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Cervical Ripening in the Outpatient Setting

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Cervical Ripening in the Outpatient Setting

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None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

The information in this report is intended to help healthcare decision makers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of healthcare services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of evidence reports to assist public- and private-sector organizations in their efforts to improve healthcare quality in the United States.

The Patient-Centered Outcomes Research Institute (PCORI) funds comparative effectiveness research that can help patients and those who care for them make better informed decisions about their health care choices. PCORI partners with AHRQ to help fulfill PCORI's authorizing mandate to engage in evidence synthesis and make results of comparative effectiveness research available to patients and providers. PCORI identifies topics for review based on broad stakeholder interest. PCORI requested this report from AHRQ, which assigned this report to the Pacific Northwest EPC.

EPCs systematically review the relevant scientific literature on the assigned topic and conduct appropriate analyses when developing their reports. AHRQ encourages the EPCs to collaborate with a broad range of medical and research organizations to ensure that the evidence reports they produce will become building blocks for healthcare quality improvement throughout the Nation. The reports undergo peer review and public comment prior to their release.

EPC reports provide organizations with comprehensive, evidence-based information on common medical conditions and new healthcare technologies and strategies. They also identify research gaps in the selected scientific area, identify methodological and scientific weaknesses, suggest research needs, and move the field forward through an unbiased, evidence-based assessment of the available literature. Thus, EPC evidence reports may inform individual health plans, providers, and purchasers as well as the healthcare system as a whole by providing important information to help improve healthcare quality.

If you have comments on this evidence report, they may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 5600 Fishers Lane, Rockville, MD 20857, or by email to epc@ahrq.hhs.gov.

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Key Informants

In designing the study questions, the EPC consulted several Key Informants who represent the end-users of research. The EPC sought the Key Informant input on the priority areas for research and synthesis. Key Informants are not involved in the analysis of the evidence or the writing of the report. Therefore, in the end, study questions, design, methodological approaches, and/or conclusions do not necessarily represent the views of individual Key Informants.

Key Informants must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any conflicts of interest.

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In designing the study questions and methodology at the outset of this report, the EPC consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicted opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

Technical Experts must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

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Peer Reviewers

Prior to publication of the final evidence report, EPCs sought input from independent Peer Reviewers without financial conflicts of interest. However, the conclusions and synthesis of the scientific literature presented in this report do not necessarily represent the views of individual reviewers.

Peer Reviewers must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential nonfinancial conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential nonfinancial conflicts of interest identified.

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Cervical Ripening in the Outpatient Setting

Structured Abstract

Objectives. To assess the comparative effectiveness and potential harms of cervical ripening in the outpatient setting (vs. inpatient, vs. other outpatient intervention) and of fetal surveillance when a prostaglandin is used for cervical ripening.

Data sources. Electronic databases (Ovid® MEDLINE®, Embase®, CINAHL®, Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews) to July 2020; reference lists; and a Federal Register notice.

Review methods. Using predefined criteria and dual review, we selected randomized controlled trials (RCTs) and cohort studies of cervical ripening comparing prostaglandins and mechanical methods in outpatient versus inpatient settings; one outpatient method versus another (including placebo or expectant management); and different methods/protocols for fetal surveillance in cervical ripening using prostaglandins. When data from similar study designs, populations, and outcomes were available, random effects using profile likelihood meta-analyses were conducted. Inconsistency (using I^2) and small sample size bias (publication bias, if ≥10 studies) were assessed. Strength of evidence (SOE) was assessed. All review methods followed Agency for Healthcare Research and Quality Evidence-based Practice Center methods guidance.

Results. We included 30 RCTs and 10 cohort studies (73% fair quality) involving 9,618 women. The evidence is most applicable to women aged 25 to 30 years with singleton, vertex presentation and low-risk pregnancies. No studies on fetal surveillance were found. The frequency of cesarean delivery (2 RCTs, 4 cohort studies) or suspected neonatal sepsis (2 RCTs) was not significantly different using outpatient versus inpatient ***dinoprostone*** for cervical ripening (SOE: low). In comparisons of outpatient versus inpatient ***single-balloon catheters*** (3 RCTs, 2 cohort studies), differences between groups on cesarean delivery, birth trauma (e.g., cephalohematoma), and uterine infection were small and not statistically significant (SOE: low), and while shoulder dystocia occurred less frequently in the outpatient group (1 RCT; 3% vs. 11%), the difference was not statistically significant (SOE: low). In comparing ***outpatient catheters*** and ***inpatient dinoprostone*** (1 double-balloon and 1 single-balloon RCT)**,** the difference between groups for both cesarean delivery and postpartum hemorrhage was small and not statistically significant (SOE: low). Evidence on other outcomes in these comparisons and for ***misoprostol***, ***double-balloon catheters,*** and ***hygroscopic dilators*** was insufficient to draw conclusions.

In head to head comparisons in the outpatient setting, the frequency of cesarean delivery was not significantly different between 2.5 mg and 5 mg ***dinoprostone*** gel, or latex and silicone ***single-balloon catheters*** (1 RCT each, SOE: low). Differences between ***prostaglandins*** and placebo for cervical ripening were small and not significantly different for cesarean delivery (12 RCTs), shoulder dystocia (3 RCTs), or uterine infection (7 RCTs) (SOE: low). These findings did not change according to the specific ***prostaglandin,*** route of administration, study quality, or gestational age. Small, nonsignificant differences in the frequency of cesarean delivery (6 RCTs) and uterine infection (3 RCTs) were also found between ***dinoprostone*** and either membrane sweeping or expectant management (SOE: low). These findings did not change according to the specific prostaglandin or study quality. Evidence on other comparisons (e.g., single-balloon

catheter vs. dinoprostone) or other outcomes was insufficient. For all comparisons, there was insufficient evidence on other important outcomes such as perinatal mortality and time from admission to vaginal birth. Limitations of the evidence include the quantity, quality, and sample sizes of trials for specific interventions, particularly rare harm outcomes.

Conclusions. In women with low-risk pregnancies, the risk of cesarean delivery and fetal, neonatal, or maternal harms using either dinoprostone or single-balloon catheters was not significantly different for cervical ripening in the outpatient versus inpatient setting, and similar when compared with placebo, expectant management, or membrane sweeping in the outpatient setting. This evidence is low strength, and future studies are needed to confirm these findings.

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Evidence Summary

Main Points

- The highest strength of evidence for outcomes of outpatient cervical ripening found in this report was low, with several important outcomes having insufficient evidence. A rating of low-strength evidence means that there is low certainty in the magnitude or direction of the findings, and that future studies could change the conclusions.
- Low-strength evidence suggested that outpatient cervical ripening with dinoprostone (intravaginal insert or intracervical gel) or single-balloon catheters (30–50 ml fill) were not significantly different for cesarean delivery, fetal/neonatal infection with dinoprostone and maternal infection, birth trauma or shoulder dystocia with single-balloon catheters in comparison with the same intervention in the inpatient setting.
- Low-strength evidence suggested that cesarean delivery and postpartum hemorrhage were not significantly different between cervical ripening with catheters (double-balloon or single-balloon) in the outpatient setting and dinoprostone in the inpatient setting.
- The evidence on outpatient cervical ripening with misoprostol, double-balloon catheters, or hygroscopic dilators was insufficient.
- Low-strength evidence suggested that the risk of cesarean delivery with dinoprostone intracervical gel 2.5 mg versus 5.0 mg, and with silicone versus latex single-balloon catheters in the outpatient setting was not significantly different. Evidence was insufficient to draw conclusions on other outcomes or other direct comparisons of interventions.
- Low-strength evidence suggested that in the outpatient setting, the risk of cesarean delivery with prostaglandins was not significantly different than placebo, expectant management, and membrane sweeping. The incidence of meconium aspiration syndrome, shoulder dystocia, and uterine infection, primarily with dinoprostone, were not significantly different than placebo.
- There was no evidence comparing different mechanical methods with each other, with membrane sweeping or with expectant management in the outpatient setting.
- For all comparisons, there was insufficient evidence on time from admission to vaginal birth, perinatal mortality, fetal/neonatal intracranial or subgaleal hemorrhage, hypoxic-ischemic encephalopathy, and maternal hemorrhage requiring transfusion.
- Comparative evidence on fetal surveillance for cervical ripening with a prostaglandin was not found.

Background and Purpose

The purpose of this review is to assess the comparative effectiveness and potential harms of cervical ripening in the outpatient versus the inpatient setting. The intended audience includes the American College of Obstetricians and Gynecologists' guideline developers, clinicians who deliver neonates (e.g., obstetricians, nurse-midwives, family physicians), other personnel who administer and monitor cervical ripening, and health system policymakers. In addition to these clinical implications, we hope to inform the future research necessary to provide high-quality, evidence-based care to all pregnant women.

Methods

We employed methods consistent with those outlined in the Agency for Healthcare Research and Quality Evidence-based Practice Center Program methods guidance (https://effectivehealthcare.ahrq.gov/topics/cer-methods-guide/overview), and we describe these in the full report. Our searches covered publication dates up to July 2020.

Results

We included 40 mostly fair-quality studies (30 randomized controlled trials [RCTs], 10 cohort studies), with 9,618 women. The majority of the evidence (22 RCTs, 1 cohort study) pertained to the comparative effectiveness and harms of cervical ripening methods in the outpatient setting. Participants' mean age was 28.8 years, most were nulliparous, mean baseline Bishop score was 3.4, and gestational age was 40.6 weeks. Most studies excluded women with prior cesarean delivery, but few studies excluded women with diabetes or hypertension of any type. Post-term pregnancy was the most common reason for cervical ripening. Tables A–C summarize our findings; the full report provides more outcomes and details. If a prespecified, primary outcome is not listed in a table below that means that no study reported on that outcome (e.g., time from admission to vaginal delivery) or the evidence was insufficient to draw conclusions (i.e., due to imprecise estimates [too few patients or events], lack of corroborating evidence [a single study], and study limitations). The highest strength of evidence found for any outcome was low strength. No studies that met inclusion criteria were identified which addressed the comparative effectiveness and harms of fetal surveillance for cervical ripening with a prostaglandin in any setting.

Table A. Primary birth outcome: cesarean delivery

Key Question	Intervention	Findings[a]	Studies	Incidence	Relative Risk (95% CI) I^2 for Pooled Analyses[b]
Key Question 1: Prostaglandin Outpatient vs. Inpatient	Dinoprostone outpatient vs. inpatient	Low-strength evidence of little or no difference	2 RCTs (n=1,120)	23% vs. 23%	RR 0.97 (0.75 to 1.25)
	Dinoprostone outpatient vs. inpatient	Low-strength evidence of little or no difference	4 cohort studies (n=2,511)	33% vs. 33%	RR 0.79 (0.67 to 0.98)
Key Question 2: Mechanical Method Outpatient vs. Inpatient	Single-balloon catheter outpatient vs. inpatient	Low-strength evidence of a small, but nonsignificant, difference	3 RCTs (n=370)	12% vs. 20%	RR 0.59 (0.21 to 1.03)
	Single-balloon catheter outpatient vs. inpatient	Low-strength evidence of a small, but nonsignificant, difference	2 cohort studies (n=1,057)	33% vs. 30%	RR 0.95 (0.72 to 1.22)
	Outpatient catheter vs. inpatient dinoprostone	Low-strength evidence of a small, but nonsignificant, difference	2 RCTs (n=549)	33% vs. 26%	RR 1.24 (0.88 to 1.70)
Key Question 3: Outpatient Comparison of Methods	Dinoprostone gel 2.5 mg vs. 5.0 mg	Low-strength evidence of little or no difference	1 RCT (n=116)	20% vs. 19%	RR 1.07 (0.51 to 2.22)
	Prostaglandin vs. placebo	Low-strength evidence of a small, but nonsignificant, difference	12 RCTs (n=924)	16% vs. 21%	RR 0.80 (0.58 to 1.09), I^2=4.3%

Key Question	Intervention	Findings[a]	Studies	Incidence	Relative Risk (95% CI) I^2 for Pooled Analyses[b]
Key Question 3: Outpatient Comparison of Methods (continued)	Prostaglandin vs. expectant management	Low-strength evidence of little or no difference	4 RCTs (n=615)	27% vs. 26%	RR .95 (0.68 to 1.33)
	Dinoprostone vs. membrane sweeping	Low-strength evidence of a small, but nonsignificant, difference	3 RCTs (n=339)	22% vs. 15%	RR 1.44 (0.85 to 2.36)
	Silicone vs. latex single-balloon catheters	Low-strength evidence of little or no difference	1 RCT (n=534)	39% vs. 40%	RR 0.98 (0.80 to 1.22)

CI = confidence interval; RCT = randomized controlled trial; RR = relative risk

[a] Difference of < 5% = little or no difference; 5% to 10% = small difference; 11% to 20% = moderate difference; >20% = large difference.

[b] I^2=0% unless otherwise indicated.

Table B. Primary fetal harms outcomes

Key Question	Intervention	Outcome	Findings[a]	Studies	Incidence	Relative Risk (95% CI) I^2 for Pooled Analyses[b]
Key Question 1: Prostaglandin Outpatient vs. Inpatient	Dinoprostone outpatient vs. inpatient	Infection	Low-strength evidence of little or no difference	2 RCTs (n=1,120)	4% vs. 3%	RR 1.39 (0.67 to 3.03)
Key Question 2: Mechanical Method Outpatient vs. Inpatient	Single-balloon catheter outpatient vs. inpatient	Birth Trauma[c]	Low-strength evidence of little or no difference	1 RCT (n=129)	2% vs. 3%	RR 0.49 (0.05 to 5.30)
	Single-balloon catheter outpatient vs. inpatient	Shoulder dystocia	Low-strength evidence of a moderate, but nonsignificant, difference	1 RCT (n=129)	3% vs. 11%	RR 0.28 (0.06 to 1.30)
Key Question 3: Outpatient Comparison of Methods	Dinoprostone vs. placebo	Meconium Aspiration Syndrome[d]	Low-strength evidence of a small, but nonsignificant, difference	2 RCTs (n=134)	2% vs. 4%	RR 0.76 (0.03 to 22.33)
	Prostaglandins vs. placebo	Shoulder dystocia	Low-strength evidence of a small, but nonsignificant, difference	3 RCTs (n=270) 2 RCTs (n=150)	3% vs. 0.70% 6% vs. 1%	RD 0.01 (–0.02 to 0.04)[e] RR 3.40 (0.55 to 20.95)

CI = confidence interval; RCT = randomized controlled trial; RD = risk difference; RR = relative risk

[a] Difference of ≤1% = little or no difference; >1% to 3% = small difference; >3% to 8% = moderate difference; >8% = large difference

[b] I^2=0% unless otherwise indicated.

