-Wallis-test.
*statistical significant in bivariate analysis (X^2-test).
^ or # statistically significant in bivariate analysis (Mann-Whitney-*U* test).

Subgroup analyses for lower birthweight percentiles showed the same differences for an adverse neonatal outcome between a Foley catheter and misoprostol (Table 4). In the subgroup birthweight <p5, the numbers being 7/137 (5.1 %) versus 13/94 (13.8 %), respectively (RR 0.40; 95 %CI 0.15–0.9) and for birthweight < p3, 4/85 (4.7 %) versus 10/62 (16.1 %), respectively (RR 0.29; 95 %CI 0.10–0.89).

Table 4
Primary outcome for subgroup birthweight < 5th and < 3rd percentile.

Birthweight <5th percentile	Foley catheter n = 137	Misoprostol n = 94	PGE_2 n = 39	*p*-value	*Foley vs misoprostol RR (95%CI; p-value)*	*Foley vs PGE2 RR(95%CI; p-value)*
Composed adverse neonatal outcome (%)	7 (5.1%)*	13 (13.8%)*	2 (5.1%)	0.045	0.40 (0.15–0.89; *0.021*)	1.00 (0.20–5.04; *0.996*)
Apgar <7 after 5 min (%)	0*	4 (4.3%)*	0	0.022	NA	NA
pH in umbilical artery ≤7.05 (%)	4/108 (3.7%)	3/72 (4.2%)	2/34 (5.9%)	0.859	0.89 (0.21–1.07; *0.875*)	0.63 (0.93–1.12; *0.582*)
NICU admission (%)	3 (2.2%)*	9 (9.6%)*	0	0.01	0.23 (0.06–0.82; *0.013*)	NA
Birthweight <3rd percentile	Foley catheter n = 85	Misoprostol n = 62	PGE_2 n = 27	*p*-value	*Foley vs misoprostol RR (95%CI; p-value)*	*Foley vs PGE2 RR(95%CI; p-value)*
Composed adverse neonatal outcome (%)	4 (4.7%)*	10 (16.1%)*	1 (3.7%)	0.031	0.29 (0.10–0.89; *0.020*)	1.27 (0.15–10.90; *0.826*)
Apgar <7 after 5 min (%)	0	2 (3.2%)	0	0.161	NA	NA
pH in umbilical artery ≤7.05 (%)	2/70 (2.9%)	2/49 (4.1%)	1/24 (4.2%)	0.92	0.70 (0.10–4.80; *0.715*)	0.69 (0.07–7.23; *0.753*)
NICU admission (%)	2 (2.4%)*	9 (14.5%)*	0	0.004	0.16 (0.04–0.72; *0.009*)	NA

Composed adverse neonatal outcome: Apgar < 7 after 5 min and/or pH in umbilical artery ≤ 7.05 and/or NICU admission.
Values are given as numbers (%).
*statistically significant in bivariate analysis (X^2-test).

Discussion

Main findings

In our subgroup analyses of two multicenter randomized controlled trials, we found that a Foley catheter is probably a safer induction method for SGA neonates compared to misoprostol. The results show a lower rate of a composed outcome of adverse neonatal events. Also, individual components of this outcome, being Apgar score < 7 after 5 min and NICU admission were lower with the use of Foley catheter compared to misoprostol. Between a foley catheter and PGE2, no difference in adverse neonatal outcomes were observed.

Strengths and weaknesses

The main strength of our study was the availability of a large, combined database of women with term pregnancies, whose induction method was determined by randomization to either a Foley catheter, oral misoprostol or PGE2. We therefore had access to a substantial subgroup of pregnancies in which an SGA neonate was born (n = 425), which makes our study the largest randomized prospective study present. Unfortunately, the group of women who received PGE2 was relatively small and as a result, no valid judgement for PGE2 in comparison the other methods could be made.

The presence of suspected FGR (defined as an EFW < 10th percentile in trial protocols) turned out to be a too small of a subgroup and might have been underreported. This led us to the decision to choose birthweight < 10th percentile. An explanation for a possible underreporting might be that the effect of induction methods in FGR pregnancies was not the focus of the original trials. Therefore, it was possible that, if FGR was not the main indication of induction, the presence of an EFW < 10th percentile was not registered as such.

Also, it is not known if all women had a recent biometry measurement before randomization. This could also explain the discrepancy between cases of suspected FGR (n = 183) and SGA (n = 425). Also, especially during the PROBAAT-1 trial, little was known on safety and efficiency of mechanical induction, which could have caused a selection bias, meaning clinicians could have withheld study participation for women with pregnancies with severe FGR. We acknowledge that suspected FGR would have made a more ideal subgroup as actual birthweight is not known at forehand. Also, we acknowledge that the definition of suspected FGR in the original trial protocols is outdated. Unfortunately, a subgroup formed on recent standards for the diagnosis of FGR with the data available, was not possible [15]. This makes that our study findings cannot be directly extrapolated for suspected FGR. On the other hand, the main goal of fetal biometry is to estimate the actual weight of the neonate. However, fetal biometry still has a relatively high false negative rate for detection of birthweight below 10th percentile [16]. This implicates that in even more pregnancies an undetected SGA-fetus could be present which raises the question whether induction with a Foley catheter is more preferable in case of an EFW in the lower percentile range.

The fact that we performed a subgroup analysis, and the outcomes of our study were not predefined in our original trail protocol creates a risk of a type 2 error. In general, this means the more analyses you perform, the higher the risk (1in 20) for a false positive result. However, looking at the consistency of our result and statistical significance being even stronger in different subgroups of SGA (< 3rd percentile), we think a type 2 error is unlikely.

Interpretation in light of what is known

To our knowledge, this is the first study in which a foley catheter was compared to oral misoprostol specific in SGA pregnancies. Studies on the effect of different induction methods in SGA pregnancies are sparse and mainly of low-quality evidence. Our results differ from studies in which a foley catheter is compared to vaginal misoprostol, where no differences in adverse neonatal outcomes were found [12,13].

We found one randomized controlled trial in which different induction methods were compared in SGA pregnancies [12]. Chavacula et al. randomized 100 women diagnosed with FGR in a tertiary center in South India to either 25 µg vaginal misoprostol or a foley catheter. In this relatively small study, no difference was found in perinatal outcomes such as NICU admission or Apgar score < 7 after 5 min. Familiari et al. recently published a systematic review with meta-analyses of randomized and non-randomized studies, which to date is the most comprehensive study regarding safety issues of different induction methods, being vaginal misoprostol, vaginal PGE2 and a Foley catheter, in SGA pregnancies [13]. They included 12 studies, one of them being the RCT of Chavacula et al., two prospective studies and nine retrospective studies. Data from this meta-analyses suggests that induction with a foley catheter might reduce intrapartum adverse events (composed outcome of tachysystole, non–reassuring fetal heartrate, caesarean section and/or operative birth for fetal distress, fever or meconium-stained amniotic fluid), but found no evidence for a difference in adverse neonatal outcomes (composed outcome of NICU admissions, pH < 7.20 in the umbilical cord artery or Apgar score < 7 after 5 min) between a foley catheter, vaginal applied misoprostol and vaginal PGE2. Although data was pooled, the authors state that substantial heterogeneity was present and therefore a direct comparison was not possible.

Conclusion

In case of labor induction in women with an unfavorable cervix, a foley catheter seems to have a better safety profile for SGA neonates compared to low dose oral misoprostol. For this group, a Foley catheter might reduce NICU admissions and Apgar scores < 7 after 5 min. No valid judgement could be made in comparison to PGE2. We suggest to incorporate the possibility of a lower rate of adverse neonatal outcomes with the use of a Foley catheter in the shared decision process regarding induction of labor due to suspected FGR

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Chapter 4

Methods of induction of labor in women with obesity: a secondary analysis of two multicenter randomized controlled trials

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Abstract

Introduction

Obesity is an increasing public health concern worldwide and can lead to more complications in pregnancy and during and after birth. Obese women have a higher chance of requiring induction of labor for various indications. The aim of this study is to assess which method of induction of labor is most safe and effective in obese women.

Material and methods

This is a secondary analysis of two RCT's about induction of labor. Women with a term singleton pregnancy in cephalic presentation, an unfavorable cervix, intact membranes and without a previous cesarean section were randomly allocated to cervical priming with a Foley catheter or prostaglandin-E2-gel (PROBAAT-I) or to a Foley catheter or oral misoprostol (PROBAAT-II). The in- and exclusion criteria for the studies were identical. Induction methods were compared in obese women (body mass index ≥ 30.0) and interaction analyses were performed between obese and non-obese women. Main outcomes were cesarean section and postpartum hemorrhage (blood loss > 1000 ml).

Results

A total of 2664 patients were included in both trials of which 517 were obese: 254 women received a Foley catheter, 176 oral misoprostol and 87 PGE2. A cesarean section was performed in 29.1% of women allocated to Foley versus 22.2% in the misoprostol and 23.0% in the PGE2 group. Comparisons between groups revealed no statistically significant differences: Foley vs misoprostol RR 1.31; 95%CI 0.94-1.84 and Foley vs PGE2 RR 1.27; 95%CI 0.83-1.95. The rates of postpartum hemorrhage were comparable (10.6%, 11.4% and 6.9%, respectively; p=0.512). In obese women, more often a switch to another method occurred in the Foley group, (20.1% vs 6.3% in misoprostol vs. 1.1% in the PGE2 group; p=<0.001). The risk of a failed Foley placement was higher in obese compared to non-obese women (8.3% vs 3.2%; aOR 3.12, 95%CI 1.65-5.90).

Conclusion

We did not find a significant difference in cesarean rate between methods, however a modest increase with the use of a Foley catheter compared to prostaglandins cannot be ruled out. The finding of a higher risk of failed placement of a Foley catheter in obese women can be used in shared decision making.

Keywords

Obesity; labor, induced; cervical ripening; Foley catheter; prostaglandins; PGE1; PGE2; misoprostol

Introduction

Obesity, defined as a body mass index (BMI) ≥ 30.0 kg/m2, is an increasing public health concern worldwide [1]. Also among women of reproductive age; in the Netherlands in 1981, 10.2% of women aged between 20 and 30 were overweight (BMI between 25 and 30) and 2.3% obese. In 2021, nearly one third (32.8%) was overweight and 11.4% was obese [2].

Obesity increases the risk of pregnancy-related complications, such as hypertensive disorders of pregnancy (HDP), gestational diabetes and postdate pregnancy [3-5]. Obese women have an increased risk of a cesarean section (CS), both for spontaneous labor and when labor is induced, and postpartum hemorrhage (PPH). Neonates of obese women are more likely to be large for gestational age (LGA) [4-11]. However, a recent meta-analysis by Krogh et al compared induction of labor with expectant management amongst obese women and found a lower risk of CS in case of IOL compared to expectant management (19.7% vs 24.5%, RR 0.71, 95% CI 0.63-0.81) [12].

Obese women have a higher risk of requiring induction of labor (IOL) due to the increased pregnancy related complications. A large retrospective cohort study conducted in the UK between 2004 and 2008 included women with singleton postdate pregnancies. It showed a higher BMI was associated with an increased risk of postdate pregnancy and an increased IOL rate. A total of 43.6% of morbidly obese women (BMI > 40) required induction (n=603) compared to 34.4% of women with obesity (BMI 30-35) (n=3061), 30.5% of overweight women (BMI 25-30) (n=2051) and 26.2% of women with a normal weight (BMI 20-25) (n=9530) [13].

In the last decade the IOL rate in Dutch pregnant women has increased significantly from 16.2% in 2009 to 27.5% in 2021 [14]. In approximately half of the inductions of labor, cervical priming is necessary [15]. Priming can be performed either mechanically (usually a Foley catheter) or pharmacologically (oral or vaginal prostaglandins) [16]. It is unknown if the need of cervical priming as part of IOL is different between obese and non-obese women.

Little is known in literature about the most safe and effective method of cervical priming in obese women. Since both obesity and IOL rates are rising, it is important to assess the most safe and effective method of cervical priming as part of induction of labor in obese women. The aim of this study is to assess safety and effectiveness of methods of cervical priming (a Foley catheter, oral misoprostol and vaginal PGE2) in IOL in obese women.

Methods

Study design and ethics statement

This is a post-hoc analysis of two Dutch multicenter randomized controlled trials: the PROBAAT-I and PROBAAT-II. The trials were conducted in 12 and 29 Dutch hospitals in 2009-2010 and 2012-2013, respectively. They were approved by a medical ethical review committee and conducted according to the principles of the Declaration of Helsinki (version 2004) and in accordance with the Medical Research Involving Human Subjects Act (WMO). No further approval was required for this study due to its nature. Both trials were registered in the Netherlands National Trial Registry under trial registration codes NTR1646 and NTR3466 (since 2022 taken over by the International Clinical Trials Registry Platform).

In the PROBAAT-I, patients were randomized between treatment with a 30 mL Foley catheter or vaginal prostaglandin E2 (PGE2) gel. In the PROBAAT-II study, patients were allocated to a 30 mL Foley catheter group or to 25 µgram oral misoprostol. More detailed information on trial protocols are found in earlier publications [17, 18].

Inclusion and exclusion criteria

Both PROBAAT-trials included pregnant women scheduled for induction of labor with a gestational age (GA) of ≥ 37 weeks, a vital singleton pregnancy in cephalic presentation with intact membranes and an unfavorable cervix (defined as a Bishop score < 6). Exclusion criteria were a history of a CS, age below 18 years, a placenta previa, lethal fetal congenital anomalies or hypersensitivity to one of the products used.

The length and weight were registered at the intake of pregnancy in the 1st trimester and the weight was considered to be the pre-pregnancy weight. It is unknown if the height and weight were measured by a healthcare worker or estimated by the patient herself. Obesity was defined as a BMI ≥ 30.0 [19]. For the subgroup analyses, women were eligible if their BMI was 30.0 or higher.

Outcome measures

Primary outcomes were rates of CS and PPH defined as a postpartum blood loss of more than 1000 ml. Maternal secondary outcomes were change of induction method, induction to vaginal birth interval, use of synthetic oxytocin, use of epidural analgesia and maternal death. Neonatal secondary outcomes were Apgar score < 7 after 5 minutes, pH of the umbilical artery ≤ 7.05, admission to the neonatal intensive care unit (NICU) and neonatal death.

Statistical analysis

For this post-hoc analysis, datasets of the PROBAAT-I and PROBAAT-II trial were merged. The data of patients allocated to the Foley group of PROBAAT-I and II were combined, since design, inclusion and exclusion criteria were identical, except for the (other) treatment arms. Data was analyzed on an intention to treat basis (in accordance with the original PROBAAT-trials). Firstly, for the subgroup analysis, the dataset was split: women were eligible with a BMI ≥ 30.0.

Numerical variables were summarized as means with standard deviations if the distribution was normal and analyzed with a one-way ANOVA. When distributions were skewed, they were summarized as medians with interquartile ranges (IQR) and analyzed with a Kruskal-Wallis-test. The X2 test was used to compare categorical variables. A p-value of <0.05 was considered to indicate statistical significance.

Secondly, the whole dataset was used (including non-obese women) to assess the presence of a statistical interaction between BMI and randomization arm.
The association between BMI or obesity and study outcomes was studied by calculating odds ratios (OR) with corresponding 95% confidence intervals (CI) using logistic regression analysis. To study the presence of statistical interaction between BMI and randomization arm on the study outcomes CS and PPH the following steps were taken: firstly, missing BMI-values were imputed using multiple imputation. Secondly, the interaction between BMI and each study outcome was assessed in two separate analyses. In the first analysis BMI was dichotomized using a cut-off value of 30.0 kg/m2 [16].

In a second analysis, BMI was used as a continuous variable after log-transformation to create a parametric distribution. For both the dichotomized and continuous (log)BMI-values, the presence of statistical interaction between study outcomes and BMI was studied using multivariable logistic regression analysis. Interaction terms for BMI and treatment modality were adjusted for trial cohort effect (PROBAAT-I vs PROBAAT-II). No other confounders were taken into account considering the fact that patients were randomized to their treatment modality.

Statistical analyses were performed in both R-Studio version 4.0.3.1.32 (imputation package MICE) (RStudio: Integrated Development for R, PBC; Boston, MA, USA:) and SPSS version 25.0 (IBM Corp; Armonk, NY, USA)

Results

In the original trials, a total of 819 and 1845 eligible women were randomized in the PROBAAT-1 or PROBAAT-II trial, respectively. Of these 2664 women, a total of 517 women (19.4%) were obese with a BMI ≥ 30.0. Of the obese women, 254 were allocated to cervical priming with a Foley catheter, 176 to oral misoprostol and 87 to vaginal PGE2 (see Figure 1).

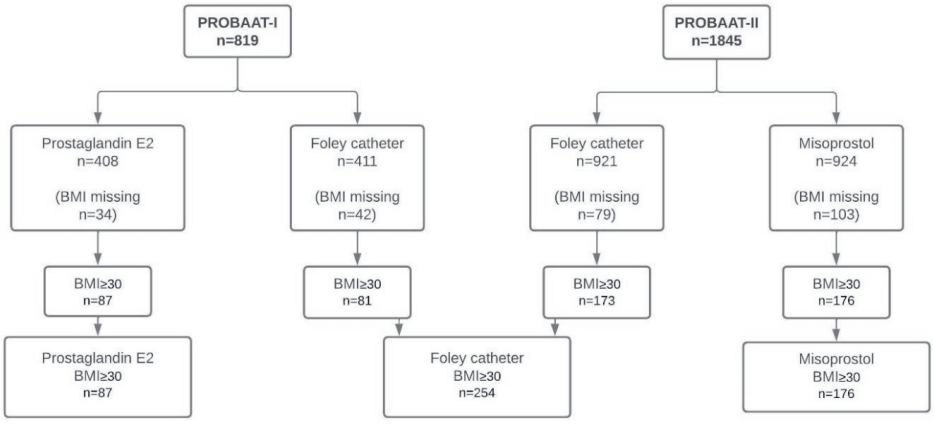

Figure 1. Allocation to treatment arms

The variable BMI was missing in 258 (9.7%) of all patients and the missing values were equally distributed between the treatment groups. In the Foley group BMI was missing in 121 women (9.1%), in the misoprostol group in 103 cases (11.1%) and 34 cases in the PGE2 group (8.3%).

Baseline characteristics of the obese women in both trials are presented in Table 1. Gestational age, parity and BMI was evenly distributed between the three treatment groups.

Table 1. Baseline characteristics of the obese women in the PROBAAT-I and II trial

	Foley catheter n=254 (%)	Misoprostol n=176 (%)	PGE2 n=87 (%)	*p*-value
Gestational age (weeks + days), median [IQR]	39+4 [38+2-41+1]	39+1 [38+2-41+0]	39+5 [38+2-41+1]	0.457†
Parity				
Nulliparous	149 (58.7)	105 (59.7)	50 (57.5)	0.942
Body mass index, median [IQR]	33.3 [31.2-36.6]	33.1 [31.2-36.1]	34.3 [31.6-37.9]	0.241†
Ethnic origin				
Caucasian	254 (73.2)	131 (74.4)	65 (74.7)	0.093
Non-Caucasian	53 (20.9)	39 (16.5%)	21 (24.1)	
Unknown	15 (5.9)	16 (9.1)	1 (1.1)	
Maternal age (years), mean (±SD)	31 (±5.3)	32 (±5.1)	32 (±4.8)	0.612‡
Indication for induction				
Fetal growth restriction	8 (3.1)	11 (6.1)*	0*	0.033
Oligohydramnios	8 (3.1)	9 (5.1)	1 (1.1)	0.236
Hypertensive disorder	92 (36.2)	51 (29.0)	13 (42.5)	0.076
Postdate (≥41 weeks)	69 (27.2)	44 (25.0)	24 (27.6)	0.855
Insulin dependent diabetes	25 (9.8)	24 (13.6)	12 (13.8)	0.399
Cholestasis	3 (1.2)	5 (2.8)	0	0.172
Decreased fetal movements	16 (6.3)	16 (9.1)	3 (3.4)	0.211
Elective	63 (24.8)*	57 (32.4)^	8 (9.2)*^	<0.001
Other	18 (7.1)	10 (5.7)	12 (13.8)	0.059
Bishop Score				
0-2	122/198 (61.6)	83/141 (58.9)	54/87 (59.4)	0.846
3-5	76/198 (38.4)	58/141 (41.1)	33/87 (37.9)	0.846
Birth weight, mean (±SD)	3484 (±507)	3487 (±489)	3473 (±440)	0.729

†Kruskal-Wallis-test
‡ one-way ANOVA

* or ^: statistically significant in bivariate analysis using (X2 test or Fisher's exact test when appropriate).

for induction was not equally distributed for fetal growth restriction (FGR) (Foley 3.1% vs misoprostol 6.1% vs PGE2 0%; p=0.033). However, these numbers did not differ in bivariate analyses between a Foley and oral misoprostol or Foley and PGE2. Also, "elective" as indication for IOL was not equally distributed, (24.8% vs 32.4% vs 9.2%; p=<0.001) but differed in the bivariate analysis only between a Foley and PGE2. Other indications were similar. Overall, obese women had a higher odds of a cesarean section compared to non-obese women (25.7% vs 18.2%, OR 1.56, 95% CI 1.24 - 1.96, p-value <0.001).

Primary outcomes

The maternal outcomes are presented in Table 2. The CS rate appeared higher in the group of obese women allocated to Foley catheter (74/154; 29.1%) compared the group allocated to oral misoprostol (39/176; 22.2%; RR 1.31; 95% CI 0.94-1.84) although statistical significance was not reached. Compared to PGE2 (20/87; 23%), no difference was found (RR 1.54; 95% CI 0.66-3.61). In the Foley group, more cesarean sections were performed for failed progress in the first stage of labor compared to the PGE2 group, being 16.5% versus 6.9%, respectively (RR 2.40; 95% CI 1.06-5.44). In the misoprostol group, this was 11.9%, Foley vs misoprostol RR 1.39, 95% CI 0.85-2.26.

A PPH occurred in 27 obese women (10.6%) assigned to a Foley catheter; in 20 women (11.4%) of the misoprostol group and in 6 women (6.9%) of the PGE2 group. These findings were non-significant (p=0.512). Obesity itself was not statistically associated with PPH rates compared to non-obese women, OR 1.25, 95% CI 0.90 – 1.74).

Table 2. Obstetric outcomes of different methods of cervical priming in women with obesity

	Foley catheter n=254 (%)	Misoprostol n=176 (%)	PGE2 n=87 (%)	*p*-value	*Foley vs misoprostol RR (95% CI; p-value)*	*Foley vs PGE2 RR (95% CI; p-value)*
Mode of birth						
Spontaneous	161 (63.4)	113 (64.2)	56 (64.4)	0.979	0.99 (0.85-1.14; 0.862)	0.99 (0.82-1.18; 0.869)
Vaginal assisted	19 (7.5)	24 (13.6)	11 (12.6)	0.093	0.54 (0.31-0.97; 0.036)	0.59 (0.29-1.19; 0.142)
Cesarean section	74 (29.1)	39 (22.2)	20 (23.0)	0.217	1.31 (0.94-1.84; 0.106)	1.27 (0.83-1.95; 0.268)
Indication vaginal assisted						
Failure to progress	8 (3.1)	10 (5.7)	3 (3.4)	0.404	0.55 (0.22-1.38; 0.197)	0.91 (0.25-3.37; 0.892)
Fetal distress	11 (4.3)	16 (9.1)	8 (9.2)	0.095	0.47 (0.22-1.00; 0.045)	0.47 (0.19-1.13; 0.88)
Other	1 (0.4)	0	0	0.595	n/a	n/a
Indication cesarean section						
Failure to progress	48 (18.9)	24 (13.6)	9 (10.3)	0.110	1.39 (0.88-2.18; 0.151)	1.82 (0.94-3.57; 0.065)
1st stage	42 (16.5)	21 (11.9)	6 (6.9)	0.059	1.39 (0.85-2.26; 0.184)	2.40 (1.06-5.44; 0.026)
2nd stage	6 (2.4)	3 (1.7)	3 (3.4)	0.676	1.39 (0.35-5.47; 0.639)	0.69 (0.18-2.68; 0.585)
Fetal distress	24 (9.4)	14 (8.0)	11 (12.6)	0.474	1.18 (0.63-2.23; 0.591)	0.75 (0.38-1.46; 0.397)
Other	2 (0.0)	1 (0.6)	0	0.706	1.39 (0.13-15.17; 0.788)	n/a
Postpartum hemorrhage	27 (10.6)	20 (11.4)	6 (6.9)	0.512	0.94 (0.54-1.61; 0.811)	1.54 (0.66-3.61; 0.309)
Time from start induction to vaginal birth in hours, median [IQR]	29 [17-40]	29 [18-50]	21 [12-37]	0.044[1]	n/a	n/a
Vaginal birth <24 hours	63/180 (35.0)	48/137 (35.0)	37/67 (55.2)	0.008	1.00 (0.74-1.35; 0.995)	0.63 (0.47-0.85; 0.004)
Vaginal birth <48 hours	141/180 (78.3)	100/137 (73.0)	57/67 (85.1)	0.144	1.07 (0.95-1.22; 0.270)	0.92 (0.81-1.04; 0.238)
Oxytocin (%)	220 (86.6)	132 (75.0)	58 (66.5)	<0.001	1.15 (1.05-1.27; 0.002)	1.30 (1.11-1.52; <0.001)
Epidural (%)	118 (46.5)	81 (46.0)	31 (35.6)	0.189	1.01 (0.82-1.24; 0.929	1.30 (0.96-1.78; 0.079)
Maternal death	0	0	0	n/a	n/a	n/a

[1]Kruskal-Wallis-test
n/a = not applicable

Secondary outcomes

For the comparisons between the IOL methods, obese women allocated to a Foley catheter had a longer duration from start of induction to a vaginal birth compared to the women allocated to PGE2. Also, a Foley catheter increased the use of oxytocin (86.6%) compared to both PGE2 (66,5%; RR 1.30; 95% CI: 1.11-1.52) and misoprostol (75%; RR 1.15; 95% CI 1.05-1.27). A vaginally assisted birth occurred less in obese women allocated to a Foley (n=19, 7.5%) compared to oral misoprostol (n=24;13.6%; RR 0.54; 95% CI 0.31 – 0.97). Compared to PGE2 (n=11; 12.6%), no statistical difference was found (0.59 (0.29-1.19; 0.142).