[c] There were 3 cases total (1 in the outpatient and 2 in the inpatient group) which included 1 case each of brachial plexus injury, cephalohematoma, and scalp laceration plus cephalohematoma; authors did not report which specific injuries occurred in which group)

[d] Neonatal intensive care unit admission required, not specified as the Syndrome

[e] RD analysis is presented because one RCT reported no events and would not be included in a RR analysis. Of note, one of the other two trials reported a higher proportion of neonates with shoulder dystocia in the dinoprostone group (7.0% vs. 2.1%), but there was also a difference in the proportion of neonates with birth weight >4000 gm in the dinoprostone group (33% vs. 15%).

Table C. Primary maternal harms outcomes

Key Question	Intervention	Outcome	Findings[a]	Studies	Incidence	Relative Risk (95% CI) I^2 for pooled analyses[b]
Key Question 2: Mechanical Method Outpatient vs. Inpatient	Single-balloon catheter outpatient vs. inpatient	Uterine Infection	Low-strength evidence of little or no difference	2 RCTs (n=259)	5% vs. 5%	RR 0.99 (0.31 to 3.19)
	Outpatient catheter vs. inpatient dinoprostone	Postpartum Hemorrhage	Low-strength evidence of a small, but nonsignificant, difference	2 RCTs (n=549)	28% vs. 25%	RR 1.10 (0.62 to 1.56)
Key Question 3: Outpatient Comparison of Methods	Prostaglandins vs. placebo	Uterine Infection	Low-strength evidence of a small, but nonsignificant, difference	7 RCTs (n=771)	7% vs. 10%	RR 0.75 (0.40 to 1.39)
	Prostaglandins vs. expected management	Uterine Infection	Low-strength evidence of little or no difference	1 RCT (n=294)	6% vs. 5%	RR 1.21 (0.45 to 3.24)
	Prostaglandins vs. membrane sweeping	Uterine Infection	Low-strength evidence of a small, but nonsignificant, difference	2 RCTs (n=269)	7% vs. 4%	RR 1.22 (0.56 to 2.75)

CI = confidence interval; RCT = randomized controlled trial; RR = relative risk

[a] Difference of ≤1% = little or no difference; >1% to 3% = small difference; >3% to 8% = moderate difference; >8% = large difference

[b] I^2=0% unless otherwise indicated.

Strengths and Limitations

The evidence comparing interventions in the outpatient and inpatient settings suffers from too few RCTs with too small of sample sizes (range 48 to 827; mean 172), particularly when assessing harms that are rare. Evidence quantity and quality is low for specific interventions. These are: (1) misoprostol and double-balloon catheters (comparing each in the outpatient versus inpatient settings), (2) direct comparisons of single- and double-balloon catheters and catheters versus prostaglandins, (3) hygroscopic dilators, and (4) the various formulations and routes of administration of dinoprostone or misoprostol. These studies enrolled narrowly defined populations and did not analyze effects in important subgroups such as women over 30 or 35, Group B Streptococcus (GBS) status, diabetes, hypertension, fetal growth restriction, and gestational age categories. The studies generally either excluded women with such characteristics or failed to report on them in detail. There was variation in outcome definition and reporting across the studies, with many reporting outcomes not defined as specified in the protocol for this review. Differences in rare harms, such as hypoxic-ischemic encephalopathy, would require much larger studies (i.e., statistical power) than are currently available.

Implications and Conclusions

This report can inform guidance for clinicians and pregnant women on the relative benefits and harms of outpatient cervical ripening. This report found low strength of evidence that outpatient cervical ripening with dinoprostone and single-balloon catheters does not impose increased risk of cesarean delivery. We also found no indications of important signals of increased risk of fetal/neonatal and maternal harms, although not all such harms were adequately studied. The evidence is most applicable to younger women with singleton, vertex presentation

pregnancies and low or no obstetric or medical risk factors. It does not identify the characteristics of pregnant women and fetuses that will benefit most or have the lowest risk of harm. There is evidence that women prefer, and were satisfied with, outpatient cervical ripening, although the decision-making process is complex. Filling the gaps in the evidence will require RCTs with sample sizes large enough to evaluate important harms; that evaluate important subgroups of the population; and study outpatient misoprostol, double-balloon catheters. Observational studies should be prospective and use appropriate methods to control for confounding and effect modification.

Introduction

Background

Induction of labor (IOL) is the process of initiating labor by using medications, mechanical methods (devices), or other techniques, with the goal of achieving vaginal birth with minimal risks.[1] IOL has shown maternal/child benefit when the health of a pregnant woman or fetus is at risk (e.g., maternal hypertension or diabetes, fetal growth restriction, and in postterm pregnancies).[2,3] In addition to these medically-indicated deliveries, IOL is also done on an elective basis; reasons include scheduling at the request of pregnant women or to ensure availability of appropriate providers.[4] A recent large randomized study of low-risk nulliparous pregnant women (the ARRIVE trial [A Randomized Trial of Induction Versus Expectant Management])[5] demonstrated that induction of labor at 39 weeks, compared with expectant management, resulted in lower cesarean delivery rates and no difference in neonatal outcomes.[2,3] IOL rates are rising dramatically in the United States, reaching 25.7 percent in 2017.[6] Labor induction occurs in approximately one-quarter of term pregnancies, with estimates of 77 to 85 percent due to medical indications.[7-9]

Cervical ripening, often an initial component of labor induction, is the process of softening and effacing the cervix as well as stimulating early cervical dilation. Based on data from trials of labor induction, approximately 83 to 85 percent of women with an indication for induction require cervical ripening.[10,11] Common cervical ripening methods include pharmacologic options, such as prostaglandins (prostaglandin E1, misoprostol, and prostaglandin E2, dinoprostone), and mechanical options, such as inserting a balloon catheter or hygroscopic dilator into the endocervix. See Appendix A for descriptions of commonly used interventions, including contraindications for their use.

Traditionally cervical ripening has been performed as an inpatient procedure, and while there is variation, it can require substantial time and resources to accomplish successfully due to multiple factors. While prostaglandins (vaginal or oral) and mechanical methods (e.g., balloon catheters) are the most commonly used methods of cervical ripening in the inpatient setting, there is institution and provider-level variation in the dose, administration route and frequency of administration. Some women's cervixes will rapidly respond to a cervical ripening intervention, while others require extended time with more than one intervention attempted if the first one fails. While interventions used for cervical ripening are generally not costly, the hospital inpatient resources used, including highly skilled labor and delivery staff, contribute to increased costs when cervical ripening care is provided in the inpatient setting.

For a variety of reasons, some women may prefer to be at home during the cervical ripening process, and because of the resources and variation involved, providers are also interested in exploring methods of cervical ripening in the outpatient setting that have minimal or no increased risk. Informed by these considerations, there is growing interest in, and evidence for, outpatient cervical ripening. It has been proposed that outpatient cervical ripening may facilitate more efficient and more satisfying IOL, also reducing inpatient length of stay compared to inpatient cervical ripening.

There are concerns regarding potential maternal/fetal risks of outpatient cervical ripening in comparison with the inpatient setting. These risks may be compounded by known and theoretical iatrogenic effects of medication and mechanical cervical stimulation. However, the risks of may be mitigated through the choice of cervical ripening method and clinical management. For example, prostaglandin use has been associated with tachysystole and fetal distress. Careful

review of existing literature is needed to elucidate whether these outcomes occur more frequently when cervical ripening is accomplished in the outpatient versus inpatient setting and whether they increase fetal or maternal morbidity. In addition, maternal or fetal characteristics may differentially affect these risks. Finally, understanding the range of feasible outpatient cervical ripening options, and what form of fetal surveillance should be used (if any), is an important aspect of this review.

A woman's preferences and satisfaction related to the setting of cervical ripening also need to be considered. Some may actively seek outpatient cervical ripening and others may strongly prefer inpatient cervical ripening. This likely variation in preferences and satisfaction has been identified as an important contextual question of this review.

Despite potential cost saving and sometimes strong personal preferences favoring outpatient cervical ripening, this approach to care is still debated. Controversy is driven by interpretation of risk, clinician's discipline and experience (e.g., obstetrician vs. midwife),[12,13] and geographical practice variation. Clinician and institutional risk-aversion driven by potential legal litigation is also a consideration. The 2009 American College of Obstetricians and Gynecologists (ACOG) Practice Bulletin on induction of labor summarized evidence on cervical ripening in the outpatient setting, based on only two studies available at that time (one on a prostaglandin, one on a single-balloon catheter),[14] ultimately not reaching a recommendation. A 2017 Cochrane review found that evidence on outpatient versus inpatient cervical ripening was insufficient to address differences in maternal and fetal/neonatal health outcomes, such as cesarean delivery, between settings.[15] This review included only randomized controlled trials, and included interventions not available in the United States, or that are used primarily to stimulate or maintain contractions rather than primarily for cervical ripening. Many cervical ripening studies have been conducted in non-U.S. settings, where patient acceptance and understanding of risk may be different, in addition to variation in provider philosophy and health system resources. There is a need to assess the benefits of outpatient versus inpatient cervical ripening, without increasing risk (rise in cesarean delivery rate, adverse neonatal outcomes), framed within considerations of cost, patient autotomy, and satisfaction. This is the crux of the decisional dilemma. When cervical ripening is indicated, what methods can be recommended as effective, but with no increased risks, in the outpatient setting and what surveillance best serves women induced with prostaglandin in the outpatient setting?

Purpose and Scope of the Systematic Review

This systematic review assessed the comparative effectiveness and potential harms of cervical ripening in the outpatient versus the inpatient setting, comparison of benefits and harms of different methods of cervical ripening in the outpatient setting, and evidence on benefits and harms of fetal surveillance during labor when a prostaglandin was used for cervical ripening in any setting. The intended audience includes the ACOG's guideline developers, practitioners who deliver infants (e.g., obstetricians, family physicians, nurse-midwives), other personnel who administer and monitor cervical ripening, and health system policymakers. In addition to these clinical implications, we hope to inform the future research necessary to provide high-quality, evidence-based care to all pregnant women.

Methods

Review Approach

The methods for this systematic review followed the Agency for Healthcare Research and Quality (AHRQ) Methods Guide for Effectiveness and Comparative Effectiveness Reviews (available at https://effectivehealthcare.ahrq.gov/topics/cer-methods-guide/overview). This systematic review reports in accordance with the Preferred Items for Reporting in Systematic Reviews and Meta-Analyses (PRISMA).[16]

Key Questions

An initial set of Key Questions (KQs) and a Contextual Question were posted on the AHRQ Effective Health Care (EHC) Program website for public input from May 10 to May 30, 2019, prior to the initiation of this review, and a public stakeholder webinar was held by the Patient-Centered Outcomes Research Institute (PCORI). Changes to the KQs based on public comment include expanding defined subgroups and removing specific brand names for mechanical devices. Subsequently, a group of Key Informants and a separate group of Technical Experts Panel (TEP), including representatives of American College of Obstetricians and Gynecologists' (ACOG) guideline group, provided comments on the scope of the review. The following KQss and inclusion criteria reflect suggestions received and are in the final protocol. The final protocol was posted on the EHC website on January 16, 2020 (https://effectivehealthcare.ahrq.gov/products/cervical-ripening/protocol) and submitted to PROSPERO for registration (ID CRD42020167406).

KQ 1: How do the effectiveness and harms of cervical ripening using prostaglandins compare in the outpatient versus inpatient setting?

1a: How do effectiveness and harms vary by choice of prostaglandin?

1b: Do effectiveness and harms vary by important patient characteristics (gestational age, parity, uncomplicated pregnancy, prior cesarean delivery, etc.)?

KQ 2: How do the effectiveness and harms of cervical ripening using mechanical methods (e.g., balloon catheters) compare in the outpatient versus inpatient setting?

2a: How do effectiveness and harms vary by choice of mechanical method in the inpatient versus the outpatient setting?

2b: Do effectiveness and harms vary by important patient characteristics (gestational age, parity, uncomplicated pregnancy, prior cesarean delivery, etc.)?

KQ 3: How do the effectiveness and harms of cervical ripening in the *outpatient setting* vary by method of cervical ripening compared with each other, placebo, or expectant management?

3a: Do effectiveness and harms vary by important patient characteristics (gestational age, parity, uncomplicated pregnancy, prior cesarean delivery, etc.)?

KQ 4: How do the effectiveness and harms of different methods and protocols for fetal surveillance compare with each other or with no monitoring in pregnant women undergoing cervical ripening with prostaglandins in any setting?

4a. Do effectiveness and harms vary by important patient characteristics (gestational age, parity, uncomplicated pregnancy, prior cesarean delivery, etc.)?

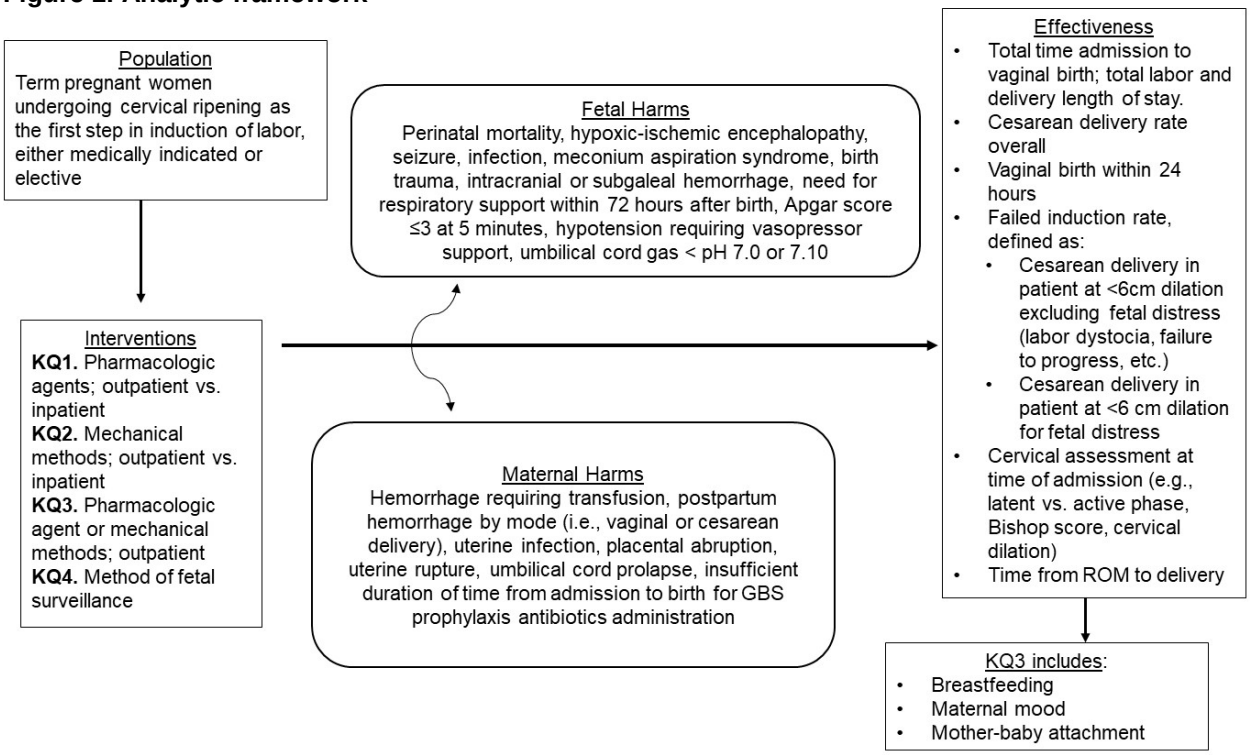
Contextual Question: What evidence informs preference for or satisfaction with different methods of cervical ripening in the outpatient setting or outpatient compared to the inpatient setting?