The use of epidural analgesics was not significantly different between the groups. For the neonatal outcomes, no differences were found between induction methods (see Table 3). No maternal deaths occurred in this subgroup. There were two neonatal deaths reported in the Foley group: one due to multiple congenital abnormalities, the other due to severe asphyxia.

In the obese group there was a change of induction method (registered as protocol violation) in the Foley catheter group in 51 cases (20.1%), which was significantly more compared to the misoprostol group (n=11; 6.3%) and the PGE2 group (n=1; 1.1%; p<0.001) In 21 of the 51 cases (41.2%) in the Foley catheter group, the reason was because of a failed placement. Among women who received a Foley catheter in the non-obese group, there was a change of induction method of 10.0% (96/957), in 31 cases (32.3%) this was because of failed placement of the Foley catheter (p-value < 0.001). Overall, in the obese group there was a failure placement of the Foley catheter 8.3% (51/254) compared to 3.2% in the non-obese group (31/957; aOR 3.12, 95% CI 1.65-5.90).

Table 3. Neonatal outcomes

	Foley catheter n=254 (%)	**Misoprostol n=176 (%)**	**PGE2 n=87 (%)**	***p*-value**	***Foley vs misoprostol RR (95% CI; p-value)***	***Foley vs PGE2 RR (95% CI; p-value)***
Apgar <7 after 5 minutes	7 (2.8)	4 (2.3)	1 (1.1)	0.688	1.21 (0.36-4.10; 0.750)	2.41 (0.30-19.29; 0.391)
pH in umbilical artery ≤7.05	6/184 (3.3)	3/134 (2.2)	1/67 (1.5)	0.701	1.45 (0.37-5.72; 0.857)	2.18 (0.27-17.82; 0.452)
NICU admission	8 (3.1)	5 (2.8)	1 (1.1)	0.606	1.11 (0.37-3.33; 0.854)	2.74 (0.35-21.60: 0.315)
Neonatal death	2 (0.8)	0	0	0.354	n/a	n/a

n/a = not applicable

Interaction analysis

The interaction analysis was performed on the whole dataset after multiple imputation of the missing BMI values. No statistically significant treatment effects were observed for the risk of CS or PPH, nor the presence of statistical interaction between randomization arm and obesity.

Studying BMI as a continuous log transformed variable yielded similar results, with a statistically significant increased estimated risk of CS for log BMI but not for PPH, without differences in CS or PPH risk between treatment modalities and the absence of statistical interaction between log-BMI and randomization arm (Table S1).

Table S1: Multivariate analysis

	p-value
Cesarean Section	
Interaction BMI ≥ 30 x misoprostol†	0.72
Interaction BMI ≥ 30 x PGE2†	0.38
Interaction log BMI x misoprostol‡	0.83
Interaction log BMI x PGE2‡	0.29
Post Partum Hemorrhage	
Interaction BMI ≥ 30 x misoprostol†	0.89
Interaction BMI ≥ 30 x PGE2†	0.11
Interaction log BMI x misoprostol‡	0.84
Interaction log BMI x PGE2‡	0.14

† Using BMI as a dichotomous variable with cut-off point 30

‡ Using BMI as a continuous variable after log-transformation

Discussion

In our secondary analysis of two combined randomized controlled trials, we found no statistical differences in CS and PPH rate between a Foley catheter, oral misoprostol and vaginal PGE2 in women with a BMI ≥ 30.0. One in five obese women (20.1%) allocated to a Foley catheter had a change of induction method, of which in 41% was because of failed placement of the Foley catheter. No differences were found in neonatal outcomes.

Although no significant difference in CS rate between a Foley catheter and oral misoprostol was found, the relatively high number (29.1%) of cesarean sections in obese woman allocated to a Foley catheter as compared to misoprostol (22.2%) might suggest this method to be less effective in this group of women.

Strengths and limitations

To our knowledge, this is the first article with data from randomized trials to compare three methods of cervical priming of obese women. This is also a large number of patients compared to existing trials with a total amount of 517 obese patients. BMI was a missing value in 9.7% of cases but for the interaction analysis we used multiple imputation for the missing data to study the interaction between BMI and priming method and adjusted for cohort effect. We used (log)BMI to create a parametric distribution and BMI was both analyzed as a dichotomous (cut-off point 30.0) as well as a continuous variable to study interaction.

This secondary analysis has some limitations. This was a secondary analysis, and randomization of the original trials was not stratified for BMI. Although the inclusion criteria of the two RCTs used were identical, still two cohorts from different time periods were merged for our analysis. One could argue that in the time between the two original cohorts were conducted, medical options and protocols could have improved, possibly contributing to different outcomes in the later conducted RCT. At the time the PROBAAT-II was conducted there was more experience and general use of mechanical induction with a Foley catheter compared to the time of the PROBAAT-I when the Foley catheter was used less often [20].

In this secondary (subgroup) analysis, there are some differences in baseline characteristics: in the misoprostol group more women were induced for FGR (6.1%), and elective indications (32.4%) compared to Foley (3.1% and 24.8%) and PGE2 (0 and 9.2%). In the bivariate analysis between Foley vs misoprostol and Foley vs PGE2, the difference for FGR was not statistically significant. In an earlier publication by our study group with a secondary (subgroup) analysis about inductions for FGR, it showed no significant difference in mode of birth between a Foley, misoprostol or PGE2 [21]. When the PROBAAT-I was conducted, the use of the Foley catheter was relatively new, hence we think selection bias could have played a role in a way that obstetricians were relatively careful including the women in the trial with a FGR as a vulnerable group. The difference between elective indications could be explained the PROBAAT-II was conducted 3 years later and the increase of IOL rates probably also led to more inductions for elective reasons.

Comparison with existing literature

The interesting finding was that one of five obese women allocated to a Foley catheter had a change of induction method, of which in 41% was because of failed placement of the Foley catheter. This number was two times higher compared to non-obese women, who had a change of induction method of 10.0%, 32% of which because of failed placement. After adjusting for study, parity and Bishop score, we found a threefold higher chance of failed placement in the obese group compared to the non-obese group (aOR 3.12, 95% CI 1.65-5.90). Two trials previously described failure of Foley catheter placement as a secondary outcome. An RCT by Anabusi et al. (n=181) compared mechanical induction with a double (Cook) vs single (Foley) balloon catheter amongst obese vs non-obese women and described “difficulty of placement” (it was not specified if this was failure of placement) as an outcome and found no significant difference of any balloon (both double and single) between obese vs non-obese women (80.9% vs 76.8%, p-value 0.55) [22]. A cohort study by Beckwith et al. (n=1502) compared priming of obese vs non-obese women with misoprostol 25ug vaginal every 4 hours vs Foley catheter plus Pitocin. Protocol deviation was low yet similar in the obese vs non-obese group, both 11% [23].

In studies comparing different induction methods in obese women the overall CS rates were high (26% up to 51.3%) and the results between methods of priming were diverse [23-27]. An RCT by Viteri et al. compared a transcervical Foley plus vaginal misoprostol to vaginal misoprostol alone in nulliparous obese women and found no difference in CS rates (Foley and PGE1 vs PGE1 alone: 45.1% vs 43.1%, RR 1.03, 95% CI 0.75-1.42, p-value 0.84) [26]. The CS rates were much higher with more than half of the cesareans (59/104) indicated by failed induction or failure to progress. The study protocol by Viteri et al. describes the balloon was removed after 12 hours after which further management was decided by the labor team; this was much shorter compared to 48h in the PROBAAT-trials and could perhaps have explained a quicker conclusion of a failed induction.

Beckwith et al. compared in their cohort study of 1502 women cervical priming with a Foley versus vaginal misoprostol in obese vs non obese women. They concluded that with the use of misoprostol obese women had a higher CS rate compared to non-obese women (35% vs 26%, p-value 0.03) and that with the use of Foley catheter CS rates were not significantly different between obese and non-obese women (31% vs 29%, p-value 0.69). They did not perform a comparison of Foley vs miso of obese women alone [23].

Suidan et al., a retrospective cohort of 564 women, compared IOL of obese women (BMI ≥ 30.0) with misoprostol (oral or vaginal administered) to dinoprostone and concluded misoprostol leads to a higher rate of successful cervical ripening and lower rates of CS (39.1% vs 51.3%, respectively. OR 0.61 95% CI 0.44-0.85). No difference was found between oral or vaginal administered misoprostol. Most CS were performed due to failed ripening (105/253), however, they did not describe after what duration of priming this decision was made [24].

Grange et al., a prospective and retrospective cohort study, n=92, compared IOL of obese women with a double-balloon catheter vs vaginal dinoprostone and concluded the double-balloon catheter to be more efficient than vaginal dinoprostone after 24h of priming in terms of a favorable cervix; however, the CS rate was high yet not significantly different (39.1% in both groups) [25]. Sarumi et al. compared dinoprostone (vaginal), misoprostol (oral and vaginal) and cervical catheters (both Cook and Foley) amongst obese and overweight nulliparous women and found a lower yet not significant CS rate in dinoprostone (dinoprostone 22.9%, misoprostol 33.3% and Foley/Cook catheter 32.0%, p-value 0.342), the OR was not described [27].

Conclusion

Although no significant differences in CS rate and PPH between induction methods were found in obese women, the preferred method of priming might lean less towards a Foley catheter as we found an increased risk of change of method and failed placement of the Foley catheter, which would make oral misoprostol possible more patient friendly. Also, the CS rate was relatively high in the group of women allocated to a Foley catheter compared to oral misoprostol, but without statistical significance.

Since there is little consensus in literature which method is most safe and effective in obese women, we would suggest future research to investigate the safest and most successful method of IOL for the growing group of obese pregnant women in order to minimize complications and cesarean section rate. This is especially important due to the fact that obesity is already a risk factor for perinatal complications and cesarean section in itself. Until then, we recommend to incorporate the increased risk of a failed placement in the shared decision making process for patients with obesity.

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5 Chapter

Induction of labor with Foley catheter and risk of subsequent preterm birth: follow-up study of two randomized controlled trials (PROBAAT-1 and -2)

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Abstract

Objective

To evaluate the rate of preterm birth (PTB) in a subsequent pregnancy in women who had undergone term induction using a Foley catheter compared with prostaglandins.

Methods

This was a follow-up study of two large randomized controlled trials (PROBAAT-1 and PROBAAT-2). In the original trials, women with a term singleton pregnancy with the fetus in cephalic presentation and with an indication for labor induction were randomized to receive either a 30-mL Foley catheter or prostaglandins (vaginal prostaglandin E2 in PROBAAT-1 and oral misoprostol in PROBAAT-2). Data on subsequent ongoing pregnancies > 16 weeks' gestation were collected from hospital charts from clinics participating in this follow-up study. The main outcome measure was preterm birth < 37 weeks' gestation in a subsequent pregnancy.

Results

Fourteen hospitals agreed to participate in this follow-up study. Of the 1142 eligible women, 572 had been allocated to induction of labor using a Foley catheter and 570 to induction of labor using prostaglandins. Of these, 162 (14%) were lost to follow-up. In total, 251 and 258 women had a known subsequent pregnancy > 16 weeks' gestation in the Foley catheter and prostaglandin groups, respectively. There were no differences in baseline characteristics between the groups. The overall rate of PTB in a subsequent pregnancy was 9/251 (3.6%) in the Foley catheter group vs 10/258 (3.9%) in the prostaglandin group (relative risk (RR), 0.93; 95% CI, 0.38–2.24), and the rate of spontaneous PTB was 5/251 (2.0%) vs 5/258 (1.9%) (RR, 1.03; 95% CI, 0.30–3.51).

Conclusion

In women with term singleton pregnancy, induction of labor using a 30-mL Foley catheter is not associated with an increased risk of PTB in a subsequent pregnancy, as compared to induction of labor using prostaglandins.

Introduction

Labor induction is a common obstetric procedure, which is generally carried out when the risk of continuing pregnancy outweighs the benefit. In the USA, approximately one in four women is induced and, in the last decade, the induction rate in the UK has risen to almost 30% [1,2].

Mechanical induction using a Foley catheter has gained popularity as it has a better safety profile compared to the conventionally used dinoprostone, reducing the risk of neonatal morbidity while being equally effective [3,4]. However, there is a hypothetical risk that the mechanical stretch of the cervix by the balloon can cause damage to the cervical tissue and, as a result, may affect the risk of preterm birth (PTB) in a subsequent pregnancy.

Cervical abnormalities, either congenital or as a result of trauma, are a risk factor for structural cervical weakness, which can lead to PTB. Known traumas associated with spontaneous PTB are mechanical cervical dilation during a gynecologic procedure and treatment of cervical intraepithelial neoplasia [5, 6]. It is unknown whether a balloon catheter for labor induction has a similar traumatizing effect on cervical integrity, which could lead to spontaneous PTB in a subsequent pregnancy. Studies examining the association between induction of labor using a balloon catheter and subsequent PTB are few and provide low-quality evidence, and no data from randomized controlled trials (RCTs) are available to answer the question of whether a balloon catheter increases the risk of PTB in a subsequent pregnancy [7-9].

Our previous PROBAAT trials, two large multicenter RCTs, showed that cervical ripening using a Foley catheter reduced the risk of fetal distress, as compared to cervical ripening using prostaglandin E2, whereas there was no difference in outcome when compared to cervical ripening using oral misoprostol. In both studies, no difference was seen in Cesarean section rate between the arms [3,10].

The aim of this study was to evaluate the rate of PTB in a subsequent pregnancy in women who had undergone term induction using a Foley catheter compared to prostaglandins, in order to assess the long-term safety outcome of Foley catheter induction, by performing a follow-up study of two RCTs.

Methods

We designed a follow-up study for the PROBAAT-1 and PROBAAT-2 trials. Both studies were multicenter RCTs, for which the full methods and results have been published elsewhere3, 10. In brief, the PROBAAT-1 trial randomized 819 women, between February 2009 and May 2010, to induction of labor using a 30-mL Foley catheter (n = 411) or vaginal prostaglandin E2 gel (n = 408). The PROBAAT-2 trial randomized 1845 women, between July 2012 and October 2013, to induction of labor using a 30-mL Foley catheter (n = 921) or oral misoprostol (n = 924).

In total, 27 hospitals collaborating in the Dutch Consortium for Healthcare Evaluation and Research in Obstetrics and Gynaecology (NVOG Consortium 2.0) participated in one or both of the PROBAAT trials. Both trials were approved by the Central Committee on Research Involving Human Subjects, by the ethics committee of the Academic Medical Center, Amsterdam, The Netherlands and by the board of directors of each participating hospital and were registered with the Dutch Trial Registry (NTR 1646 and NTR3466). The ethics committee judged that the Research Involving Human Subjects Act did not

apply to this retrospective follow-up study and therefore no further approval was required (date of approval 15 March 2018, ref. W18-098 #18.024). As data collection for this follow-up study was not prespecified in the original trial protocols, additional approval of data collection for the purpose of this follow-up study was obtained from the board of directors of each participating hospital.

Both PROBAAT trials included pregnant women scheduled for induction of labor beyond 37 weeks of gestation with a live singleton pregnancy with the fetus in cephalic presentation, intact membranes and an unfavorable cervix (Bishop score < 6). Women younger than 18 years of age and those with a previous Cesarean section, placenta previa, lethal fetal congenital anomaly or known hypersensitivity to one of the products used for induction were ineligible.

The pregnancy at the time of the PROBAAT trials was considered the index pregnancy. For this follow-up study, we included only women who had a subsequent ongoing pregnancy beyond 16 weeks' gestation after participation in one of the PROBAAT trials. In the subsequent pregnancy, gestational age was determined by first-trimester measurement of crown–rump length. No routine cervical length screening was performed, and progesterone was administered only when indicated according to local protocol. No further exclusion criteria were specified.

Details on randomization and interventions for each trial have been described previously3, 10. In short, after written informed consent was provided, women were allocated randomly to induction of labor using either a Foley catheter or prostaglandins by their attending physician, in a 1:1 ratio, using an online program.

In both studies, women allocated to induction using a Foley catheter had a 16-Fr or 18-Fr Foley catheter introduced through the cervix, either digitally or using a vaginal speculum. After the Foley catheter had passed the internal ostium, the balloon was filled with 30 mL of 0.9% saline or sterile water. The external end of the Foley catheter was taped to the inner thigh without traction. If the Bishop score remained < 6 after 24 h, the location of the Foley catheter was checked. When still in correct position, the Foley catheter was either left in place (PROBAAT-2) or replaced with a new one after 24 h (PROBAAT-1). If the Bishop score remained < 6 after 48 h, the catheter was replaced.

Women allocated to prostaglandin E2 (in PROBAAT-1) were treated mostly with a starting dose of 1 mg prostaglandin E2 gel, followed by 1 mg after 6 h, with a maximum of two doses per 24 h, inserted into the posterior vaginal fornix. An initial dose of 2 mg was allowed in nulliparous women, as prescribed by the manufacturer (Pfizer, New York, NY, USA). Women allocated to oral misoprostol (in PROBAAT-2) received 50 µg capsules once every 4 h for a maximum of three times daily.

In both trials, if the cervix was still unfavorable for amniotomy after 48 h of treatment, women were generally assigned a day of rest followed by another 48 h of induction.

For this follow-up study, the databases of both studies were combined, and study allocation was regrouped into Foley catheter or prostaglandins. To assess eligibility, electronic hospital records of women who participated in one of the PROBAAT trials were searched manually by the first and second authors. If a subsequent ongoing pregnancy after the index pregnancy had occurred, the required data for this study were collected. If it was not clear if there had been a subsequent pregnancy, the case

was classified as lost to follow-up. For women who had more than one subsequent, ongoing pregnancy, only the first was included. Missing data are noted in the tables. To eliminate the potential bias of an unknown history of mechanical dilatation before a surgical abortion or PTB, we also performed an analysis limited to women who had two consecutive pregnancies and were primigravid during the index pregnancy.

The main outcome of this follow-up study was PTB < 37 weeks' gestation in a subsequent pregnancy. Other outcomes were spontaneous PTB < 34 and < 37 weeks' gestation, gestational age at delivery, type of onset of labor, mode of delivery and birth weight in a subsequent pregnancy. For the outcome spontaneous PTB in a subsequent pregnancy, women with iatrogenic onset of labor (i.e. induction of labor or planned Cesarean section) or multiple pregnancy were excluded.

Data were analyzed on an intention-to-treat basis. Numerical variables were summarized as mean ± SD and analyzed using the t-test if the distribution was normal. When the distribution was skewed, they were summarized as median with interquartile range and analyzed using Mann–Whitney U-test. The $\chi 2$ test or Fisher's exact test was used to compare categorical variables. Treatment effect was presented as relative risk (RR) with 95% CI. A P-value of < 0.05 was considered to indicate statistical significance. Statistical analyses were performed using SPSS version 21.0 (IBM Corp., Armonk, NY, USA).

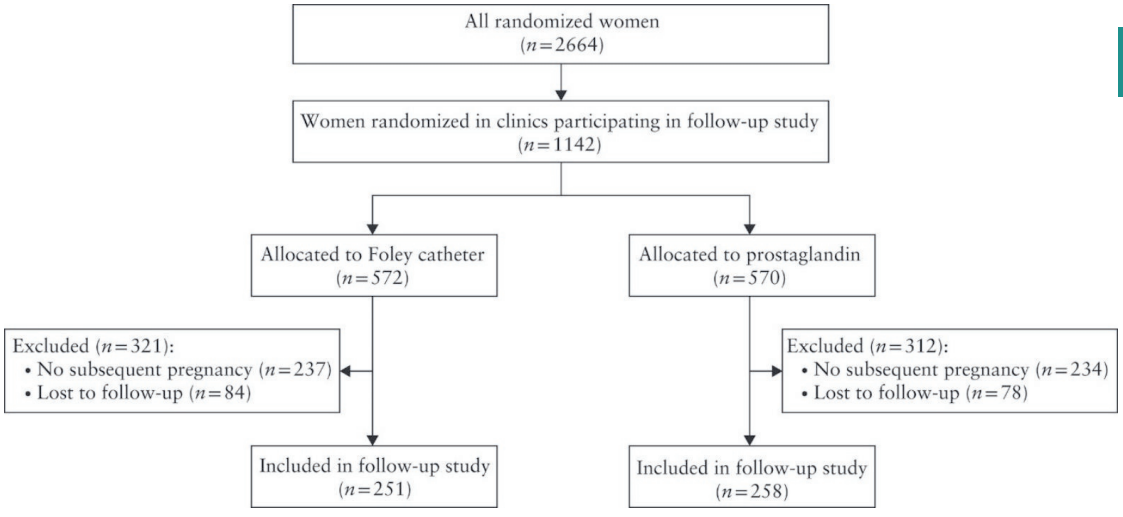

Figure 1: Flowchart summarizing inclusion in follow-up study of women randomized to induction of labor using Foley catheter or prostaglandin, who had subsequent pregnancy

Results

Of the 27 hospitals that participated in the PROBAAT trials, 14 agreed to participate in this follow-up study. The main reason for hospitals not participating in this follow-up study was the time-consuming process with no funding available to compensate the hospitals for their work. Data were collected between January 2018 and November 2018.

During the original trial periods, 2664 women were randomized in the PROBAAT trials, of whom 1142 were randomized in the 14 hospitals participating in the current study (Figure 1). The baseline characteristics of the women from clinics that participated in this follow-up study were comparable to those from clinics that did not participate, except for parity, the rate of which was slightly higher in women in the participating clinics (Table S1).

Of the 1142 women randomized in the 14 participating hospitals, 572 had been allocated to induction of labor using a Foley catheter and 570 to induction of labor using prostaglandins. Of these women, 237 (41%) and 234 (41%) did not have a subsequent, ongoing pregnancy, and 84 (15%) and 78 (14%) were lost to follow-up, respectively. We therefore included 251 women in the Foley catheter group and 258 women in the prostaglandin group (Figure 1).

Table 1 – baseline characteristics index pregnancy

	Foley catheter n=251	Prostaglandins n=258	*p*-value
Parity			0.465
nulliparous	204 (81%)	203 (79%)	
multiparous	47 (19%)	55 (21%)	
Body Mass Index	25[1] [22-28]	26[2] [22-29]	0.849†
Ethnic origin[3]			0.858
Caucasian	202 (84%)	208 (83%)	
Non-Caucasian	40 (16%)	43 (17%)	
Maternal age (years)	29 (±4.5)	30 (±4.4)	0.052‡
Mode of delivery in PROBAAT trial			0.181
Spontaneous delivery	164 (65%)	172 (67%)	
Assisted vaginal delivery	28 (11%)	42 (16%)	
Caesarean section	59 (24%)	44 (17%)	

Values are given as numbers , (%), mean (±SD) or median [IQR]. † Mann-Whitney-U test ‡ t-test
[1] 26 cases missing
[2] 34 cases missing
[3] 16 cases missing

Baseline characteristics of the women with a subsequent pregnancy after the PROBAAT studies are shown in Table 1. The groups were comparable with respect to age, body mass index at booking, ethnicity, parity and mode of delivery of the index pregnancy. For women who had an ongoing pregnancy prior to the index pregnancy, no information was available on whether they had a previous PTB. In the Foley catheter group, six women had a multiple gestation in the subsequent pregnancy,

compared with five in the prostaglandin group. There was no record of any of the included women receiving progesterone for prevention of PTB in the subsequent pregnancy.

Table 2 obstetrical outcomes subsequent pregnancy

	Foley catheter n=251	Prostaglandins n=258	RR (95%CI)	*p*-value
PTB (all women)	9 (3.6%)	10 (3.9%)	0.93 (0.38-2.24)	0.864
Spontaneous PTB[5]	5 (2.0%)	5 (1.9%)	1.03 (0.30-3.51)	0.965
Spontaneous PTB <34 weeks[5]	0	2 (1.0%)	na	0.256*
Gestational age (weeks +days)	39+5 [1] [38+5 – 41+0]	39+4[2] [38+2 – 40+5]	na	0.068†
Multiple pregnancy	6 (2.4%)	5 (1.9%)	1.23 (0.38-3.99)	0.726
Onset of labor[3]				
Spontaneous	105 (53%)	129 (57%)	0.93 (0.78-1.10)	0.372
Induction	68 (34%)	75 (33%)	1.03 (0.79-1.35)	0.830
Elective caesarean section	26 (13%)	22 (10%)	1.34 (0.77-2.29)	0.279
Mode of delivery[4]				
Spontaneous	190 (79%)	199 (82%)	0.96 (0.88-1.05)	0.401
Assisted	8 (3.0%)	5 (2.2%)	1.61 (0.54-4.86)	0.391
Caesarean section	44 (18%)	40 (16%)	1.11 (0.75-1.64)	0.602
Birth weight (grams)	3566 (±544)[3]	3530 (±511)[4]	na	0.501‡

Values are given as numbers (%), mean (±SD) or median [IQR]. † Mann-Whitney-U test ‡ t-test * Fisher's exact test
na = not applicable
[1] missing values: 33 **[2] missing values: 52**
[3] onset unknown: Foley: 52 – PGE: 32
[4] mode delivery unknown: Foley: 9 – PGE: 14
[5] singleton pregnancies only

No difference was found in the rate of PTB < 37 weeks' gestation in the subsequent pregnancy between the Foley catheter and prostaglandin groups (9/251 (3.6%) vs 10/258 (3.9%); RR, 0.93; 95% CI, 0.38–2.24). After excluding women with iatrogenic PTB and those with multiple pregnancy, the rate of PTB < 37 weeks in the subsequent pregnancy remained comparable between the groups, occurring in five women per group (2.0% vs 1.9%; RR, 1.03; 95% CI, 0.30–3.51). In the Foley catheter group, no woman had subsequent spontaneous PTB < 34 weeks' gestation, compared with two women in the prostaglandin group. No differences between the groups were found in gestational age at delivery, type of onset of labor, mode of delivery or neonatal birth weight in the subsequent pregnancy (Table 2)

Per protocol analysis of women who actually received their allocated treatment method did not affect the results. Eleven women allocated to Foley catheter were induced with prostaglandin, mainly because of failed placement. Four women allocated to prostaglandin received a Foley catheter at some point during the induction process. None of the women who had crossover of induction methods had PTB in the subsequent pregnancy. Post-hoc analysis of women with two consecutive singleton

pregnancies and who were primigravid during the index pregnancy, showed no difference in the rate of PTB < 37 weeks in the second pregnancy between the Foley catheter and prostaglandin groups (4/172 (2.3%) vs 2/143 (1.4%); RR, 1.66; 95% CI, 0.31–8.95). Analyzing separately oral misoprostol and prostaglandin E2 vs Foley catheter had no effect on the observed outcome.