The Contextual Question is addressed in the Discussion chapter of this report.

Analytic Framework

The analytic framework (Figure 1) illustrates the population, interventions, outcomes, and adverse effects that guided the literature search and synthesis.

Figure 1. Analytic framework



GBS = Group B Streptococcus; KQ = Key Question; ROM = rupture of membrane

Study Selection

We searched Ovid® MEDLINE®, Embase®, CINAHL®, Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews from database inception to July 2020 to identify studies eligible for this review, according to the criteria listed in Table 1 for eligible populations, interventions, comparisons, and outcomes. We included randomized controlled trials (RCTs) and comparative cohort studies or case-control studies that attempted to control for potential confounding. In our protocol, we indicated that we would include only observational studies with more than 200 women enrolled, if inadequate evidence was found in RCT evidence for primary outcomes on any KQ. We ultimately decided to remove the sample size threshold due to limited evidence and all abstracts of previously excluded observational studies were subsequently re-reviewed. We excluded interventions not available in the United States and outcomes not listed. While we initially planned to exclude women with contraindications to outpatient cervical ripening, specifically multiple pregnancy, prior uterine rupture, and breech presentation of the fetus, we ultimately included a few studies that did enroll women with twin pregnancies and with breech presentation fetuses. A Federal Register notice requesting Supplemental Evidence and Data for Systematic review (SEADS) did not result in any new evidence being identified. We used dual review to select studies. Full details on review methods, including complete search strategies, can be found in the Methods Appendix B.

Table 1. Criteria for population, intervention, comparison, and outcomes of eligible studies[a,b]

PICO	Inclusion Key Question 1: Prostaglandin Outpatient Vs. Inpatient
Population	Pregnant women ≥37 weeks undergoing cervical ripening
Interventions and Comparisons	KQ 1 and 3: Pharmacologic agents (prostaglandins) KQ 2 and 3: Mechanical methods (single- and double-balloon catheters, dilators) KQ 1 and 2: The comparison is setting (inpatient versus outpatient) KQ 3: The comparison is different methods in the outpatient setting KQ 4: Any method of fetal surveillance during cervical ripening with a prostaglandin compared with another method/protocol, or no monitoring, in any setting.
Outcomes, Birth-related	**Primary[a]: total time from admission to vaginal birth; total labor and delivery length of stay;** and **cesarean delivery rate overall[c]** Secondary: Vaginal birth within 24 hours; Failed induction, defined as cesarean delivery in patient at <6cm dilation: 1) for fetal distress, and 2) excluding fetal distress (e.g., labor dystocia); Cervical assessment at time of admission; Time from ROM to delivery. In addition, for KQ 3, breastfeeding, maternal mood, and mother-baby attachment
Outcomes. Fetal/Neonate Harms	**Primary[a]: Perinatal Mortality; Hypoxic-ischemic encephalopathy; Seizure; Infection** (confirmed sepsis or pneumonia); **Meconium aspiration syndrome**; **Birth trauma** (e.g., bone fracture); and **Intracranial or subgaleal hemorrhage** Secondary: Respiratory support within 72 hours of birth; Apgar score ≤3 at 5 minutes[a]; Hypotension requiring vasopressor support; and Umbilical cord gas < pH 7.0 or 7.10
Outcomes. Maternal Harms	**Primary[a]: Hemorrhage requiring transfusion; Postpartum hemorrhage by mode** (vaginal, cesarean delivery); **Uterine infection** (i.e., chorioamnionitis) Secondary: Placental abruption; Uterine rupture; Umbilical cord prolapse; and Inadequate time for GBS prophylaxis antibiotics

GBS = Group B Streptococcus; KQ = Key Question; PICO = population, interventions,comparisons, outcomes; ROM = rupture of membrane

[a] **(Bolded) items indicate Primary Outcomes**

[b] See Appendix A for descriptions of interventions

[c] Reduced rate is the desired direction of this outcome

Data Extraction and Risk of Bias Assessment

Data were abstracted from included studies into evidence tables, including study and patient characteristics and study results, with data verified for accuracy and completeness by a second

team member. The risk of bias of included studies was assessed according to established methods,[17,18] with RCTs assessed based on criteria established in the *Cochrane Handbook for Systematic Reviews of Interventions*,[19,20] and cohort studies evaluated using criteria developed by the U.S. Preventive Services Task Force.[21] Based on the risk of bias assessment. Individual included studies were rated as being "good," "fair," or "poor" quality.

Data Synthesis and Analysis

We analyzed the evidence according to Key Question, using both narrative (qualitative) and quantitative (meta-analysis) methods (where possible). In both approaches, we grouped the drugs (KQs 1 and 3) by type of prostaglandin (prostaglandin E1 [PGE1], misoprostol, versus prostaglandin E2 [PGE2], dinoprostone). We evaluated any variation in results according to the dose, formulation, or route within those categories using qualitative synthesis, as there were too few studies to conduct subgroup or sensitivity analyses on these factors. For the mechanical methods (KQs 2 and 3), we evaluated single- and double-balloon catheters separate from hygroscopic dilators, and evaluated variation by type of catheter (single- versus double-balloon). We conducted meta-analysis on the prioritized (primary) outcomes noted in Table 1 above, when there were at least two studies reporting the same outcome, within the intervention groups described here. Identification of the primary outcomes was done with input from our Technical Expert Panel (TEP), partner (ACOG), and sponsor (PCORI) of this report. For the outcome of cesarean delivery, a positive effect would be to reduce, or at least not increase, the incidence. Secondary outcomes were only pooled if there were at least three studies available. Profile-likelihood random effects models were used for meta-analysis,[22] with heterogeneity assessed using both the χ^2 test and the I-squared (I^2) statistic.[23] Small study effects (potential publication bias) was analyzed using Funnel plots and the Egger test where there were at least 10 studies combined in meta-analyses. For dichotomous outcomes, we calculated relative risks and 95% confidence intervals. We calculated relative risks rather than absolute risk differences (and 95% CI) to account for variation in the underlying risk for the outcome in different study populations. To give the clearest picture, we present both the absolute incidence and change in each group, alongside the RR (95% CI). However, to narratively describe the comparisons, we described the magnitude of absolute differences in the following terms. For cesarean delivery, a difference of less than 5% was "little or no difference", differences of 5% to 10% "small difference", 11% to 20%, "moderate difference", and greater than 20%, "large difference". For harm outcomes, a difference of 1% or less was "little or no difference", differences of >1% to 3% "small difference", >% to 8%, "moderate difference", and greater than 8%, "large difference". For this assessment, incidences were rounded. We established these thresholds using expert opinion and consensus. We are not certain that these thresholds translate directly into clinically meaningful differences. They are an attempt to provide a framework for interpretation of the findings.

Our a priori plan for subgroup analysis included the population characteristics laid out in the subquestions of the Key Questions above. Important maternal subgroups: parity, maternal age, Group B Streptococcus (GBS) status, diabetes (pregestational, gestational), hypertension (chronic, preeclampsia without severe features, gestational). Important fetal subgroups: fetal growth restriction, gestational age (<39 weeks, 39 to 41 weeks, >41 weeks), though only a few subgroup analyses were conducted given the limited data. We assessed applicability based on the source of potential study participants, number of women randomized relative to the number of

women enrolled, and characteristics of the population, intervention (including process details), and care setting.

Grading the Strength of the Body of Evidence

The strength of evidence (SOE) of primary outcome-intervention pairs were evaluated using the AHRQ methods.[24] For example, the SOE on the risk for cesarean delivery with dinoprostone (PGE2) compared with placebo in the outpatient setting was evaluated separately to the evidence on this population, intervention and setting with misoprostol (PGE1). Details on the methods used are presented in the Methods Appendix B and primary outcomes are those bolded in Table 1, above. We note that where there was both RCTs and observational study evidence, we evaluated these separately and used the observational study evidence to supplement the RCT evidence in order to come to a final rating. Additionally, for bodies of evidence with only a single study, we rated consistency as unknown (rather than not applicable). In these cases, we did not automatically downgrade the evidence to "insufficient" but considered the sample size or number of events available for analysis.

Results

Description of Included Evidence

Searches identified 10,853 references, from which 698 articles were selected for full-text review after dual review of abstracts. Following dual review of full-text of these articles, 40 unique studies (in 43 publications)[25-67] that addressed a Key Question were included. Thirty randomized controlled trials (RCTs) and 10 cohort studies were included, evaluating 9,618 women. The majority of the evidence pertained to Key Question 3 comparing interventions in the outpatient setting (22 RCTs, 1 cohort study). The Key Questions comparing cervical ripening in the inpatient and outpatient setting included eight RCTs (2 for Key Question 1 on prostaglandins and 6 for Key Question 2 on mechanical methods) and all nine cohort studies (6 for Key Question 1 and 3 for Key Question 2). We did not identify any studies eligible for Key Question 4, addressing fetal surveillance during labor when a prostaglandin was used for cervical ripening in any setting. Four studies were rated good quality, 29 fair quality, and 7 poor quality. In addition, eight studies were identified to help address the Contextual Question (CQ).[68-75] A flow diagram of the search results and selection of studies and a list of included studies can be found in Appendix C and D, respectively.

The characteristics of women enrolled in the included studies are summarized in Table 2, below, and more detailed information by study in Appendix C, Table C-2. Participants' weighted mean age was 28.8 years and weighted body mass index (BMI) was 26.7. BMI was reported in only 18% of studies (6 RCTs[26,34,40,48,52,53] and 1 cohort study)[61], and the timing of measurement was not reported. Race was reported in 33% of studies. While more than half included mostly white women (64% to 84%), three included mostly African American women (61% to 88%), and one included mostly Latino women (96%). The majority of participants were nulliparous (65%); only five studies reported mean parity (weighted mean 0.25). Most studies (65%) excluded women with prior cesarean delivery, one RCT limited recruitment to women with prior vaginal birth[40] while another RCT only recruited women with prior cesarean delivery.[54] Relatively few studies excluded women with preexisting diabetes (13%), gestational diabetes (10%), chronic hypertension (18%), or gestational hypertension (20%), hence a small proportion of women enrolled had gestational diabetes (GDM, 6%), though one RCT reported 69 percent of participants had GDM.[45] Postterm pregnancy was the most frequently reported reason for cervical ripening (61% of all participants). Weighted mean Bishop score at baseline was 3.4 and mean gestational age (GA) was 40.6 weeks. Details of the interventions used in each study can be found in Appendix C, Tables C-3 to C-5. Most studies were conducted in the United States (60%), and less than half (45%) reported funding source; a nonprofit organization was the most prevalent source of funding for those that did report the source (50%). Evidence Tables of study and patient population characteristics and study results for each individual study can be found in Appendix E. In addition, supplemental forest plots, risk of bias assessments for individual studies, strength of evidence summary tables, a list of excluded studies with reason for exclusion, and a reference list for the Appendixes can be found in Appendix F, G, H, I, and J, respectively."

Table 2. Baseline characteristics of women enrolled in included studies

Weighted Means	KQ 1 RCTs	KQ 1 Cohort Studies	KQ 2 RCTs	KQ 2 Cohort Studies	KQ 3 RCTs	KQ 3 Cohort Studies
Number of studies	2	6	6	3	22	1
N population	1127	3963	1214	1142	2741	153
N range	300–827	76–1343	48–695	42–615	49–534	NA
N mean	564	661	202	381	125	NA
Age (years)	28.2	30.5	29.8	24.2	26.1	30.5
Race, nonwhite (n studies)	NR	43.1% (2)	41.4% (3)	NR	63.7% (8)	NR
BMI (kg/m^2)	NR	25.8	27.3	NR	28.5	NR
Parity	NR	0.23	NR	0.5	0.81	NR
Bishop score (0 to 13)	4[a]	3.3	2.9	NR	3.6	NR
Gestational age (weeks)	NR[b]	41.2	40.5	40.3	40.1	NR[c]
Nulliparous	68.6%	79.1%	62.6%	54.4%	51.8%	64.7%
Prior cesarean delivery	0%	0%	6.3%[d]	15.7%[d]	35.4%[e]	0%
Elective IOL	10.1%	0.6%	24.0%	3.3%	43.6%	2%
Postterm IOL	83.6%	72.3%	57.5%	51.8%	32.8%	84.3%
Medically-indicated IOL	4.6%	26.6%	18.1%	39.5%	21.1%	13.1%

BMI = body mass index; IOL = induction of labor; KQ = Key Question; RCT = randomized controlled trial; NA = not applicable; NR = not reported

[a] Only 1 study reported the median Bishop score at baseline

[b] One RCT reported mean 40.71 weeks, the other RCT reported median 40.14 weeks

[c] Gestational age was ≥41 weeks in 80% and 37–40 weeks in 20% of women.

[d] Based on only one study. All other studies did not report percentage of participants with cesarean delivery or excluded them.

[e] Based on three trials that included participants with prior cesarean delivery. Twelve other trials excluded participants with prior cesarean delivery.

Results are organized by Key Question and then by comparison. For Key Question 1 and Key Question 3, we refer to the prostaglandins as dinoprostone (prostaglandin E2 [PGE2]) and misoprostol (prostaglandin E1 [PGE1]). Outcomes are reported in the following order: birth outcomes, fetal/neonate harms outcomes, and maternal harms outcomes, with primary outcomes of interest within each category listed first followed by any secondary outcomes reported. The strength of the evidence (SOE) is reported for primary outcomes, but not assessed for secondary outcomes; findings from secondary outcomes are presented here to give additional insights into the evidence. In many cases the outcomes of interest were not reported as specified for this report. For example, for the prioritized primary outcome of time from admission to vaginal birth, many studies reported only time from admission to delivery by any mode. We included such related outcomes for completeness when the authors reported them, but they did not contribute to the conclusions (i.e., SOE). Outcomes that were not reported are not listed or noted below; if a prespecified outcome does not appear within a section that means that no study reported on that outcome.

Our rule for reporting percentages in the text of the report was to report the percent per group as a whole number, except if the incidence was ≤1 percent in either group, when we report two decimal places and the n/N for each group. Information on subgroups, if available, is reported where relevant by outcome. No RCT data were available to evaluate differential effectiveness or harms (i.e., effect modification) for subgroups specified in our protocol for any Key Question. The study characteristics and results are summarized in the sections below, and detailed individual study results can be found in Appendix E-2.

Key Question 1. Prostaglandins for Cervical Ripening in Outpatient Versus Inpatient Setting

Key Points

- Based on 2 RCTs and 1 cohort study, there was little to no difference in the frequency of cesarean delivery for outpatient versus inpatient cervical ripening using ***dinoprostone*** (SOE: low).
- Based on 2 RCTs, the frequency of fetal/neonatal infection was low overall, with little to no difference between outpatient versus inpatient cervical ripening using ***dinoprostone*** (SOE: low).
- Evidence on ***misoprostol*** was insufficient to draw conclusions, based on 1 small (n=273) cohort study.

Summary of Findings

Two fair-quality RCTs[27,66] involving 1,122 women, one conducted in Canada and the other in Australia, compared outpatient versus inpatient dinoprostone use for cervical ripening (Appendix E). Funding was government in one,[66] and multiple sources in the other.[27] Six cohort studies compared prostaglandin use for cervical ripening in the outpatient versus inpatient setting; five[25,30,32,55,61] assessed dinoprostone (N=3,690, with two studies having an overlap of 793 women in their study populations, out of 1,343 in one and 1,179 in the other[30,55]), and one (N=273) assessed misoprostol.[29] For meta-analyses and SOE assessments, only the larger of the two studies with overlapping data were considered.[55] One cohort study of dinoprostone was rated poor quality due to concerns over patient selection, dissimilarity in baseline patient characteristics without control for confounding, questions on attrition (see Appendix G). The other cohort studies were fair quality. Three cohort studies did not report their source of funding;[25,29,61] two were industry funded,[30,55] and one received support from a variety of sources.[32] Two of the cohort studies were performed in the United States,[29,32] one in the United Kingdom,[61] and three in Canada.[25,30,55] Results of these studies are presented below.

Dinoprostone (PGE2)

Two fair-quality RCTs (N=1,127) compared outpatient versus inpatient dinoprostone for cervical ripening.[27,66] In one trial,[27] a single dose of intravaginal controlled release dinoprostone insert 10 mg was administered. In the other trial,[66] nulliparous women received 2 mg and multiparous women received 1 mg intravaginal dinoprostone gel. Only 51 percent of those randomized received an initial dose of dinoprostone, and of these, 30 percent required a second dose and 6 percent required a third dose. In the outpatient groups, women were monitored for 40 to 60 minutes following dinoprostone insertion, and returned for reassessment after 12 hours (or the next morning). In one trial, women had telephone assessment every four hours, and nonstress testing at the followup visit.[27] Women assigned to the inpatient group had monitoring that mirrored the outpatient protocols.

Both trials enrolled women with uncomplicated singleton term pregnancies, with cephalic presenting fetuses and excluded women with a uterine scar as well as those with fetal growth restriction, preeclampsia, or rupture of membrane (ROM). Other exclusions varied between trials; exclusion criteria in one trial were modified halfway through to exclude women with a BMI >35 and those with diet-controlled diabetes.[66] Neither trial reported mean BMI. The

weighted mean patient age was 28 years, and the weighted mean gestational age was 40 weeks. Median baseline Bishop score was 4 for both outpatients and inpatients in one trial[27] (the other trial did not report baseline Bishop score).[66] Sixty-nine percent of women were nulliparous. Reasons for induction included postterm pregnancy (not defined) in 84 percent, elective/social in 10 percent (1 trial),[66] medical necessity in 3.6 percent (1 trial),[27] and other in 3.3 percent of women (2 trials).[27,66] Characteristics of enrolled women are in Appendix E-1.

Five retrospective cohort studies compared outpatient and inpatient dinoprostone use for cervical ripening.[25,30,32,55,61] The two overlapping fair-quality studies investigated intravaginal, controlled release 10 mg dinoprostone inserts,[30,55] and the other studies evaluated dinoprostone gel: one fair-quality study used 1 mg intravaginally[61] and the other two used the gel intracervically (a fair-quality study[32] used 0.5 mg and a poor-quality study[25] used 2 mg). In one large cohort study, only 59 percent (597/907) completed in-home cervical ripening.[61] Except for one cohort study[32] where a single dose was used, additional doses were given as determined at the followup visits (criteria for administering addition doses not provided). All included women carrying singleton, vertex presenting fetuses and while all excluded women with prior uterine surgery, exclusions across studies varied. Three excluded women with ROM, and two excluded women with medical or fetal risk factors (e.g., hypertension). The two cohort studies with overlapping populations[30,55] differed in their inclusion criteria, with the more recent study including only women who presented for induction for postterm pregnancy or premature rupture of membrane (PROM).[30] Continuous fetal heart rate (FHR) monitoring was done for 30 minutes[61] to 1 hour[30,32,55] post dinoprostone insertion; one study reported a maximum of 2 hours of monitoring.[25] Across four studies, the weighted mean age was 31 years[25,30,32,61] and mean gestational age was 41 weeks, while a fifth study (N=1,343)[55] reported that 54 percent of women had a gestational age between 37 and 41 weeks and 46 percent had a gestational age >41 weeks. The weighted mean Bishop score at baseline was 3.9 (3 studies) and 55 percent of women were nulliparous (3 studies). Reason for induction was postterm pregnancy in 72 percent, elective in 0.6 percent (2 studies), and medical necessity in 27 percent of women (4 studies). Postterm pregnancy was defined as >41 weeks (2 studies), between 41 weeks and 3 days and 42 weeks (1 study), and not defined in two studies. Only one study reported BMI (mean 25.8 kg/m^2).[61] Characteristics of enrolled women are in Appendix E-1.

The only primary birth outcome reported was cesarean delivery, which was found to be not significantly different between outpatient and inpatient use (SOE: low). Fetal, neonatal, and maternal harms appeared to be rare across included studies but were poorly reported; studies generally did not report on most of our prespecified outcomes. The frequencies of fetal/neonatal infection (not confirmed) (SOE: low), hypoxic-ischemic encephalopathy, meconium aspiration (not specified as the syndrome) and postpartum hemorrhage requiring transfusion (SOE: insufficient) were not significantly different for outpatients and inpatients. However, individual study sample sizes were likely too small detect differences in rare events.

Birth Outcomes

Cesarean Delivery

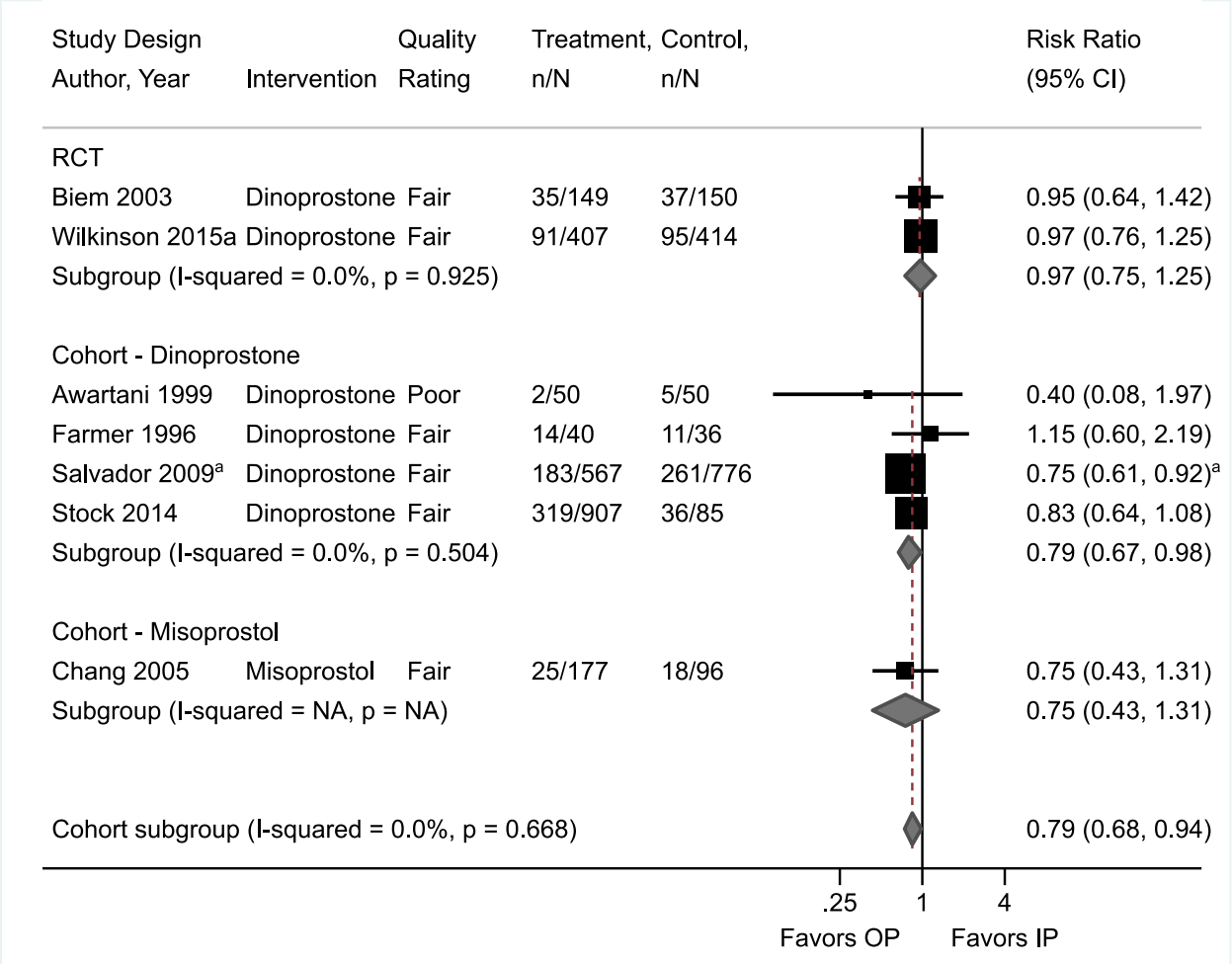
Based on pooled analysis, there is low-strength evidence that the frequency of cesarean delivery in outpatients and inpatients was the same (2 RCTs, 23% vs. 23%; relative risk [RR] 0.97, 95% confidence interval [CI] 0.75 to 1.25, I^2=0%).[27,66] Although overall cesarean delivery frequency was higher in cohort studies (33% vs. 23% for RCTs), pooled incidence was again the same for outpatients and inpatients (4 cohort studies, 33% vs. 33%; RR 0.79, 95% CI 0.67 to

0.98, I^2=0%; Figure 2). Exclusion of the poor-quality cohort study did not change the estimate (3 cohort studies, 34% vs. 34%; pooled RR 0.80, 95% CI 0.68 to 1.01, I^2=0%). In a subgroup analysis in one cohort study[30] the frequency of cesarean delivery in women with postterm pregnancies (adjusted odds ratio [OR] 0.74, 95% CI 0.54 to 1.01) was not significantly different to that of the full population (postterm and PROM, adjusted OR 0.71, 95% CI 0.54 to 0.95). This study was not included in the meta-analysis due to substantial overlap in patient populations with another study from the same institution.[55]

Total Time From Admission to Vaginal Birth

None of the included studies reported the prespecified primary birth outcomes related to duration of labor according to mode (i.e., vaginal birth); therefore, the strength of evidence was not assessed for this outcome. One cohort study (N=992) reported the time from admission to delivery (not specified by mode), finding 26.25 hours in the outpatient group and 24.28 hours in the inpatient group, with the difference not being statistically significant (mean difference [MD] 1.97 hours, 95% CI –1.18 to 5.13).[61] Other studies reported only the total length of hospital stay, again not stratified by mode of delivery. Two RCTs reported similar durations of stay for outpatients and inpatients (MD –0.58 hours, 95% CI –6.40 to 4.73), I^2=0%).[27,66] Across two small cohort studies, the duration of hospital stay was significantly shorter among outpatients compared with inpatients (pooled MD –17.34 hours, 95% CI –32.90 to –6.08, I^2=23.3%; Appendix F).[25,32]

Figure 2. Meta-analysis of cesarean delivery with prostaglandins for cervical ripening: outpatient versus inpatient



CI = confidence interval; IP = inpatient; NA = not applicable; OP = outpatient; RCT = randomized controlled trial
[a] RR estimate calculated from author's adjusted odds ratio comparing outpatient with inpatient; adjusted for age, gestational age, reasons for induction, use of epidural, birth weight, parity.

Secondary Birth Outcomes

Few studies reported secondary outcomes identified for this review. Three studies reported vaginal birth within 24 hours of cervical ripening.[30,55,66] In a fair-quality RCT (N=425), although the incidence was numerically lower in the outpatient group (41% vs. 50%), the difference was not statistically significant (RR 0.84, 95% CI 0.68 to 1.03).[66] The two cohort studies with overlapping populations reported a significantly lower proportion of women delivered vaginally within 24 hours of a single dose of dinoprostone in the outpatient (12%) versus the inpatient (41%) group (reported in the study as inpatient versus outpatient), the adjusted OR is 2.16 (95% CI 1.57 to 2.97).[30,55] The other cohort study (N=992) reported on the frequency of delivery via any mode by 24 hours, with similar rates across the groups (23% vs. 27%; RR 0.84, 95% CI 0.58 to 1.22).[61]

Failed induction was variably defined, and no study's definition met our protocol-specification that the cervical dilation must be <6 cm. Three studies reported on the frequency of cesarean delivery for fetal distress, with none finding a difference between outpatient and

inpatient groups that reached statistical significance.[32,55,66] An RCT (N=821) found somewhat fewer cesarean deliveries due to fetal distress in outpatients compared with inpatients (9% vs. 12%; RR 0.78, 95% CI 0.52 to 1.18).[66] Two cohort studies also reported on cesarean delivery for fetal distress, where the incidence was much lower in both groups (0.5%) and not significantly different between outpatient and inpatient groups (RR 0.88, 95% CI 0.11 to 7.35, I^2=0%).[32,55]

Strength of evidence was not assessed for secondary outcomes; these findings are presented here to give additional insights into the evidence.