Discussion

Main findings

The findings of this follow-up study of two RCTs comparing mechanical induction of labor using a Foley catheter to induction using prostaglandins, have shown that Foley catheter is not associated with an increased risk of PTB in the subsequent pregnancy.

Strengths and limitations

Our follow-up data were based on two large RCTs, which minimized the risk of bias for other, sometimes unknown, confounding factors. In these RCTs, baseline characteristics were similar between the groups, and the methods of induction were well-defined. Also, the fact that, in the control arms of both studies, women were induced by pharmacological methods, rather than having spontaneous onset of labor, allows comparison to a relevant control group, as the findings of some studies have suggested that spontaneous term birth up to 39 weeks' gestation could be associated with subsequent PTB [8,11]. However, some undetected bias could still be present. For instance, no information was available on whether mechanical cervical dilation during a gynecologic procedure or treatment of cervical intraepithelial neoplasia was performed in the period between the index pregnancy and subsequent pregnancy [5,6]. Also, no information was available on some other known factors associated with an increased risk of PTB, such as the interval between the index pregnancy and subsequent pregnancy, the incidence of PTB in a previous pregnancy before the index pregnancy or socioeconomic factors [12,13]. Despite the possible presence of confounders, the study design makes it likely that, if present, they are equally distributed between both groups.

In the 14 participating hospitals with 1142 included patients, of whom 509 had a known subsequent pregnancy, the loss-to-follow-up rate was 14%, which is generally accepted [14]. Since we only had access to hospital records, women with a low-risk subsequent pregnancy who had only midwife-led care might have been missed. However, the PTB rate in the lost to follow-up group is likely to be zero, because women with preterm labor are usually referred to the same hospital (regional referral system).

While we included 509 women, our study could be underpowered to detect a clinically relevant difference in the rate of PTB between the groups. For example, given the 3.9% rate of PTB < 37 weeks' gestation found in the prostaglandin group, a sample size of 1134 women would be required to detect a two-fold increase in PTB (power, 80%; alpha error, 5%). Moreover, the sample size had to be even higher for more clinically relevant cut-off points, such as PTB < 34 or < 32 weeks. However, this study did not show any trend towards a difference in the rate of PTB between the groups, and the a-priori risk of PTB in our population is very low.

Interpretation

Our findings are in line with those of other studies addressing the same research question [7-9]. Zafran and colleagues compared, in their cohort study of 366 women with two or more known pregnancies, term induction of labor using a balloon catheter (60-mL Foley catheter or Cook double balloon) with term induction using vaginal prostaglandin E2, as well as with spontaneous onset of labor and found no difference in the rate of spontaneous PTB < 37 weeks' gestation in a subsequent pregnancy (0.8% vs 0.9% vs 3.1%; P = 0.38). Sciscione and colleagues compared, in their cohort study of 126 women with two or more known pregnancies, term induction of labor using a 30-mL Foley catheter with applied traction to term induction using vaginal prostaglandin E2, and also found no difference in the rate of PTB < 37 weeks' gestation in a subsequent pregnancy (3.2% vs 4.7%; P = 0.53). Levine and colleagues also found no association between induction of labor using a Foley catheter, as compared with spontaneous onset of labor, and PTB in a subsequent pregnancy in their cohort of 887 women (adjusted odds ratio, 0.41; 95% CI, 0.15–1.12).

Although all of the above studies addressed the same research question, heterogeneity exists between studies with regard to the balloon volume and whether or not traction was applied. In our study, a 30-mL Foley catheter was placed above the internal ostium and used without traction. Looking at contributing factors for cervical weakness, it is reasonable to believe that using a larger balloon volume or a double Cook balloon, in which an 80-mL balloon is placed above and below the internal ostium, or applying traction, could have the potential to cause more cervical tissue damage and therefore have more effect on cervical integrity. However, such an association was not found by researchers who used these methods [7,9]. High-volume balloons, double balloons or applying traction are used to expedite labor. However, not all of these strategies have been proven to shorten this process. Although a double balloon or applying traction may shorten the period from start of induction to expulsion of the balloon, these approaches do not increase the number of vaginal deliveries within 24 h and have the disadvantage of causing more pain during the induction process [15-18].

In the present follow-up study, the PTB rate was 3.7%, which is low in comparison to the national PTB rate of 7.2% in The Netherlands [19]. This could be explained by the fact that women in this study had induction of labor at term in their index pregnancy and had a relatively low-risk pregnancy, which could influence the baseline risk of PTB in this specific population. This hypothesis is also supported by the comparable numbers of PTB in relatively similar populations. Baer and colleagues, in a Californian cohort of 133 662 women, found a PTB rate of 3.2% after a previous term birth between 39 and 42 weeks of gestation [20]. Furthermore, Zafran et al. and Sciscione and colleagues found relatively low numbers of PTB in the subsequent pregnancy after term induction using a Foley catheter (0.5% (spontaneous PTB) and 3.2%, respectively) [7,9]. Levine and colleagues are the only ones to report a PTB rate of 10% in a subsequent pregnancy after term labor induction. However, the spontaneous PTB rate was 6%, while in women induced with a Foley catheter, the spontaneous PTB rate was 4%.

Conclusion

In women with an unripe cervix scheduled for induction of labor, induction using a Foley catheter does not seem to increase the risk of PTB in a subsequent pregnancy, as compared with induction using prostaglandins.

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Chapter 6

General discussion and future use and research

General discussion

In pregnancies where labour is considered to be induced, the main goal is to achieve a vaginal birth in the safest way possible for the patient and the unborn child, preferable in a reasonable timeframe. However, the indications for induction of labour show a wide variety, ranging between upon request in a low-risk pregnancy to being of vital importance to prevent further deterioration of a severe obstetric or fetal illness. This makes it challenging to find a balance between safety and efficiency, but also to determine which risks are acceptable for each person in their specific situation. This dynamic makes it difficult to call one induction method superior to another in general, but challenges healthcare workers to customise information on the benefits and risks of different methods to the person in front of them during their consultations, so the most optimal method can be chosen in a shared decision process. This thesis provides additional knowledge on the short- and long-term safety aspects and effectiveness of a balloon catheter in comparison to other commonly used induction methods, in a general as well as is in different subgroup populations.

Neonatal safety

The less urgent the indication for induction of labour is, the more important it becomes to keep the risk of iatrogenic complications as low as possible. However, safety is sometimes a complicated issue in the care for pregnant people, as there are two persons to take into account. A major concern of labour induction is the risk of uterine hyperstimulation, which for the child can result in fetal distress and as a result, fetal hypoxia [1,2]. For the patient, uterine hyperstimulation can increase the risk of a caesarean section for suspected fetal distress and it is known to be a risk factor for a post-partum haemorrhage (PPH) [3].

In our systematic review with meta-analyses described in **chapter 2**, we found that compared to vaginal PGE2, a balloon catheter reduces the risk of outcomes that are associated with neonatal morbidity, being the risk of uterine hyperstimulation with fetal heart rate changes, pH <7.10 in the umbilic artery and fetal distress for which a caesarean section is required. These findings are in line with previous studies with the same objective [4-7]. However, even though all these studies found circumstantial evidence for a possible reduction of neonatal morbidity, none of these studies found direct evidence of an actual reduction of neonatal morbidity with the use of a balloon catheter compared to PGE2. So, in light of what was already known, our finding that induction with a balloon catheter reduces the risk of severe neonatal morbidity (defined as an composite outcome of neonatal seizures, birth asphyxia, neonatal encephalopathy or disability in childhood) by 50%, is an essential finding.

Although we were able to make a valid judgement on severe neonatal morbidity between a balloon catheter and PGE2, this outcome should still be interpreted with caution. Only a few studies in the meta-analyses, eight out of twenty-eight studies, reported on this composite outcome and even though there was no heterogeneity, a bias for this result could still exist. Also, most of the numbers within this composite outcome were cases of perinatal asphyxia, for which a definition was missing in most studies. In the literature, the definition of perinatal asphyxia also differs and has changed over time. The guidelines of the American Academy of Paediatrics (AAP) and the American College of Obstetrics and Gynaecology (ACOG) previously considered all of the following criteria in diagnosing asphyxia: (1) profound metabolic or mixed acidaemia (pH <7.00) in a umbilical artery blood sample, if

obtained, (2) persistence of an Apgar score of 0–3 for longer than 5 min, (3) neonatal neurologic sequelae (e.g., seizures, coma, hypotonia), and (5) multiple organ involvement (e.g., kidney, lungs, liver, heart, intestines) [8]. The definition of perinatal asphyxia by healthcare organisations has now changed to a condition of impaired gas exchange or inadequate blood flow that leads to persistent hypoxemia and hypercarbia that occurs in temporal proximity to labour (peripartum) and delivery (intrapartum) [9].

Despite these considerations, it is now evident that induction with a balloon catheter is superior compared to vaginal PGE2 as multiple safety outcomes are in favour of a balloon catheter and both methods being equally effective regarding caesarean section and a vaginal delivery not achieved within 24 hours. We therefore plead to abandon the use of vaginal PGE2 as a first-choice induction agent as more safe, effective and cheaper methods are available. Also, we advise to refrain from doing further research on induction of labour with vaginal PGE2 as the confidence intervals in our meta-analyses (**chapter 2**) suggest that more data on this subject will unlikely alter the outcome.

Beside that healthcare professionals and researchers should be aware of these findings, the presented evidence should also be pivotal for professional healthcare organisation and policymakers to decide which place vaginal PGE2 still has as a first choice induction method in their guidelines. To this date, vaginal PGE2 is still recommended as an induction agent and is still used in clinics worldwide [10-16]. However, the Dutch Society of Obstetrics and Gynaecology (NVOG) is one of the few healthcare organisation that does not recommend PGE2 anymore as first choice induction agent, but rather to use a Foley balloon catheter or low dose oral misoprostol [17]. Vaginal PGE2 is only mentioned as optional. Croll and colleagues found that this recommendation from the NVOG has been implemented successfully as after publication of the revisited guideline PGE2 is only used in Dutch hospitals if other induction methods failed and in none of the 66 hospitals who responded to their questionnaire, as a first choice method anymore [18].

What we experienced during the data-extraction process of our meta-analyses (**chapter 2**) and what we shortly describe above, is that many of our safety outcomes of interest were not reported in the included studies. We found the main focus of the studies to be on mode of birth and duration of time till delivery. For instance, many studies in our meta-analyses did not report on perinatal death. This could be because no deaths occurred. However, that would be interpretation and could not be verified, which meant that these numbers could not be included in our meta-analyses. We therefore advise that in study protocols on future research on induction of labour include the reporting on severe, low-incidence adverse outcomes. A tool which could help future researchers in designing their study are uniform core outcome sets [19]. Dos Santos and colleagues recently designed a core outcome set for induction of labour by using a Delphi method to reach consensus within an expert panel on which outcomes should be included [20]. A next step which could help future meta-analyses would be standardisation on how these outcomes are defined and how they are operationalised (categorical or numeric). We think stimulating or even mandate the use of core outcome sets in randomised controlled trials would make future meta-analyses more reliable and would contribute to early detection of differences in severe, low-incidence adverse outcomes.