Fetal/Neonate Harm Outcomes

Harms were poorly reported across studies. Studies were likely underpowered to detect most fetal and neonatal outcomes or differences between outpatients and inpatients, given their rare frequency.

Perinatal Mortality

Death at three months occurred in one infant in the outpatient group due to meconium aspiration following a long labor involving additional dinoprostone insertion, use of oxytocin, and cesarean delivery in one cohort study.[61] This evidence is insufficient to draw conclusions.

Hypoxic-Ischemic Encephalopathy

The risk of encephalopathy was very low in two studies reporting this outcome, with too few patients to determine differences between groups. A fair-quality RCT[66] reported low risk of hypoxic-ischemic encephalopathy (0.74% [3/407] vs. 0.72% [3/414]) and one cohort study[61] reported "neonatal encephalopathy" (cause not specified, 0.11% [1/907] vs. 0% [0/85]). This evidence is insufficient to draw conclusions.

Infection

Although none of the included studies reported confirmed neonatal infection, there is low-strength evidence that neonatal infection as a cause for admission to an intensive care unit was uncommon and similar between outpatients (4%) and inpatients (3%) across two RCTs (N=1,120; RR 1.39, 95% CI 0.67 to 3.03, I^2=0%; Appendix F).

Meconium Aspiration Syndrome

None of the studies reported explicitly on meconium aspiration syndrome. In a single RCT, one neonate from the outpatient group required neonatal intensive care unit (NICU) admission for meconium aspiration: 0.67% (1/149) vs. 0% (0/150).[27] One cohort study reported a neonatal death in the outpatient group that was attributed to meconium aspiration (0.11% [1/907] vs. 0% [0/85]).[61] This evidence is insufficient to draw conclusions.

Secondary Fetal/Neonatal Outcomes

Few studies reported secondary outcomes prioritized for this review. No study reported the need for respiratory support, but one RCT reported respiratory problems (not specified) requiring admission to a "special care nursery" (presumed similar to NICU) in the same proportions between women having outpatient versus inpatient cervical ripening (4% vs. 4%; RR 0.90, 95% CI 0.47 to 1.75).[66] The frequency of Apgar scores ≤3 at 5 minutes was also similar between outpatients and inpatients (0% [0/149] vs. 0.67% [1/150]) in one RCT,[27] as were Apgar scores <7 in the other RCT[66] and across four cohort studies[25,30,55,61] (RR 1.00, 95% CI 0.29 to 4.61). One cohort study reported the mean Apgar score at 5 minutes was 8.9 in both groups.[55] One RCT

(N=299)[27] reported the mean umbilical cord pH to be very comparable between groups (7.25 versus 7.24). A retrospective cohort study (N=992)[61] reported that 3 percent of the outpatient group had cord pH <7.0 compared with none in the inpatient group. However, 70 percent of neonate records were missing this outcome. As a proxy for other important neonatal outcomes, two studies reported admission to NICU (at varying timepoint after birth), with little difference in rates between groups.[25,30]

Strength of evidence was not assessed for secondary outcomes; these findings are presented here to give additional insights into the evidence.

Maternal Harm Outcomes

Harms were poorly reported across the studies. Maternal hemorrhage requiring transfusion was the only outcome reported as defined by our protocol. A single RCT reported that maternal hemorrhage requiring transfusion was rare, with little difference between outpatients and inpatients (0.67% [1/149] vs. 0% [0/150]; RR 3.02, 95% CI 0.12 to 73.55)[27]; however, the evidence is insufficient to draw conclusions. The findings were similar when limited to hemorrhage requiring hysterectomy following a cesarean delivery (0% vs. 0.76%; RR 0.34, 95% CI 0.01 to 8.17). One small cohort study (N=76) reported the incidence of infection, not confirmed or specifically uterine, with no cases in either group.[32] Secondary maternal harm outcomes were also rare, with little differences between groups (Table 3). Strength of evidence was not assessed for secondary outcomes; these findings are presented here to give additional insights into the evidence.

Table 3. Secondary maternal harms outcomes: outpatient versus inpatient cervical ripening with dinoprostone

Outcome	Study Design Sample Size	Incidence	Relative Risk (95% CI)
Postpartum hemorrhage >1000 mL	Cohort study N=992[61]	13% vs. 9%	RR 1.34 (0.68 to 2.64)
Placental abruption	RCT N=299[27]	0.7% vs. 1.3%	RR 0.50 (0.05 to 5.49)
	Cohort study N=100[25]	0% vs. 0%	Not calculated
Uterine rupture	RCT N=299[27]	0% vs. 0.7%	RR 0.34 (0.01 to 8.17)
	Cohort study N=992[61]	0% vs. 0%	Not calculated

CI = confidence interval; mL = milliliter; RCT = randomized controlled trial; RR= relative risk

In addition to the study that conducted subgroup analysis for time to delivery based on parity, another cohort study[30] compared outpatient versus inpatient dinoprostone use in women who either had postterm pregnancies or PROM. Results from analyses confined to postterm pregnancies were similar to those of full population (postterm and PROM) for cesarean delivery, vaginal birth within 24 hours of first dinoprostone insertion, 5-minute Apgar score ≤7, and for NICU admission >12 hours.

Misoprostol (PGE1)

Evidence on misoprostol in the outpatient versus inpatient setting was very limited, with one small, fair-quality prospective cohort study (N=273)[29] of a single dose of intravaginal misoprostol 50 µg for cervical ripening given the evening prior to scheduled induction of lab. All women were monitored for one hour post-dose, and women in the outpatient group were

discharged if the FHR was reactive and no regular contractions were noted, with explicit instructions to return if contractions started (every 5 minutes), suspected ROM, lack of perceived fetal movement, or vaginal bleeding. All women were reassessed the following morning to determine the need for a repeat dose of misoprostol. Those with history of rapid delivery, grand multiparity, active medical problems, FHR decelerations, prior uterine surgery, ROM, placenta previa, or vaginal bleeding were excluded from outpatient cervical ripening. Inpatients had coexisting complications (e.g., diabetes, gestational hypertension, precipitous delivery, poor obstetric history) but frequencies were not reported. More women in the outpatient group had baseline cervical dilation of ≥2 cm (40% versus 29%). The mean patient age was 26 years, 46 percent were nulliparous, 64 percent were classified as non-Hispanic white, 22 percent as Hispanic, and 14 percent American Indian. The mean gestational age was between 40 and 41 weeks and 6 days in 59.6 percent of women, and baseline cervical dilation was ≥2 cm in 36 percent of women. This study did not report reasons for induction, BMI, and Group B Streptococcus (GBS) colonization. No women had a history of cesarean delivery. (See Appendix E-1 for patient and study characteristics.)

The primary birth outcomes reported were time from hospital admission to vaginal birth and cesarean delivery. Outpatient cervical ripening was associated with a shorter time from admission to vaginal birth compared with inpatient cervical ripening in both nulliparous and multiparous women. Slightly lower cesarean delivery rates (not statistically significant) were also observed in outpatients. The evidence for all outcomes was insufficient to draw conclusions.

Birth Outcomes

Cesarean Delivery Frequency and Time From Admission to Vaginal Birth

The frequency of cesarean delivery was slightly lower for outpatients (14%) versus inpatients (19%), but differences were not statistically significant (RR 0.75, 95% CI 0.43 to 1.31; Figure 2 above and Appendix E-2). Mean time from hospital admission to vaginal birth was somewhat shorter for both nulliparous (MD –3.1 hours, 95% CI –4.74 to –1.46) and multiparous outpatients (MD –5.30 hours, 95% CI –6.84 to –3.76) versus inpatients. Spontaneous vaginal birth was more common in outpatients (80% vs. 64%; RR 1.26, 95% CI 1.07 to 1.50). The study did not adjust for the differences in baseline cervical dilation between groups.

Secondary Birth Outcomes

There were no cesarean deliveries for failed induction (defined as cervical dilation of ≤3 cm after intervention) in either group. Risk of cesarean delivery for failure to progress was similar between groups (5% vs. 6%). On admission, more outpatients had advanced cervical dilation (4 to 9 cm) compared with inpatients (10% vs. 2%; RR 5.0, 95% CI 1.2 to 21.5). (See Appendix E-2 and Appendix F) Strength of evidence was not assessed for secondary outcomes; these findings are presented here to give additional insights into the evidence.

Fetal/Neonatal Harm Outcomes

Fetal and neonatal harms were poorly reported. Suspected neonatal sepsis (confirmation not reported) was the only primary outcome reported and was rare (0.40% [1/177] versus 0% [0/96]). Neonatal breathing difficulties (not defined) were less common in outpatients (3% vs. 7%; RR 0.39, 95% CI 0.13 to 1.19) as was nonreassuring FHR on admission (9% vs. 14%; RR 0.65, 95% CI 9.34 to 1.28) but neither were statistically significant. No neonates in either group had 5-minute Apgar scores ≤ 3; scores between 4 and 6 occurred in 0.8 percent versus 1.8 percent of

neonates. There was little difference in the frequency of neonates with Apgar scores <7 at 5 minutes between outpatients and inpatients. Authors reported that meconium was “uncommon and not more frequent in outpatients” and that the frequency of newborn complications requiring >3-day hospitalization was "unaffected by” outpatient status. (Appendix E-2) Strength of evidence was not assessed for secondary outcomes; these findings are presented here to give additional insights into the evidence.

Maternal Harm Outcomes

Authors only reported that no cases of placental abruption or rupture were recorded.

Key Question 2. Mechanical Methods for Cervical Ripening in Outpatient Versus Inpatient Setting

Key Points

- For the comparison of outpatient versus inpatient ***single-balloon catheter*** for cervical ripening, although differences were not statistically significant, there was a moderate difference between groups in the frequency of shoulder dystocia (1 RCT), a small difference for cesarean delivery (3 RCTs, 2 cohort studies), and little to no difference in the frequencies of birth trauma (1 RCT) and maternal infection (2 RCTs); (SOE: low).
- The evidence comparing outpatient versus inpatient ***double-balloon catheter***, based on a single small (n=48) trial, was insufficient to draw conclusions.
- Evidence comparing any ***outpatient catheter*** (1 double-balloon RCT, 1 single-balloon RCT) versus ***inpatient dinoprostone*** found small not statistically significant differences for cesarean delivery and postpartum hemorrhage (SOE: low). Evidence on fetal/neonatal harms was insufficient to draw conclusions.
- Evidence on ***hygroscopic dilators*** was based on one small cohort study (n=42) and was insufficient to draw conclusions.

Summary of Findings

Single-Balloon Catheter

Three fair-quality RCTs (N=370) compared outpatient with inpatient single-balloon (Foley) catheters (Appendix E).[40,52,58] Two studies specified that catheters were placed by physicians or residents and one study did not report the type of provider inserting the catheter. Balloons were filled to 30 ml in two studies and 40 ml in one study. One trial included concomitant oxytocin in the inpatient group.[40] Following catheter placement, all three trials conducted FHR monitoring prior to sending the outpatient group home (for 20 to 30 minutes in 2 trials[40,58] and duration not reported in the third[52]). In the absence of labor or clinical events (e.g., vaginal bleeding, decreased fetal movements, or ROM) women in the outpatient arms were instructed to return to the hospital the next day[40,58] or in 24 hours.[52] Women in the inpatient arms in all three trials were admitted to the hospital following catheter placement. Study inclusion criteria required gestational age ≥37 weeks in one study,[58] 39 to 42 weeks in one study,[40] and ≥41 weeks in the third study.[52] Two studies[52,58] required Bishop score ≤5 for enrollment, and the third required cervical dilation <3 cm, or if dilation was at least 2 cm, cervical effacement had to be <80

percent.[40] One study required enrollment of parous women.[40] Two RCTs were conducted in the United States and one in Portugal; none of the trials reported funding source.

We also included a fair-quality retrospective cohort study[47] (N=615) that compared outpatient versus inpatient single-balloon catheter at a single center in Australia (Appendix E). The study did not report the type of provider placing the catheter, and balloons were reported to be filled to 30 ml. In both groups, fetal monitoring was conducted before and after catheter placement (duration of monitoring was not reported). Following monitoring, women in the outpatient group were sent home with instructions to return the next morning, and women in the inpatient group were admitted to the hospital with continuous fetal monitoring. One other poor-quality cohort study was identified (Appendix E).[39]

The characteristics of women enrolled in these studies are detailed in Appendix E-1. Across the three trials, weighted mean maternal age was 28.8 years and mean gestational age was 39.7 weeks. One trial only enrolled parous women,[40] one trial included 74.6 percent nulliparous women,[52] and the last trial did not report parity but reported a mean gravidity of 1.8.[58] Mean Bishop score was 2.2 in one trial,[52] median of 2 in another,[58] and median of 2.0 using modified Bishop score in the third study.[40] The proportion of women with comorbidities such as diabetes and hypertension were mostly not reported except for gestational diabetes, which affected 3 percent of women across two trials.[40,58] The reason for cervical ripening varied by study; with all undergoing elective induction in one,[40] reported as elective in 43 percent in a second, with other reasons for induction being post due date (33%) or medically-indicated (19%).

In the cohort study, mean maternal age was 24 years and mean gestational age was 40.4 weeks. The mean modified Bishop score at time of catheter placement was 1.85. The authors did not report BMI. Forty-seven percent of women were nulliparous. A slightly smaller proportion of women in the outpatient group were parous (48.5%) compared with the inpatient group (58.4%; p=0.02). There were also numerous between-group differences in indication for induction between the outpatient and inpatient groups, including the proportion of postterm pregnancies (41% vs. 4%, p<0.001), oligohydramnios (11% vs. 28%, p<0.001), preeclampsia (0.3% vs. 32%, p<0.001), abnormal FHR (2% vs. 10%, p<0.001), and maternal diabetes (17% vs. 5%, p<0.001). The study was conducted in the United States and funding was not reported.

All studies reported cesarean delivery, and while there was a trend towards lower risk in the outpatient catheter groups, this difference was not statistically significant. These studies sporadically reported on maternal and fetal/neonatal harm outcomes, and were likely too small to identify real differences in risk. For all outcomes, the evidence did not identify clear differences between outpatient and inpatient single-balloon catheters, and is low strength or insufficient.

Birth Outcomes

Cesarean Delivery

Evidence from three RCTs consistently showed that outpatient single-balloon catheter use was associated with a lower incidence of cesarean delivery compared with inpatient use, although the difference did not reach statistical significance (Appendix E-2).[40,52,58] When pooled, the risk of cesarean delivery remained lower in the outpatient group, but the estimate was also not statistically significant (3 RCTs, pooled RR 0.59, 95% CI 0.21 to 1.03, I^2=0%; Figure 3). This meta-analysis included one study that did not report the overall incidence of cesarean delivery, but the incidence of cesarean delivery due to failed induction, which was significantly lower in the outpatient group (3% vs. 17%; RR 0.18, 95% CI 0.41 to 1.10).[52] Pooled results from two cohort studies were similar to the RCT finding, with a nonsignificant lower risk of cesarean

delivery in the outpatient catheter group (33% vs. 30%; RR 0.95, 95% CI 0.72 to 1.22, I^2=0%).[39,47] The strength of this evidence is low.

Total Time From Admission to Vaginal Birth and Total Labor and Delivery Length of Stay

No study reported outcomes of time to delivery according to the prespecified definitions (i.e., according to mode). Evidence on related outcomes are presented here, but do not contribute to the strength of evidence on birth outcomes. One RCT reported time from admission to the labor and delivery unit to delivery (vaginal or cesarean delivery).[40] The study found that women who had undergone outpatient and inpatient cervical ripening had similar time from admission to delivery (12.4 vs. 13.5 hours; MD –1.10, 95% CI –3.59 to 1.39)..

Although not a prespecified primary outcome for this review, total time of hospital stay was shorter in the outpatient groups in two RCTs[40,52] and one cohort study.[47] In all three studies, the inpatient group was admitted immediately following catheter placement, while the outpatient group was sent home with instructions to return the next day. When the RCTs were pooled, the mean difference between outpatient and inpatient groups was –7.15 hours (95% CI –18.94 to 4.47, I^2=87%). There is a high degree of heterogeneity in this analysis, as the two studies reported magnitudes of difference (favoring outpatient setting) that were quite different (–12 hours in one and –2.4 hours in the other). The difference between groups in the cohort study was longer (–24 hours) and statistically significant (95% CI –32.81 to –15.19). One study conducted subgroup analysis, comparing the total time from labor unit admission to delivery based on cervical dilation <2 cm (n=28 outpatient and 36 inpatient), finding a nonstatistically significant mean difference between groups of –1.2 hours (95% CI –4.85 to 2.45).[40]

Secondary Birth Outcomes

One RCT reported a lower risk of cesarean delivery due to failed induction in the outpatient single-balloon catheter group versus inpatient (3% vs. 17%; RR 0.18, 95% CI 0.41 to 1.10).[52] A fair-quality cohort study (N=615) found a significantly more women in the outpatient group requiring cesarean delivery due to arrest of labor, when limiting the analysis to women with a cesarean delivery.[47] When analyzing across all women in each group, the difference was not significant, likely due to the imbalance in the numbers of women in each group (25% vs. 20%; RR 1.21, 95% CI 0.90 to 1.64). Cesarean delivery due to fetal distress was also similar when considering all patients in each group (15% vs. 11%; RR 1.27, 95% CI 0.74 to 2.19).

One RCT reported higher Bishop scores at the time of admission in the outpatient group (5.70) than the inpatient group (2.10) (MD 3.60, 95% CI 2.95 to 4.25).[52] Two RCTs and the cohort study reported similar or identical Bishop scores on admission in both outpatient and inpatient groups.[40,47,58]

Strength of evidence was not assessed for secondary outcomes; these findings are presented here to give additional insights into the evidence.

Fetal/Neonatal Harm Outcomes

Low strength evidence found that the incidence of birth trauma or shoulder dystocia was not significantly different between outpatient single-balloon catheter versus inpatient In one trial, there was little difference in the incidence of birth trauma (1 case each of cephalohematoma, cephalohematoma plus scalp laceration, and brachial plexus injury; authors did not report which specific injuries occurred in which group) between outpatient and inpatient groups (2% [1/65] vs. 3% [2/64]; RR 0.49, 95% CI 0.05 to 5.30). Also in this trial, shoulder dystocia was less likely to

occur in the outpatient group (3% [2/65] vs. 11% [7/64]; RR 0.28, 95% CI 0.06 to 1.30).[40] The magnitude of difference was moderate, but not statistically significant. The strength of evidence for these outcomes is low. In the same study, there was one case of NICU admission for meconium aspiration syndrome, but the authors did not indicate to which group the infant was randomized. A cohort study found no difference between outpatient and inpatient groups in risk of culture-confirmed neonatal sepsis (2% vs. 2%; RR 0.75, 95% CI 0.24 to 2.34)[47]; however, this evidence is insufficient to draw conclusions.

Regarding secondary fetal/neonatal harm outcomes, one trial reported that one infant in each group required respiratory support within 72 hours after birth (2% vs. 2%; RR 1.00, 95% CI 0.06 to 15.65).[52] The numbers of neonates with Apgar score of <7 at 5 minutes were very small (0 to 1 per intervention group) in two trials, resulting in imprecise risk estimates that indicated no difference between groups (2 RCTs, 0.77% [1/130] vs. 1.6% [2/129]; pooled RR 0.62, 95% CI 0.08 to 4.98, I^2=0%).[40,52] In the cohort study, results for Apgar score <7 at 5 minutes were consistent with the trials (1.3% [4/300] vs. 1.3% [4/315], RR 1.05, 95% CI 0.26 to 4.16).[47] Strength of evidence was not assessed for secondary outcomes; these findings are presented here to give additional insights into the evidence.

Maternal Harm Outcomes

One trial found that postpartum hemorrhage, defined as blood loss >1,000 ml, rarely occurred in either the outpatient or inpatient groups (0% [0/65] vs. 2% [1/64]; RR 0.33, 95% CI 0.01 to 7.91).[40] This evidence is insufficient.

Two trials reported the same incidence of any uterine infection (chorioamnionitis or endometritis) in the outpatient and inpatient groups (5% for both, pooled RR 0.99, 95% CI 0.31 to 3.19, I^2=0%; Appendix F).[40,52] Two cohort studies reported endometritis.[39,47] While the incidence was slightly greater in the outpatient group (7% vs. 4%), pooled analysis indicates that the difference was not statistically significant (RR 1.70, 95% CI 0.90 to 3.69, I^2=0%; Appendix F). This evidence is low strength.

Double-Balloon Catheter

One small (N=48) fair-quality trial compared cervical ripening with a double-balloon catheter (Cook®) in the outpatient versus inpatient setting (Appendix E).[65] In both groups, women underwent 20 minutes of cardiotocograph monitoring, followed by catheter insertion by a doctor or midwife trained in catheter assertion if cardiotocographic monitoring was reassuring. Monitoring continued for 20 minutes after catheter insertion in both groups. Women in the outpatient group were then discharged home with instructions to return to the hospital the following morning or at the onset of labor or clinical complications (e.g., vaginal bleeding). Outpatient group participants did not need to return to the hospital early in the event of catheter expulsion. Both groups received a double-balloon catheter; each balloon was inflated with 70 to 80 milliliters of water. Study eligibility criteria included ≥37 to ≤42 weeks gestation, Bishop score <7, intact membranes, and singleton pregnancy. Women with a history of cesarean delivery were excluded. The study was conducted in Australia and funded by a nonprofit organization.

The details on characteristics of women enrolled in this study can be found in Appendix E-1. The mean maternal age was 29 years, and mean gestational age was 40.75 weeks. Authors did not report BMI or other anthropomorphic measures. Seventy-five percent of women were nulliparous. Cervical dilation at the time of catheter insertion was not reported, but mean Bishop

score was 0 to 2 in 27 percent of the population, 3 to 4 in 52 percent, ≥5 in 17 percent, and not reported for 4 percent. Nearly one-third of catheters (29%) were spontaneously expelled.

Outpatient double-balloon catheter use was associated with shorter times from hospital admission to vaginal birth compared with inpatient catheterization. There were no statistically significant differences between outpatient and inpatient groups for other outcomes. Low event rates resulted in risk estimates that were generally imprecise, and study authors noted that the trial was not designed nor adequately powered to detect differences between groups for clinical outcomes. Due to these limitations and combined with the small sample size, the strength of evidence is insufficient to recommend outpatient versus inpatient double-balloon catheter for all outcomes.

Birth Outcomes

Cesarean Delivery

Rate of cesarean delivery was lower in the outpatient catheter group versus the inpatient group (18% vs. 33%) but the difference did not reach statistical significance (RR 0.55, 95% CI 0.20 to 1.51; Figure 3). This evidence is insufficient to draw conclusions.

Total Time From Admission to Vaginal Birth

Time from admission to vaginal birth was significantly shorter in the outpatient group (mean 14.25 hours) than the inpatient group (mean 21.45 hours; MD –7.2 hours, 95% CI –11.45 to –2.95). Related outcomes such as time from catheter insertion to both active labor (17.5 vs. 19.5 hours; MD –2.0 hours, 95% CI –4.02 to 0.02) and vaginal birth (24.5 vs. 29.0 hours; MD –4.5 hours, 95% CI –8.96 to –0.04) were also shorter in the outpatient group, though only time to vaginal birth reached statistical significance. This evidence is insufficient to draw conclusions.

Secondary Birth Outcomes

The proportion of women who delivered within 24 hours of catheter insertion was 33 percent in the outpatient group and 27 percent in the inpatient group (RR 1.25, 95% CI 0.47 to 3.29). The trial narratively reported no cases of failed induction in either group, though there was one cesarean delivery in the inpatient group due to fetal distress (0% [0/33] vs. 7% [1/15]; RR 0.16, 95% CI 0.01 to 3.64). Strength of evidence was not assessed for secondary outcomes; these findings are presented here to give additional insights into the evidence.

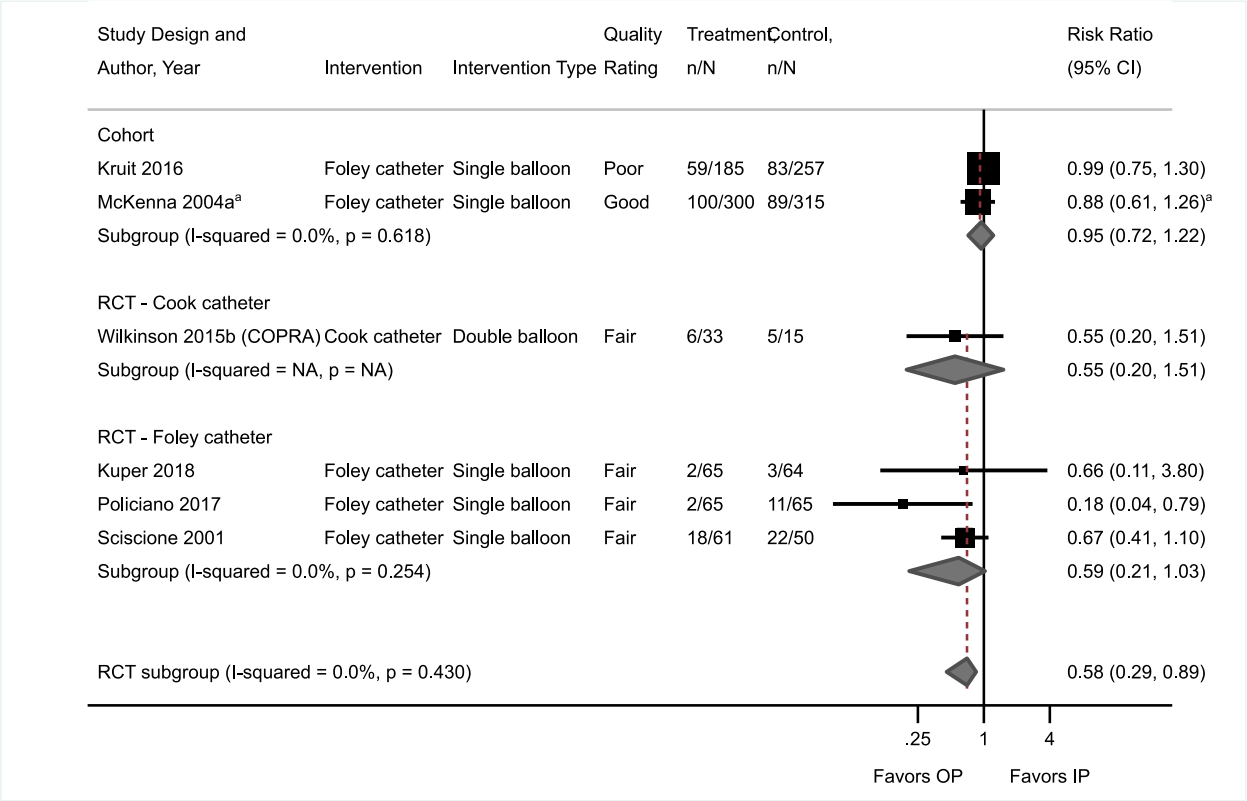
Fetal/Neonatal Harm Outcomes

No perinatal deaths were reported in either the outpatient or inpatient catheter groups, nor were there any cases of neonatal infection reported in either group. There was one case of meconium aspiration in the outpatient catheter group (3%; 1/33) compared with no cases in the inpatient group (0%; 0/15), resulting in an imprecise risk estimate (RR 1.41, 95% CI 0.06 to 32.78). This case was not specified as meeting criteria for meconium aspiration syndrome, however. This evidence is insufficient to draw conclusions. Regarding secondary outcomes, two neonates in the outpatient catheter group (6%) had Apgar score <7 at 5 minutes versus none in the inpatient group; the relative risk was 2.35 (95% CI 0.12 to 46.22). Strength of evidence was not assessed for secondary outcomes; these findings are presented here to give additional insights into the evidence.

Maternal Harm Outcomes

Postpartum hemorrhage, defined in this study as blood loss of >500 milliliters for vaginal birth and >1 liter for cesarean delivery, was slightly higher, but not significantly so, in the outpatient group (18% vs. 13%; RR 1.36, 95% CI 0.31 to 5.99). This evidence is insufficient to draw conclusions.

Figure 3. Meta-analysis of cesarean delivery with catheters for cervical ripening: outpatient versus inpatient



CI = confidence interval; IP = inpatient; NA = not applicable; OP = outpatient; RCT = randomized controlled trial

[a] RR estimate calculated from author's adjusted odds ratio comparing outpatient with inpatient; adjusted for nulliparity, postterm gestation, oligohydramnios, preeclampsia, diabetes, abnormal fetal heart test and large-for-gestational-age.

Hygroscopic Dilators

A small, poor-quality cohort study (N=42) compared the use of a hygroscopic dilator (Dilapan®) in outpatient versus inpatient settings.[64] The study reported that the number of sticks administered was "as many as the cervix could accommodate," and the mean was 6 in the outpatient group and 5 in the inpatient group. The type of provider placing the sticks was not reported. The results are reported here as this was the only study identified comparing a hygroscopic dilator in the outpatient versus inpatient setting. Study inclusion criteria required ≥37 weeks gestation with no active labor or contraindication to labor, Bishop score ≤4 and documented fetal well-being. Details of patient characteristics can be found in Appendix E-1. The mean age of enrolled women was 23 years and 15 percent had BMI ≥30; mean gestational age was 40 weeks. Mean gravidity was 1.65 and mean parity was 0.5. Authors did not report the reason for induction. The study was conducted in the United States and the funding source was not reported.