The differences found in neonatal safety between a balloon catheter and vaginal PGE2 in a general population of pregnant people, was not seen in a small subgroup of persons who gave birth to SGA neonates (**chapter 3**), whom are known to be at risk of fetal distress, especially during induction of labour [21]. An explanation for this discrepancy could be the relatively small subgroup (n=64) who received vaginal PGE2 and were eligible for the subgroup analysis. However, in the same subgroup analysis, a composite outcome of neonatal safety, being Apgar score <7 after 5 minutes and/or NICU admission and/or pH <7.05, was in favour of a Foley balloon catheter (n=214) compared to low dose oral misoprostol (n=149). Also the individual components, Apgar score <7 after 5 minutes and NICU admissions appeared to be lower after the use of Foley balloon catheter compared to oral misoprostol. This in comparison to the general population in our meta-analyses (**chapter 2**), where the results of these individual components were too imprecise to make a valid judgement. The hypothesis for why in this relatively small subgroup these neonatal outcomes were significantly different and not in the relatively large pooled data from a general population, may be because the effect of uterine hyperstimulation on the fetal wellbeing might be more profound in pregnancies at risk of fetal distress, which is supported by the fact that the difference in adverse neonatal outcomes were even more profound in the subgroups of neonates with a birthweight <5th and <3rd percentile. However, we should acknowledge that the chosen outcomes are short-term outcomes and are not suitable to predict long term neonatal development impairment. For instance, an Apgar score is not interchangeable with perinatal asphyxia and is a poor predictor for individual adverse neurological development [22]. Nonetheless, we recommend a Foley balloon catheter as the first method of choice in case of suspected fetal growth restriction and/or an estimated fetal weight below the 10th percentile.

Efficiency and patient safety

Beside that induction methods should be safe, their main purpose is achieving a vaginal birth within an acceptable timeframe. In **Chapter 2** we found no differences in mode of birth between a balloon catheter and PGE2 for the outcome vaginal birth not achieved within 24 hours. However, between a balloon catheter and low dose oral misoprostol, we found that a balloon might increase the risk of a caesarean section and probably increases the risk of a vaginal birth not achieved within 24 hours. These data suggest that oral misoprostol might be more efficient compared to induction with a balloon catheter, but some issues have risen when analysing these data. We believe that an induction method is sometimes as effective as we let it to be. From previous studies we know the cervical ripening time with a balloon catheter can be prolonged compared to misoprostol or PGE2 within the first 24 hours [4,23,24]. So, rushing during this process instead of being patience during cervical ripening could lead to iatrogenic adverse outcomes, such as a failed induction or a caesarean section for failed progression in the first stage of labour. For instance, in our meta-analyses (**chapter 2**) there was a wide variety in maximum ripening time and definition of when induction was declared as failed. These numbers varied from 6 hours up to 96 hours. How the process was managed could have been of influence on the risk of a caesarean section between a balloon catheter and oral misoprostol. In the relatively large study of Mundle and colleagues included in our meta-analyses, there was a maximum priming duration of 12 hours when a balloon catheter was used compared to a maximum of 24 hours when oral misoprostol was used and showed an overall caesarean section rate of 50% [25]. In most studies, it was not known how long after oxytocin augmentation cervical changes were awaited upon before a caesarean section was performed for the indication of failure to progress. Especially after cervical ripening with a balloon catheter, it can sometimes take a prolonged period of time before the onset of active labour occurs [26,27]. We therefore recommend to healthcare professionals as well as to

healthcare organisations, to incorporate a clear definition of the onset of active labour after induction of labour and of failed induction in protocols and guidelines for patients without a previous caesarean section. In case of induced labour, we advise to speak of the onset of active labour ≥5cm dilatation [26]. Before that point is reached, we advise to wait a minimum of 15 hours start of oxytocin augmentation upon the transition to active labour before labelling induction as failed as multiple studies show this is an acceptable threshold between chances of achieving a vaginal birth and increasing risks such as PPH and chorioamnionitis [26,28,29].

As there might be a difference in effectiveness between induction methods in a general population, it would be interesting to know on how effective and safe induction methods are in pregnancies with an increased risk of a failed induction or a caesarean section for a failed progression, for instance in pregnant persons with obesity (BMI>30). Although there are studies on risk of induction of labour in people with obesity, till now there was a considerable lack of high-quality evidence regarding the most safe and effective methods in this specific subgroup. Although we found a relatively high caesarean section rate of 29% when a Foley balloon catheter was used (**chapter 4**), this was not statistically significant compared to oral misoprostol (22,2%) or vaginal PGE2 (23%). Also, a vaginal birth within 24 hours was comparable to oral misoprostol, but lower compared to vaginal PGE2.

Even though we found no difference in safety and effectiveness between a Foley balloon catheter, oral misoprostol and vaginal PGE2 in the subgroup of persons with obesity, an interesting finding was a significant higher number of protocol violations in the group of participants randomised to a Foley balloon catheter compared to oral misoprostol, as well as vaginal PGE2, these numbers being 20.1% versus 6.3% versus 1.1%, respectively. In almost half of all the cases of protocol violation in the balloon catheter group, this was because of a failed placement of the balloon. When compared to the subgroup of participants who were non-obese, we even found an OR of 3.12 (95% CI: 1.65-5.90) for a failed placement of the balloon. If this was an incidental finding or there really is a higher chance of a failed placement is not clear, nor the reason why the placements fail. A possibility could be experience in placing a Foley balloon catheter by the healthcare professionals, which was probably low during the studies period, and in which obesity could have been a difficulty factor. Observational studies could show some insight if this is still an issue in daily practice.

Even though the protocol violation could affect the outcomes observed, our findings reported in **chapter 4** are now the highest quality of evidence we have regarding safety and effectiveness of a Foley balloon catheter and oral misoprostol in people with obesity. We recommend to incorporate the increased risk of a failed placement for this subgroup in the shared decision making process. And because of this outcome and even though no differences in safety and efficiency were found, the preferred method might lean more towards oral misoprostol.

Another obstetrical safety outcome we looked at was the risk of preterm birth (PTB) in a subsequent pregnancy after the use of a Foley balloon catheter. In **chapter 5** we found that a Foley balloon catheter probably does not increase this presumed risk. Although we acknowledge that, with our sample size of 509 patients, this outcome is underpowered, this study is still important. In our data, with a risk of PTB in a consequent pregnancy of 3.7% in the Foley balloon group versus 3.9% in the PGE group, we didn't see any sign towards a possible difference. Also, the a priori risk of PTB was relatively low compared to the PTB rate of 7% in the overall Dutch population [30]. The publication of our follow up

data from a randomised controlled trial rejecting the hypothesis of a possible PTB risk could help with further implementation of induction with a balloon catheter worldwide. However, in our study we can only make a judgement on the 30cc Foley balloon catheter, applied without traction. Some clinics use high volume balloons (≥60cc), double balloons (Cook® or Atad®), or apply traction to expedite labour. When looking at contributing factors for cervical weakness, it is reasonable to believe a larger balloon volume, could have the potential to cause more cervical tissue damage and therefore have more effect on the cervical integrity, even though in small observational studies, these associations were not found [31-33]. Although a double balloon or applying traction may shorten the period from start induction to expulsion of the balloon, these approaches do not increase the number of vaginal births within 24 hours and have the disadvantage of causing more pain during the induction process [34-36]. With this in mind and because substantial advantages of high volume balloons and double balloons are lacking (**chapter 2**), we advise to use low volume (≤50cc) without traction for the induction of labour.

Implications for practice and future research

The studies reported in this thesis, additional to what was already known on the safety and effectiveness of a balloon catheter and oral misoprostol, show that both methods are safe and effective in a general population. However, each method has their own advantages and disadvantages. In this thesis we did not look at patient satisfaction, which is also an important subject, but just as with other outcomes, is not always generalisable. Because preference is personal, and one disadvantage could be less important to one person compared to another. This could be the reason that studies on patient satisfaction and preference between a balloon catheter and oral misoprostol seem to be inconclusive and even contradictory [37-41]. For instance, in the study of Ten Eikelder and colleagues and Druenne and colleagues, the persons who received a Balloon catheter preferred more often a different induction method in future induction of labour [38,39]. This in comparison to the study of Place and colleagues, where the persons who received a balloon catheter were more often satisfied with the labour induction method chosen for them and would select the same method in a next pregnancy more often compared to the persons who received misoprostol [40]. These studies have in common that they were done in a setting where the choice of an induction method was made by others, by the healthcare professionals or by randomisation, rather than by choice of the participant. More interesting it would be to know how satisfied people are with an induction method after a shared decision-making process, such was done in the study of Dupuis and colleagues [41]. What they found was that patients were equally satisfied with the method they chose, which could be a Foley balloon catheter, oral misoprostol or vaginal PGE2, and a factor which was associated with a higher satisfaction rate was adequate information. These results support our vision on giving honest evidence-based information on the induction process, safety and effectiveness of a certain method and why it is important to help patients choose a method based on what is important to them. Also, letting patients decide based on their personal preferences might contribute to a more positive birth experience, as autonomy during childbirth is an important aspect in achieving this [42].

Patient's preferences on induction of labour could also regard to the setting where this intervention takes place, for instance outside of the hospital. Especially induction with a Foley balloon catheter offers opportunities for outpatient induction because of the low risk of uterine hyperstimulation during the ripening period. Evidence available on safety of outpatient induction with a balloon catheter, even though being of low quality mainly because there is not enough data to make a valid judgement on rare adverse outcomes, show that cervical ripening in an outpatient setting is equally

safe compared to inpatient induction [43-46]. Besides it is safe, evidence suggest it could improve patient satisfaction and reduce hospital admission time which in present days is an important issue with maternity wards being over demanded in the Netherlands [45,47]. The opportunities that arise with further implementation of a balloon catheter for induction of labour worldwide might even be more profound in low-income countries were adequate monitoring during induction is not always optimal. Recently, the World Health Organisation (WHO) updated their recommendation on outpatient induction. It now state it's a reasonable option for patients who are considered to be at low risk for complications during induction to spend the priming period at home, following a shared decision-making between the provider and the patient and in the context of a well-organised programme with adequate staff resources available to remotely monitor patients at home [47]. Although the WHO speaks about home, an option could also be outpatient close by a hospital, which in low-and middle income countries could be optional if capacity problems is withholding healthcare workers to offer induction of labour to people when medical issues arise.

The last years outpatient induction has become common practice in the Netherlands [48]. However, studies on induction of labour in a shared healthcare model are sparse. One prospective observational study of 190 low risk patients induced for post term pregnancy (≤41 weeks) is available regarding a policy of a balloon placement in the hospital and rupturing the membranes by the community midwife and expective management of 24 hours afterwards [49]. This study showed that 33% of the participants actually gave birth under the care of their midwife, for primiparas this number was 23% and for multiparas 48%. No adverse events were reported. Although many participants still delivered in hospital care, a one in three chance could for some people be a reasonable opportunity. However, more research on a shared healthcare model and outpatient induction is warranted regarding safety, organisational issues (such as the availability of the healthcare system to respond adequately in case of referral or acute situations), and patient satisfaction. Also, on outpatient induction with a Foley balloon catheter but also with oral misoprostol, more data is needed to make a valid judgement on low prevalence adverse events, preferable in a RCT, but big observational studies could also contribute. However, observational studies, especially follow up studies are very often time consuming and expensive, with need for alignment of the definitions used. An option could be to incorporate the methods of induction as well as place of induction in birth registries, such as Perined, so safety data on outpatient induction could be evaluated faster and on a larger scale .

Another way to gain more insight in low-incidence adverse outcomes are meta-analyses. Unfortunately, practice learns that core variables are not always reported or not reported in a uniform matter. As a consequence, this decreases the amount of studies which can be included in a comparison and therefore can bias the results. Another form of meta-analyses which have gained popularity is performing a meta-analysis of randomised controlled trials with individual participant data (IPD) which can tackle some of these issues and gives far more insight and transparency in the imputed data and is considered to be the highest level of evidence. However, this process is time consuming, demands to overcome hurdles of legal and privacy regulations and ask for a culture in which authors are willing to make their anonymised datasets available for this purpose. To make this process more efficient and transparent, journals could be of influence if they mandate open access to the raw dataset and make them accessible on request for future IPD meta-analyses. Another benefit of such a mandate could be to help prevent plagiarism and ghost-studies to be published as this is an actual problem as we experienced with our meta-analyses (**Chapter 2**) for which a study was retracted [50, 51].

In the future, we hope that open science will be norm, but to make this possible, we have to restructure the whole system of conducting and publishing science. No more paywall articles with subscripted journals asking large fees which causes inequality in knowledge worldwide as it excludes students, professional or universities who cannot pay for access. Also, no more no high fees to for authors to publish open access for the work they have done themselves and was peer reviewed by members in the field for free. Not only access to science, but also sharing of science, promoting international collaboration so research questions and data can be placed in a broader perspective. Transparency will also lead to a smaller chance of fraud. First steps have been taken to stimulate this movement, for instance by funding organisations who are promoting or even demanding open science such as the Dutch Research Council (NWO) or broader, the UNESCO recommendations on open science [52-53].