The only birth outcome of interest reported was total length of hospital stay, which was shorter in the outpatient group. Evidence on other outcomes, reported narratively, was very limited but described as similar in both groups. The strength of evidence is insufficient for outpatient versus inpatient hygroscopic dilator for all outcomes.

Birth Outcomes

The study did not report cesarean delivery rate or other included birth outcomes.[64]

Fetal/Neonatal Harm Outcomes

Fetal and neonatal harms were not reported, although the study narratively reported as similar rates of nonreassuring FHR in both groups.[64]

Maternal Harm Outcomes

Rate of endometritis was narratively reported as similar in outpatient and inpatient groups, but no data were provided.[64] This evidence is insufficient to draw conclusions.

Catheter Versus Dinoprostone (PGE2)

Two fair-quality RCTs compared outpatient double-balloon catheters (80 ml inflation, N=695)[26] or single-balloon catheters (30 ml inflation, N=101)[34] with inpatient dinoprostone (Appendix E). Catheter insertion was performed by a resident[26] or midwife or doctor[34] following a reassuring cardiotocograph. Post-insertion FHR monitoring was performed 30 minutes after insertion in one study,[34] but was not routinely performed in the other. Thirty minutes after insertion, women in the outpatient group was discharged home with instructions to return the following morning. Women were instructed to return sooner if labor began or there were other clinical signs (e.g., vaginal bleeding, unmanageable pain, or catheter expulsion). In the inpatient groups, intravaginal dinoprostone gel 2 mg or controlled-release vaginal tape 10 mg was administered by a doctor or midwife in one study,[26] while the other study used intravaginal dinoprostone gel 2 mg for nulliparous women and 1 mg for parous women, with the type of provider administering not reported. Both studies conducted 30 minutes of cardiotocographic monitoring after dinoprostone insertion, with one reassessing after 6 hours and allowing a second dose (criteria and proportion not reported).[34] Both included women with ≥37 weeks gestation, indications for induction of labor (either "low-risk" indications"[26] or "unfavorable cervix"[34]), and Bishop score <7. Both studies also excluded women with a history of cesarean delivery. Both were conducted in Australia. One reported no external funding,[26] and the other did not report its funding source.[34]

Patient characteristics are described in Appendix E-1. The weighted mean age was 30.5 years, and mean BMI was 26.4.[26,34] In both studies, the majority of women were nulliparous (73% overall) and the mean gestational age was 41 weeks. Five percent of women had gestational diabetes and one trial reported that 14 percent of women were GBS positive.[34] Post due date was the most prevalent reason for induction reported for 72 percent of women, 19 percent for medically-indicated reason, and 9 percent for social/elective reason. Bishop scores at baseline were mean 2.8 in one study[34] and median 3.0 (modified Bishop score) in the other.[26] Scores were similar between randomized groups within these studies.

Differences between outpatient catheter and inpatient dinoprostone were small and not statistically significant for any maternal or fetal/neonatal outcomes, including risk of cesarean

delivery and postpartum hemorrhage (SOE: low) or perinatal mortality, hypoxic-ischemic encephalopathy, neonatal seizure and maternal infection (SOE: insufficient).

Birth Outcomes

Cesarean Delivery

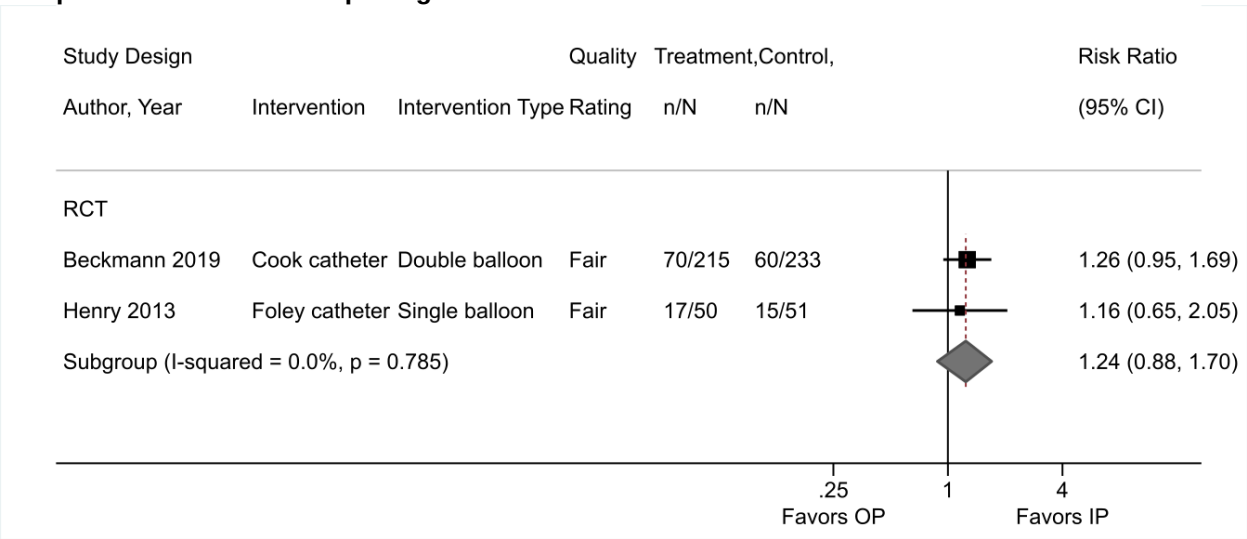
Risk of cesarean delivery was slightly higher in the outpatient catheter groups versus inpatient dinoprostone in both studies, but the pooled estimate is not statistically significant (33% vs. 26%; RR 1.24, 95% CI 0.88 to 1.70, I^2=0%; Figure 4). This is low-strength evidence. Based on type of catheter, the estimates were not significantly different (RR 1.26, 95% CI 0.95 to 1.69 for double-balloon catheter and RR 1.16, 95% CI 0.65 to 2.05 for single-balloon catheter).[26,34] One study conducted subgroup analyses of women with modified Bishop score >3 at the start of cervical ripening (N=217), finding that outpatient (double-balloon) catheter use increased the risk of cesarean delivery compared with inpatient dinoprostone, though the estimate was not statistically significant (31% vs. 20%; RR 1.53, 95% CI 0.96 to 2.46).[26] In the same subgroup, women in the outpatient catheter group were less likely to have an unassisted vaginal birth than those in the inpatient dinoprostone group (54% vs. 72%; RR 0.75, 95% CI 0.61 to 0.92).

Total Time From Admission to Vaginal Birth and Total Labor and Delivery Length of Stay

Neither study reported on the primary birth outcomes relating to time to delivery prioritized for this report; therefore, the strength of evidence was not assessed for this birth outcome.[26,34]

Other related outcomes were time from induction or time from randomization to delivery (cesarean or vaginal). In one study, there was no difference between outpatient catheters and inpatient dinoprostone in the time from induction of labor to delivery (24.2 vs. 23.7 hours; MD 0.50, 95% CI –8.38 to 9.38).[26] The other study reported time from randomization to delivery, finding a significantly shorter duration in the outpatient group (21.3 vs. 32.4 hours; MD –11.1, 95% CI –16.5 to –5.7).[34] When pooled, there was no difference between outpatient and inpatient groups (MD -6.46, 95% CI –19.3 to 8.37) though heterogeneity was high (I^2=79%).

Figure 4. Meta-analysis of cesarean delivery with outpatient catheters versus inpatient dinoprostone for cervical ripening



CI = confidence interval; IP = inpatient; OP = outpatient

Secondary Birth Outcomes

Both studies reported the rate of failed induction, though they were inconsistent in how this was defined. The studies found that use of a double-balloon catheter was associated with small, but not statistically significant increase in risk of cesarean delivery for failed induction (3% vs. 2%; RR 1.63, 95% CI 0.47 to 5.68), cesarean delivery for fetal distress (10% vs. 9%; RR 1.19, 95% CI 0.67 to 2.12),[26] or cesarean delivery due to "fetal concerns" (46% vs. 31%; RR 1.47, 95% CI 0.88 to 2.43)[34] relative to inpatient dinoprostone. One study found little difference in cervical dilation (1 cm in both groups) and modified Bishop score (3 in both groups) on admission and in time from ROM to delivery (10 vs. 8.3 hours; MD 1.70, 95% CI –3.42 to 6.82) (Appendix E-2).[26] Strength of evidence was not assessed for secondary outcomes; these findings are presented here to give additional insights into the evidence.

Fetal/Neonatal Harm Outcomes

One trial reported that there were no cases of perinatal mortality, hypoxic-ischemic encephalopathy, seizure, or need for respiratory support 72 hours after birth.[26] Confirmed infection was rare, with little difference in event rates between outpatient double-balloon catheters and inpatient dinoprostone in one study (0.93% [2/215] vs. 0% [0/233]; RR 5.42, 95% CI 0.26 to 112).[26] This evidence is insufficient (see Appendix H).

Regarding secondary outcomes, one trial reported that no neonate required respiratory support 72 hours after birth.[26] Both studies reported a lower incidence of umbilical cord arterial pH <7.10 in the catheter arms versus dinoprostone, though absolute event rates were low (range 0 to 10%) and risk estimates were not statistically significant in either study (RR 0.38, 95% CI 0.12 to 1.16[26] and RR 0.51, 95% CI 0.10 to 2.66[34]). Subgroup analysis found that risk of umbilical cord arterial pH <7.10 was consistent with overall risk estimates when analyzed according to parity (nulliparous: RR 0.46, 95% CI 0.15 to 1.44; parous: RR 0.22, 95% CI 0.01 to 4.33).[26] Strength of evidence was not assessed for secondary outcomes; these findings are presented here to give additional insights into the evidence.

Maternal Harm Outcomes

Both studies reported the rate of postpartum hemorrhage, although neither study stratified results according to mode of delivery. Outpatient double-balloon and single-balloon catheters were associated with rates of postpartum hemorrhage that were not significantly different compared with inpatient dinoprostone. In the study comparing double-balloon catheters versus dinoprostone, postpartum hemorrhage (blood loss >500 ml) occurred in 30 percent versus 26 percent of study participants (RR 1.15, 95% CI 0.86 to 1.55),[26] while in the study comparing outpatient single-balloon catheters with inpatient dinoprostone, (undefined) postpartum hemorrhage rates were 16 percent versus 22 percent, respectively (RR 0.74, 95% CI 0.33 to 1.69).[34] When pooled, there remained no statistically significant difference between outpatient catheters and inpatient dinoprostone in risk of postpartum hemorrhage (28% vs. 25%; RR 1.10, 95% CI 0.62 to 1.56, I^2=0%; Appendix F). This is low-strength evidence.

There was no statistically significant difference between catheters and dinoprostone in maternal infection (0% [0/215] vs. 0.43% [1/233]; RR 0.36, 95% CI 0.01 to 8.82) or umbilical cord prolapse (0.47% [1/215] vs. 0% [0/233]; RR 3.25, 95% CI 0.13 to 79.36) based on imprecise estimates from one study.[26] This evidence is insufficient to draw conclusions (see Appendix H).

Key Question 3. Cervical Ripening Methods in Outpatient Setting

Key Points

- In head-to-head comparisons for outpatient cervical ripening, there was little difference in the frequency of cesarean delivery for comparisons of ***dinoprostone gel 2.5 mg*** versus ***5 mg***, or ***latex*** versus ***silicone single-balloon catheters*** (1 study each). Similarly, the risk of receiving antibiotics for suspected uterine infection did not differ between catheter types (SOE: low).
- For the comparison of ***prostaglandins*** with ***placebo*** for outpatient cervical ripening, differences were small and did not reach statistical significance for cesarean delivery (12 RCTs), meconium aspiration syndrome (2 RCTs, dinoprostone), shoulder dystocia (3 RCTs), or uterine infection (7 RCTs). These findings did not change according to the specific prostaglandin or route of administration, study quality, or gestational age (SOE: low).
- Comparisons of ***prostaglandins*** (primarily dinoprostone) with ***membrane sweeping*** or ***expectant management*** (6 RCTs) found small differences in the frequency of cesarean delivery that were not statistically significant. The incidence of uterine infection was low and not different between groups (SOE: low). These findings did not change according to the specific prostaglandin or study quality.

Summary of Findings

While a few of the studies noted the types of providers that inserted or applied the cervical ripening intervention (i.e., obstetrician or midwife), it was not possible to evaluate any potential differences in outcomes based on this characteristic as results were not stratified based on this characteristic. Specific details (where reported) on how the drugs were placed or administered are given in Appendix E-1. While there were studies using various routes or methods of administration (e.g., intracervical or intravaginal for dinoprostone, oral or intravaginal for misoprostol), the results (below) did not indicate variation according to this factor, and subgroup analysis of this characteristic was not undertaken due to small numbers of studies within each outcome.

The most commonly reported primary outcome was cesarean delivery, with few studies reporting on measures of time to vaginal birth or length of stay in labor and delivery. Studies rarely reported primary fetal/neonatal or maternal harms, and when reported were less clearly defined than outlined for this review. For example, neonatal sepsis was reported without indicating that it was confirmed (versus suspected). Some secondary outcomes were reported, but again, with less specificity than desired. For example, failed induction was not defined in some, and defined without a threshold for the degree if dilation in others. In this Key Question, we included additional longer-term outcomes of breastfeeding, maternal mood, and mother-baby attachment, however, none of these studies reported on these outcomes. A few studies reported secondary neonatal harm outcomes of Apgar scores and umbilical cord pH, but none of these studies reported on secondary maternal harms.

Prostaglandin Versus Prostaglandin: Misoprostol (PGE1) Versus Dinoprostone (PGE2)

Four RCTs compared prostaglandins for cervical ripening in the outpatient setting, involving 297 women.[35,38,49,59] A fair-quality study compared intravaginal misoprostol 25 mcg with intracervical dinoprostone gel 0.5 mg,[49] and a poor-quality study compared an oral tablet of dinoprostone (0.5 mg every hour for 6 hours; not available in the United States) with a pharmacy-compounded intracervical gel 3 mg.[35] Two trials compared different doses of prostaglandins: a good-quality trial evaluated intravaginal dinoprostone gel 2.5 mg versus 5 mg,[59] and a fair-quality study oral misoprostol 25 mg versus 50 mcg.[38] Enrollment criteria varied, and were only partially specific. Reason for induction as an eligibility criterion was postterm pregnancy in one,[38] and not clearly reported in the others. For enrollment, women had to have Bishop scores of <4 in two trials,[35,59] <5 in one,[38] and <6 in the fourth.[49] All of the trials required a singleton pregnancy. Given the variation in study drugs, the protocols for drug administration and followup also varied (see Appendix E-1). All but one of the studies required a period of 2 to 3 hours of continuous FHR monitoring prior to discharge, with most studies requiring women to return 12 to 24 hours after discharge home (after 3 days for the oral misoprostol dose study).[35,49,59] None of the RCTs reported their source of funding.