Final conclusion

In a general population, labour can be safely and effectively induced with a Foley balloon catheter and low dose oral misoprostol. Both methods should be available in every clinic so patients can choose which method is optimal for them after adequate information tailored to the patient's characteristics. In case of a suspected fetal growth restriction information should contain that a Foley balloon catheter is possible safer for the neonate. People with a BMI ≥30 should know that a foley balloon catheter and oral misoprostol are equally efficient and safe, but there might be a higher chance of a failed balloon placement. We strongly advise to abandon the use of PGE2 because of the increased risk of severe neonatal morbidity and refrain from doing more research between a balloon catheter and PGE2 as the evidence on safety and effectiveness is conclusive. In a low-risk pregnancy, outpatient induction with a Foley balloon catheter seems defendable with the evidence on safety available, although more evidence is needed on low-incidence adverse outcomes. Future research could focus on outpatient induction with oral misoprostol and safety, efficiency and patient experience of outpatient induction, possibly in a shared healthcare model in collaboration with community midwives

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7 Chapter

Summary
Nederlandse samenvatting

Summary

The aim of this thesis was to further investigate obstetrical and perinatal safety outcomes of induction of labour with a balloon catheter in comparison to other induction agents in a general pregnant population as well as in specific subgroups of people. Answers generated in this thesis might help clinicians to further improve their induction policies and take a step forward towards a more tailormade approach in choosing, together with the patient and partner, the most optimal induction method.

Chapter 1 introduces a global overview of the history of induction of labour, the methods that are most commonly used worldwide, the working mechanisms of these methods and their potential advantages and disadvantages. Further we describe the aim of this thesis and our research questions.

In **Chapter 2,** we describe a systematic review and meta-analyses on the safety and of mechanical labour induction in comparison to different pharmacological methods. We included a total of 112 randomised controlled trials, with 104 studies contributing data involving 22,055 individuals. This review consists of 21 different comparisons (and 20 subgroup comparisons), where in most of the comparisons a mechanical method (balloon catheter, laminaria or extra-amniotic space infusion (EASI)) was compared to prostaglandin E2 (PGE2), misoprostol or oxytocin. We explored the combination of a mechanical method combined with a pharmacological method, as well as a single versus a double balloon.

Between induction of labour with a balloon catheter and vaginal PGE2, there may be little or no difference in vaginal deliveries not achieved within 24 hours (average risk ratio (RR) 1.01, 95% confidence interval (CI) 0.82 to 1.26; 7 studies; n=1685; I^2 = 79%; low-quality evidence) and there probably is no difference in caesarean sections between both methods (RR 1.00, 95% CI 0.92 to 1.09; 28 studies; n=6619; moderate-quality evidence). Compared to vaginal PGE2, a balloon catheter probably reduces the risk of uterine hyperstimulation with fetal heart rate (FHR) changes (RR 0.35, 95% CI 0.18 to 0.67; 6 studies; n=1966; moderate-quality evidence), serious neonatal morbidity or perinatal death (RR 0.48, 95% CI 0.25 to 0.93; 8 studies; n=2757; moderate-quality evidence). Between induction of labour with a balloon catheter and vaginal misoprostol, a balloon catheter probably reduces the risk of uterine hyperstimulation with FHR changes (RR 0.39, 95% CI 0.18 to 0.85; n=1322; 8 studies; moderate-quality evidence) but may increase the risk of a caesarean section (average RR 1.28, 95% CI 1.02 to 1.60; n=1756; 12 studies; I^2 = 45%; low-quality evidence). When compared to oral misoprostol, a balloon catheter probably increases the risk of a vaginal delivery not achieved within 24 hours (RR 1.28, 95% CI 1.13 to 1.46; n=782, 2 studies), and probably slightly increases the risk of a caesarean section (RR 1.17, 95% CI 1.04 to 1.32; n=3178; 7 studies; both moderate-quality evidence). We therefore concluded that a balloon is as effective as vaginal PGE2, but a balloon seems to have a more favourable safety profile. And with the evidence at hand, more research on this comparison does not seem warranted. A balloon also seems to have a better safety profile compared to vaginal misoprostol, but may be less effective. Although a balloon catheter may be slightly less effective compared to oral misoprostol, it remains unclear if there is a difference in safety outcomes for the neonate as the results were still too imprecise to make a valid judgement.

In 2023 we updated this review after retraction of one of the studies included within the comparison of a mechanical method combined with misoprostol compared to misoprostol alone. This retraction changed some of the outcomes of interest, being a reduction in meconium-stained liquor and NICU-admission in favour of a mechanical method combined with misoprostol to the numbers being too low to make a valid judgement on these outcomes.

Chapter 3 describes the result of a secondary analysis of a combined database of two previously published randomised controlled trials (the PROBAAT-1 and PROBAAT-2 trial) about the safety aspects of a 30cc-Foley balloon catheter, vaginal PGE2 and oral misoprostol in pregnancies with small-for-gestational-age neonates. A total of 425 patients with a term, singleton pregnancy in cephalic presentation with an indication for labour induction and a small-for-gestational-age neonate were included. Our primary outcome was a composed adverse neonatal outcome of Apgar score <7 after 5 minutes and/or a pH in the umbilical artery <7.05 and/or NICU admission. An adverse neonatal outcome occurred in 4.7% (10/214) after induction with a Foley catheter, versus 12.8% (19/149) after misoprostol (RR 0.36; 95% CI 0.17-0.76; *p*=0.005) and 4.7% (3/64) after Prostaglandin E2 (RR 0.98; 95%CI 0.28-3.51; *p*=0.996). For individual components of the composed outcome of adverse events, a difference was found between a Foley catheter and misoprostol for Apgar score <7 at 5 minutes (0.5% versus 3.4%; RR 0.14; 95%CI 0.02-1.16*; p*=0.043) and NICU admission (1.9% versus 6.1%; RR 0.31; 0.10-0.97; *p*=0.033). No differences were found for mode of birth. We therefore concluded that in pregnancies with a small-for-gestational-age neonate, a Foley catheter is probably a safer induction method compared to oral misoprostol. For PGE2, the numbers were too low to make a valid judgement compared to a Foley balloon catheter within this specific subgroup.

In **Chapter 4** we describe the results of another secondary analysis we performed on the PROBAAT-1 and PROBAAT-2 trials, on the effect of labour induction with a Foley balloon catheter, oral misoprostol or vaginal PGE2 in patients with obesity (BMI ≥30). Our primary outcomes were caesarean section and post-partum haemorrhage (PPH). A total of 517 patients with obesity and a term, singleton pregnancy in cephalic presentation with an indication for induction were included in this subgroup analysis. There were no significantly differences in caesarean section rates between a Foley balloon catheter (74/254; 29.1%), oral misoprostol (39/176; 22.2%) and vaginal PGE2 (20/87; 23.0%; *p*=0.217) or for PPH (10.6%, 11.4% and 6.9%, respectively; *p*=0.512). Protocol violation was higher in the Foley balloon group compared to oral misoprostol and vaginal PGE2 (20.1%, 6.3% and 1.1%, respectively; *p*=0.001), of which 41% was because of a failed placement. Further explored, in non-obese patients randomised for a Foley balloon, protocol violation was only 10% (p=<0.001). The risk of a failed placement was 8.3% in obese patients compared to 3.2% in non-obese patients (aOR3.12 95%; 165-5.90). We concluded that a Foley balloon catheter might be equally safe and effective in obese persons although a modest increase in caesarean section with the use of a Foley catheter compared to prostaglandins cannot be ruled out. Also, there might be an increased risk of a failed placement of the Foley balloon catheter in this specific subgroup.

In **Chapter 5** we explored the possible risk of preterm birth in a subsequent pregnancy after term induction with a 30cc Foley balloon catheter. For this purpose, we conducted a follow-up study of two previously published multicentred randomised controlled trials (PROBAAT-1 and PROBAAT-2) in which patients were randomised to either a 30cc Foley catheter or prostaglandins (Prostaglandin E2; PROBAAT 1 or oral misoprostol; PROBAAT 2). Hospital records of persons who participated in one the PROBAAT studies were screened on the presence of a subsequent pregnancy and in case of an ongoing

pregnancies > 16 weeks' gestation, were included in this follow-up study. The main outcome measure was preterm birth < 37 weeks' gestation in a subsequent pregnancy. Fourteen of the twenty-eight hospitals who participated in one or both of the PROBAAT- studies agreed to participate in this follow-up study. In total, 251 and 258 persons had a known subsequent pregnancy > 16 weeks' gestation in the Foley catheter and prostaglandin groups, respectively. The overall rate of preterm birth was 9/251 (3.6%) in the Foley catheter group versus 10/258 (3.9%) in the prostaglandin group (RR, 0.93; 95% CI, 0.38–2.24), and the rate of spontaneous preterm birth was 5/251 (2.0%) vs 5/258 (1.9%) (RR, 1.03; 95% CI, 0.30–3.51). We therefore concluded that induction of labour with a 30cc Foley catheter was not associated with an increased risk of preterm birth in a subsequent pregnancy.

In **Chapter 6** we discuss our findings in broader perspective in and in relation to what is already known in existing literature. From within this context, we made recommendations for practice and future research which are summarised in table 1

Table 1. Recommendations for practice and future research
1. Abandon the use of vaginal PGE2 as a first-choice induction agent as it increases the risk of severe adverse perinatal outcomes. As an alternative, we advise to use a Foley balloon catheter or low dose oral misoprostol instead, according to the preferences of the patient. Also, refrain from doing further research on induction of labour with vaginal PGE2 as more data on this subject will unlikely alter the outcome
2. When a balloon catheter is chosen, use a low volume (≤50cc) single balloon catheter without traction because substantial advantages of high volume balloons or double balloons are lacking. Also, a low volume balloon catheter does not appear to increase the risk of a preterm birth in a subsequent pregnancy
3. In protocols and guidelines on induction of labour with a balloon catheter, incorporate a clear definition of the onset of active labour and of failed induction. To lower the risk of a failed induction, we advise to speak of the onset of active labour ≥5cm dilatation. Before that point is reached, we advise to wait a minimum of 15 hours of oxytocin augmentation upon the transition to active labour before labelling induction as failed
4. A Foley balloon catheter is the first method of choice in case of an estimated fetal weight below the 10th percentile because of the more favourable safety profile of this method in this specific subgroup compared to oral misoprostol
5. Incorporate the possibility of an increased risk of a failed placement of a balloon catheter in the shared decision making process for people with obesity
6. Outpatient induction with a Foley balloon catheter seems defendable in low-risk pregnancies because of its favourable safety profile and the evidence on safety of outpatient induction available. However, more data is needed on low prevalence adverse outcomes, preferable in a RCT, but big observational studies could also contribute. Also, research could focus on outpatient induction with oral misoprostol and outpatient induction in a shared healthcare model in collaboration with community midwives
7. To make future meta-analyses more reliable, funding organisations could stimulate or even mandate the use of core outcome sets when funding randomised controlled trials as it could contribute to early detection of differences in severe, low-incidence adverse outcomes

Samenvatting

Hoofdstuk 1 geeft een globaal overzicht over inleiden van de baring over de jaren heen, de methoden die wereldwijd het meest worden gebruikt en de werkingsmechanismen van deze methoden met de potentiële voor- en nadelen. Verder beschrijven we het doel van dit proefschrift en de daarbij horende onderzoeksvragen.

In **hoofdstuk 2** worden de resultaten beschreven van een systematische review met meta-analyses over de effectiviteit en veiligheid van mechanisch inleiden in vergelijking met verschillende farmacologische methoden. In totaal werden 112 gerandomiseerde onderzoeken geïncludeerd, waarvan uit 104 studies met in totaal 22.055 personen data kon worden gebruikt voor de meta-analyses. Er werden 21 verschillende vergelijkingen gemaakt (en 20 subgroep vergelijkingen), waarbij in de meeste vergelijkingen een mechanische methode (ballon, hygroscopische dilatator of extra-amniotische-infusie (EASI)) werd vergeleken met prostaglandine E2 (PGE2), misoprostol of oxytocine. Daarnaast werd de combinatie van een mechanische methode met een farmacologische methode onderzocht, evenals een enkele versus een dubbele ballonkatheter.

Tussen inleiding van de bevalling met een ballonkatheter en vaginale PGE2 is er mogelijk geen verschil in het niet bereiken van een vaginale geboorte binnen 24 uur (relatief risico (RR) 1,01, 95% betrouwbaarheidsinterval (CI) 0,82 tot 1,26; 7 studies; n=1685; I^2 = 79%; bewijs van lage kwaliteit) en er is waarschijnlijk geen verschil in aantal keizersneden tussen beide methoden (RR 1,00, 95% BI 0,92 tot 1,09; 28 studies; n=6619; bewijs van matige kwaliteit). In vergelijking met vaginale PGE2 vermindert een ballonkatheter waarschijnlijk het risico op uteriene hyperstimulatie met cardiotocografie (CTG) afwijkingen (RR 0,35, 95% BI 0,18 tot 0,67; 6 studies; n=1966; bewijs van matige kwaliteit) en ernstige neonatale morbiditeit of perinatale sterfte (RR 0,48, 95% BI 0,25 tot 0,93; 8 studies; n=2757; bewijs van matige kwaliteit). Tussen inleiden van de bevalling met een ballonkatheter en vaginale misoprostol vermindert een ballonkatheter waarschijnlijk het risico op uteriene hyperstimulatie met CTG-afwijkingen (RR 0,39, 95% BI 0,18 tot 0,85; n=1322; 8 studies; bewijs van matige kwaliteit) maar kan mogelijk het risico op een keizersnede verhogen (RR 1,28, 95% BI 1,02 tot 1,60; n=1756; 12 studies; I^2 = 45%; bewijs van lage kwaliteit). In vergelijking met orale misoprostol verhoogt een ballonkatheter waarschijnlijk het risico op het niet bereiken van vaginale geboorte binnen 24 uur (RR 1,28, 95% BI 1,13 tot 1,46; n=782, 2 studies; bewijs van matige kwaliteit) en waarschijnlijk geeft een ballonkatheter een licht verhoogd risico op een keizersnede (RR 1,17, 95% BI 1,04 tot 1,32; n=3178; 7 studies; bewijs van matige kwaliteit). Op basis van deze uitkomsten concludeerden we dat een ballonkatheter net zo effectief is als vaginale PGE2, maar dat een ballonkatheter een gunstiger veiligheidsprofiel heeft. Kijkend naar sterkte van de bewijslast uit deze studie lijkt meer onderzoek naar deze vergelijking niet van toegevoegde waarde en daarom adviseren we geen verder onderzoek meer te doen naar deze vergelijking. Een ballonkatheter lijkt ook een gunstiger veiligheidsprofiel te hebben in vergelijking met vaginale misoprostol, maar kan mogelijk minder effectief zijn. Hoewel een ballonkatheter iets minder effectief lijkt in vergelijking met orale misoprostol, blijft het onduidelijk of er een verschil bestaat in veiligheid voor de pasgeborene, omdat de resultaten te onnauwkeurig waren om hierover een onderbouwd oordeel te geven.

Hoofdstuk 3 beschrijft het resultaat van een secundaire analyse uitgevoerd op een gecombineerde database van twee eerder gepubliceerde gerandomiseerde studies (PROBAAT-1 en PROBAAT-2 studie). In deze secundaire analyse is gekeken naar de veiligheidsaspecten van een 30cc Foley-

katheter, vaginale PGE2 en orale misoprostol bij zwangerschappen met een verdenking op foetale groeivertraging. In totaal werden 425 personen met een at terme éénling zwangerschap in hoofdligging met een indicatie voor het inleiden van de bevalling en waarbij er sprake was van een geboortegewicht <10^{e} percentiel (SGA neonaat) geïncludeerd. De primaire uitkomst was een samengestelde ongunstige neonatale uitkomst van een Apgar-score <7 na 5 minuten en/of een pH in de navelstrengarterie <7,05 en/of NICU-opname. Een ongunstige neonatale uitkomst trad op in 4,7% (10/214) na inleiding met een Foley-katheter, versus 12,8% (19/149) na orale misoprostol (RR 0,36; 95%CI 0,17-0,76; *p*=0,005) en in 4,7% (3/64) na Prostaglandine E2 (RR 0,98; 95%CI 0,28-3,51; *p*=0,996). Voor de individuele componenten van de samengestelde uitkomst werd een verschil gevonden tussen een Foley-katheter en misoprostol voor Apgar-score <7 na 5 minuten (0,5% versus 3,4%; RR 0,14; 95%CI 0,02-1,16*; p*= 0,043) en NICU-opname (1,9% versus 6,1%; RR 0,31; 0.10-0.97; *p*=0,033). Er werden geen verschillen gevonden in modus partus. We concludeerden daarom dat voor patiënten waarbij er een verwachte foetale groei <10^{e} percentiel is, een Foley-katheter waarschijnlijk een veiligere inleidingsmethode is in vergelijking met orale misoprostol. In vergelijking met PGE2 waren de groepen te klein om een onderbouwd oordeel te kunnen geven.

In **Hoofdstuk 4** beschrijven we de resultaten van een tweede secundaire analyse die we hebben uitgevoerd op de gecombineerde database van de PROBAAT-1 en PROBAAT-2-studies. In deze studie is gekeken naar het effect van Foley-katheter, orale misoprostol of vaginale PGE2 bij personen met obesitas (BMI ≥30). De primaire uitkomstmaten waren sectio caesarea en haemorrhagia post partum (HPP). In totaal werden 517 personen met obesitas en een a terme eenlingzwangerschap in hoofdligging met een indicatie voor inleiding geïncludeerd in deze subgroep analyse. Er waren geen significante verschillen in het percentage sectio caesarea tussen een Foley-katheter (74/254; 29,1%), orale misoprostol (39/176; 22,2%) en vaginale PGE2 (20/87; 23,0%; p=0,217) of voor HPP (10,6%, 11,4% en 6,9%, respectievelijk; p=0,512). Het percentage protocolviolation was hoger in de Foley-katheter groep in vergelijking met orale misoprostol en vaginale PGE2 (20,1%, 6,3% en 1,1%, respectievelijk; p=0,001), waarvan dit bij 41% te wijten was aan een mislukte plaatsing van de Foley-katheter. Het percentage protocolviolation bij niet-obese participanten die werden gerandomiseerd voor een Foley-katheter was slechts 10% (p=<0,001). Het risico op een mislukte Foley-katheter plaatsing was 8,3% bij personen met obesitas is vergelijking met 3,2% bij personen die geen obesitas hadden (aOR3.12 95%; 1,65-5,90). We concludeerden dat een Foley-katheter en orale misoprostol waarschijnlijk even veilig en effectief zijn bij personen met obesitas, maar dat er mogelijk een verhoogd risico is op een mislukte plaatsing van de Foley-katheter.

In **hoofdstuk 5** hebben we gekeken naar het mogelijke risico van een vroeggeboorte bij een volgende zwangerschap na inleiden van de bevalling met een 30cc Foley-katheter. Hiervoor hebben we een follow-up studie uitgevoerd van twee eerder gepubliceerde gerandomiseerde gecontroleerde studies (PROBAAT-1 en PROBAAT-2) waarin patiënten werden gerandomiseerd naar ofwel een 30cc Foley-katheter of prostaglandines (Prostaglandine E2; PROBAAT 1 of orale misoprostol; PROBAAT 2). Ziekenhuisdossiers van personen die deelnamen aan een van de PROBAAT-studies werden gescreend op de aanwezigheid van een opvolgende, doorgaande zwangerschap >16 weken zwangerschap en opgenomen in deze follow-up studie. De belangrijkste uitkomstmaat was vroeggeboorte <37 weken zwangerschap. Veertien van de achtentwintig ziekenhuizen die deelnamen aan één of beide PROBAAT-studies stemden in met deelname aan deze follow-up studie. In totaal hadden 251 en 258 personen een opvolgende zwangerschap >16 weken zwangerschap in de Foley-katheter groep en prostaglandine

groep, respectievelijk. De totale incidentie van vroeggeboorte was 9/251 (3,6%) in de Foley-katheter groep versus 10/258 (3,9%) in de prostaglandine groep (RR, 0,93; 95% CI, 0,38-2,24) en de incidentie van spontane vroeggeboorte was 5/251 (2,0%) versus 5/258 (1,9%) (RR, 1,03; 95% CI, 0,30-3,51). We concludeerden daarom dat inleiden van de bevalling met een Foley-katheter van 30cc niet gepaard gaat met een verhoogd risico op vroeggeboorte bij een volgende zwangerschap.

In de discussie in **hoofdstuk 6** plaatsten we onze bevindingen in een breder perspectief en in relatie met wat al bekend is in de bestaande literatuur. Hier vanuit zijn aanbevelingen gemaakt welke samengevat zijn in tabel 1.

Tabel 1. Aanbevelingen voor de praktijk en toekomstig onderzoek
1. Stop met het gebruik van vaginale PGE2 als een eerste keus inleidingsmethode gezien het verhoogde risico op ernstig nadelige perinatale uitkomsten. Als alternatief adviseren we het gebruik van een Foley-ballonkatheter of laag gedoseerde orale misoprostol, afhankelijk van de voorkeur van de patiënt. Daarnaast raden we af om verder onderzoek te doen naar inleiding van de bevalling met vaginale PGE2 omdat het onwaarschijnlijk is dat meer data de uitkomsten zullen veranderen.
2. Wanneer er voor een ballonkatheter wordt gekozen, gebruik dan een ballonkatheter met een laag volume (≤50cc) zonder tractie. Voor ballonnen met een hoog volume of voor dubbele ballonnen lijken er geen aanzienlijke voordelen te bestaan en voor een ballonkatheter met een laag volume is er bewijslast dat er geen verhoogd risico bestaat op een vroeggeboorte bij een volgende zwangerschap
3. Neem in protocollen en richtlijnen over inleiding van de bevalling met een ballonkatheter een duidelijke definitie op over start van de bevalling en een definitie van een mislukte inleiding. Om het risico op een mislukte inleiding te verlagen, adviseren we te spreken van de start van de bevalling bij ≥5cm ontsluiting. Voordat dit punt is bereikt, adviseren we om minimaal 15 uur na de start van oxytocine bijstimulatie te wachten op de transitie naar de start van de bevalling voordat de inleiding als mislukt wordt afgegeven.
4. Een Foley-ballonkatheter is de eerste keus inleidingsmethode als er sprake is van een geschat foetaal gewicht onder de 10^{e} percentiel gezien het gunstigere veiligheidsprofiel van deze methode in deze specifieke subgroep in vergelijking met orale misoprostol.
5. Neem het mogelijk verhoogd risico op een mislukte plaatsing van een ballonkatheter mee in de gezamenlijk besluitvorming bij personen met obesitas
6. Poliklinische inleiden met een ballonkatheter lijkt verdedigbaar in laagrisico zwangerschappen vanwege het gunstige veiligheidsprofiel en de beschikbare bewijslast over de veiligheid van poliklinisch inleiden. Desondanks is er meer onderzoek nodig naar weinig voorkomende ongunstige uitkomsten, bij voorkeur in een gerandomiseerde studie, maar grote observationele studies kunnen ook bijdragen. Verder zou toekomstig onderzoek zich kunnen richten op poliklinisch inleiden met orale misoprostol en poliklinische inleiden in een shared care model met eerstelijns verloskundigen.
7. Om toekomstige meta-analyses meer betrouwbaarder te maken kunnen financieringsorganisaties het gebruik van core-outcome-sets stimuleren of zelfs verplicht stellen bij de toekenning van financiering van gerandomiseerde studies omdat, dit kan bijdragen aan vroegtijdige opsporing van weinig voorkomende nadelige uitkomsten.

Chapter 8

List of publications
Curriculum vitae
Acknowledgements

Publications

This thesis:

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Presentations

Oral presentation **SMFM congress**: Does mechanical induction of labor increase the risk of preterm birth in a subsequent pregnancy. Las Vegas, 2019

Multiple **presentations** on national meetings including the annual meetings of Kennispoort and Nederlandse Vereniging voor obstetrie en Gynaecologie (NVOG).

Curriculum vitae

Marieke de Vaan is geboren op 3 maart 1982 in Haarsteeg, Na de middelbare school heeft zij MBO verpleegkunde gestudeerd aan de Koning Willem 1 college te Vught. Hierna is zij als verpleegkundige niveau 4 gaan werken in het Carolus Ziekenhuis in Den Bosch op de afdeling obstetrie waar zij de obstetrie en gynaecologie aantekening aan de Fontys Hogeschool te Eindhoven heeft behaald. Naast haar baan als O&G-verpleegkundige is zij de Bachelor opleiding tot verloskundige gestart aan de Katholieke Hogeschool Kempen in Turnhout, welke zij *cum laude* heeft behaald waarna zij is gaan werken binnen het Jeroen Bosch Ziekenhuis als klinisch verloskundige.

In 2012 is Marieke gestart met de opleiding tot Master Physician Assistant aan de Hogeschool in Rotterdam, welke zij in 2015 *cum laude* heeft afgerond. Naast haar baan als PA- klinisch verloskundige in het Jeroen Bosch Ziekenhuis heeft zij na het behalen van haar masteropleiding een aanstelling gekregen als hogeschooldocent binnen deze opleiding. Binnen deze functie coördineert zij het praktijkleren, begeleidt zij studenten met hun mastertheses en houdt zij zich bezig met onderwijsontwikkeling.

Marieke is naast haar baan als PA-klinisch verloskundige en Hogeschooldocent onderzoek gaan doen als buitenpromovenda aan de Universiteit van Utrecht binnen de PROBAAT-werkgroep. Vanaf 2018 werd zij hiervoor ondersteund met een promotiebeurs van de Nederlandse organisatie voor Wetenschappelijk Onderzoek (NWO).

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9 Chapter

supplemental information chapter 2