Characteristics of women enrolled are in Appendix E-1. Across the trials, the weighted mean age of women enrolled was 25 years. One trial enrolled only nulliparous women,[35] two enrolled 60 percent nulliparous (weighted mean),[49,59] and one reported that 63 percent were primagravida.[38] Weighted mean gestational age was 40 weeks. None of the studies reported BMI. Prior cesarean delivery was excluded by one,[49] present in 12 percent of participants in another,[59] and not reported in two studies.[35,38] One study reported that 12 percent of women had diabetes and 20 percent had hypertension/preeclampsia (further details not provided).[49] Postterm pregnancy was the reason for induction in all women in one study,[38] and 35 percent in two other studies (one study did not report on reasons for induction).[35,49] Bishop score at enrollment was 3 to 4 for most women in these trials.

The primary outcomes for these studies were cesarean delivery rates, with no (or only globally reported) primary fetal or maternal harm outcomes reported. Overall, differences between groups were small and not found to be statistically significant. The bodies of evidence for primary outcomes with each comparison are mainly insufficient to draw conclusions due to small sample sizes, no corroborating evidence, and imprecision of estimates. The exception was for the dose comparison of dinoprostone gel 2.5 mg vs. 5.0 mg, which was low strength for cesarean delivery.

Birth Outcomes

Cesarean Delivery

All four trials comparing prostaglandin interventions to each other for outpatient cervical ripening reported on the incidence of cesarean delivery, with none finding statistically significant differences between groups. Across the studies, 19 to 32 percent of women enrolled delivered via cesarean delivery. The highest quality of evidence was for the dose comparison of dinoprostone gel (2.5 mg vs. 5.0 mg), with 20 percent and 19 percent having a cesarean delivery (respectively) (RR 1.07, 95% CI 0.51 to 2.22; SOE: low).[59] For the comparison of misoprostol 25 mcg intravaginal and dinoprostone gel 0.5 mg intracervical, 21 percent and 19 percent (respectively) had a cesarean delivery (RR 1.13, 95% CI 0.48 to 2.63).[49] However, this evidence, and evidence

for the other two comparisons, is insufficient to draw conclusions due to small sample size (imprecision), study limitations, and unknown consistency.

Secondary Birth Outcomes

Three of the trials reported on secondary birth outcomes, however none reported the outcomes as they were specified for this review (see Appendix E-2). Differences in "failed induction" (described as <6 cm dilation after 1 to 3 doses) between groups were small and not statistically significant for any comparison.[35,49,59] The comparisons included intravaginal misoprostol 25 mcg and intracervical dinoprostone gel 0.5 mg, dinoprostone gel 2.5 mg and 5.0 mg, and oral versus intracervical dinoprostone gel. The incidence of "failed induction" ranged from 0 percent with intravaginal misoprostol to 32 percent with oral dinoprostone. In the study comparing intravaginal misoprostol and intracervical dinoprostone, failed induction was also reported as cesarean delivery due to dystocia (7% vs. 10%) and again, the difference was not statistically significant.[49] In the study of oral versus intracervical dinoprostone, failed induction defined as cesarean delivery due to fetal distress occurred in 4 percent versus 8 percent, and cesarean delivery excluding fetal distress occurred in 16 percent versus 24 percent, with the differences not being statistically significant.[35]

Similar to failed induction, the trials did not report cervical assessment in the way specified for this review (at the time of admission), though the two trials reporting on Bishop score did not find differences between groups. Among women not in labor 18 to 24 hours after treatment, the mean score was 5 in the intravaginal misoprostol and 4 in the intracervical dinoprostone groups (p=0.28).[49] In the dose-comparison study of dinoprostone gel, the proportion of women whose Bishop score changed more than 3 points from baseline to after the second dose was 44.1 percent versus 45.7 percent (p=0.29).[59]

Strength of evidence was not assessed for secondary outcomes; these findings are presented here to give additional insights into the evidence.

Fetal/Neonatal Harm Outcomes

No study comparing different prostaglandins for cervical ripening in the outpatient setting reported on the primary fetal/neonatal harm outcomes specified for this review. The dose-comparison study of dinoprostone gel reported that 1.8 percent of infants (1/55) in the 2.5 mg group and 4.7 percent (3/64) in the 5.0 mg group had cord gas pH of <7.2 (RR 0.39, 95% CI 0.04 to 3.62).[59] None of these RCTs reported on Apgar scores <3 at 5 minutes, but two reported on scores less than 7 at 5 minutes. In the dose-comparison study of dinoprostone gel, 0 percent (0/55) in the 2.5 mg group and 4.7 percent (3/64) in the 5 mg group (RR 0.17, 95% CI 0.01 to 3.14) had Apgar scores <7 at 5 minutes.[59] In the study of oral versus intracervical dinoprostone gel, 4 percent (1/25) in each group had Apgar scores <7 at 5 minutes (RR 1.00, 95% CI 0.07 to 15.12).[35] Strength of evidence was not assessed for these secondary outcomes; these findings are presented here to give additional insights into the evidence.

Maternal Harm Outcomes

The two head-to-head RCTs did not report maternal harms.[49,59] The other two trials only reported in text as no adverse events[38] or no complications resulting from the use of prostaglandins.[35]

Prostaglandin Versus Placebo

Twelve RCTs compared prostaglandins for cervical ripening with placebo in the outpatient setting, involving 1,112 women.[28,31,33,37,41,42,46,48,53,56,57,60] Four studies evaluated intravaginal misoprostol (25 mcg),[37,48,53,60] four evaluated intracervical dinoprostone gel 0.5 mg,[28,41,42,46] three evaluated intravaginal dinoprostone gel/suppository 2 mg,[31,56,57] and one evaluated oral misoprostol 100 mcg.[33] Enrollment criteria included preventing a postterm pregnancy in seven,[28,33,42,53,56,57,60] and was unclear or not reported in the others. For enrollment, women had to have a Bishop score of ≤8 in four trials,[46,48,56,57] ≤6 in three trials,[33,41,42] and ≤4 in three trials.[37,53,60] The remaining two trials did not have a required Bishop score for enrollment. At baseline, the mean Bishop score was 4.2 in one[28] and 66 percent of women had a Bishop <6 in the other.[31] Singleton pregnancy was required in nine trials[31,33,37,42,46,48,53,56,60] and not reported in three.[28,41,57] Protocols for drug administration varied widely (see Appendix E-1), both by drug (misoprostol versus dinoprostone), route (oral, intravaginal, intracervical), and indication (postterm pregnancy) ranging from a single dose, daily doses, every 3 to 4 days, or weekly (for multiple doses, up to 2 to 3 doses or until 42 to 44 weeks gestation allowed). After placement of the drug, FHR monitoring was required from 40 minutes to 2 hours prior to discharge home. Eight studies did not report their source of funding, while one received government,[60] two received nonprofit,[33,41] and one received industry funding.[42] Three of the trials were rated good quality,[48,53,60] one was rated poor,[28] and the rest were fair quality.

Characteristics of the women enrolled are in Appendix E-1. Across the trials, the weighted mean age of women enrolled was 25 years, gestational age was 39.8 weeks, and 49 percent were nulliparous. BMI was reported in only two studies (27.6 and 30.4 mg/kg/m^2).[48,53] Most of the studies did not report on, or excluded prior cesarean delivery and diabetes, with one enrolling only women with diabetes (55% gestational).[37] Other comorbidities of interest were not reported. As noted above, the reason or induction was postterm pregnancy in seven, and either a mix of reasons or unclear in the rest. Bishop score at enrollment ranged from 2.9 to 5.5.

All the RCTs reported the incidence of cesarean delivery, and most reported on the time from prostaglandin first dose to delivery (mode not specified in most). Eight studies reported primary fetal harms outcomes, including meconium aspiration syndrome, birth injury, infection, and neonatal encephalopathy. Eight studies reported on maternal primary harm outcomes, mainly postpartum hemorrhage and uterine infections.

Overall, differences between groups were small and the differences were not found to be statistically significant. The strength of evidence for primary outcomes with each comparison are low (meaning that it is likely future studies would change the estimate meaningfully) or insufficient to draw conclusions due to small sample sizes, no corroborating evidence, and imprecision of estimates. Similarly, analysis of prespecified subgroups for this review, using meta-regression of pooled studies or from within-study subgroup analyses, were inadequate to draw conclusions, primarily due to small sample sizes.

Birth Outcomes

Cesarean Delivery

Seven RCTs of dinoprostone[28,31,41,42,46,56,57] and five of misoprostol[33,37,48,53,60] reported on the frequency of cesarean delivery (N=473 and 461, respectively) compared with placebo. Although the incidence was slightly lower with prostaglandins (16% vs. 21%), the difference in the combined estimates were not statistically significant (overall pooled RR 0.80, 95% CI 0.58 to

1.09, I^2=4.3%; Figure 5). This is low-strength evidence. For this outcome, we were able to assess for small sample size bias, and did not find evidence of it using a funnel plot of an Egger test (p=0.969, Appendix F).

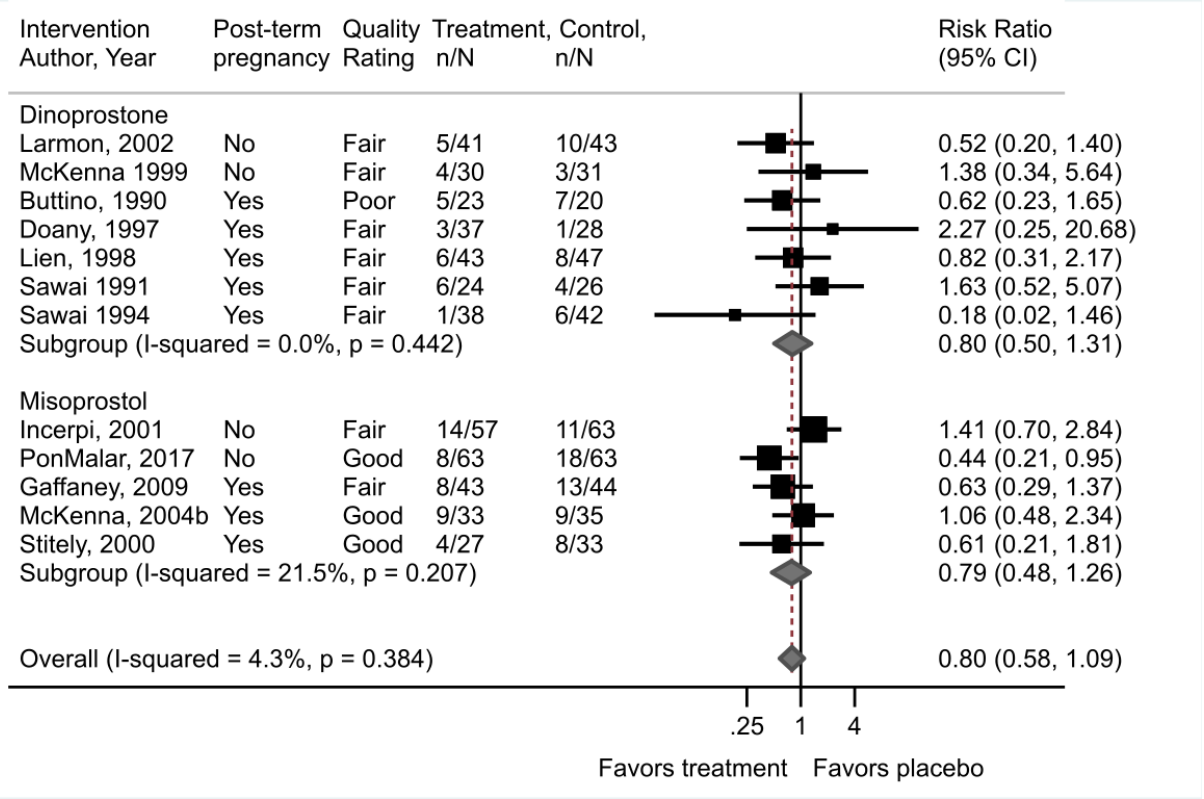
Total Time From Admission to Vaginal Birth and Total Labor and Delivery Length of Stay

A single, fair-quality RCT reported on one of the prespecified primary birth outcomes; a study of dinoprostone gel (N=80) reported that the time in labor and delivery was similar between groups, and the difference was not statistically significant (11.0 hours vs. 11.8 hours; MD –0.8, 95% CI –6.21 to 4.61).[57] This is insufficient evidence to draw conclusions due to lack of confirmatory evidence, imprecision due to small sample size, and study limitations. Subgroup analysis according to parity found that the difference in time in labor and delivery was slightly greater (i.e., favoring the prostaglandin group) in nulliparous women (10.7 hours vs. 15.3 hours; difference 4.6 hours, p=0.035) than in multiparous women (11.2 hours vs. 7.1 hours, difference 4.1 hours, p=not significant [NS]).

Three studies (N=353), two using dinoprostone gel[31,42] in women with postterm pregnancies and one using intravaginal misoprostol in women with diabetes at ≥38 weeks gestation,[37] reported on the time from admission to delivery. None stratified results by mode of delivery as prespecified for this review; therefore, strength of evidence was not assessed. The difference between groups was not statistically significant, although in two studies the time was somewhat longer in the prostaglandin groups (combined estimate across the dinoprostone studies was a difference of 1.79 hours, 95% CI –2.68 to 6.34, I^2=0% and was 30.30 hours, 95% CI –34.15 to 94.75 for misoprostol).

Although not a prespecified outcome of interest, two RCTs (N=117) evaluated time from drug/placebo placement to delivery (any mode). A good-quality RCT of intravaginal misoprostol found that the difference in time from drug/placebo placement to delivery (any mode) was greater in nulliparous women, and shorter in multiparous women. The findings are not statistically significant.[48] A poor-quality RCT found that the difference between dinoprostone and placebo in time from dosage to delivery was smaller, though still not statistically significant, in women with less favorable Bishop scores at the time of drug/placebo placement (difference of –86 hours in the overall group vs. –47 hours in those with Bishop score <5).[28] The strength of evidence for these outcomes was not assessed.

Figure 5. Meta-analysis of cesarean delivery with prostaglandins versus placebo for cervical ripening in the outpatient setting



CI = confidence interval

Meta-regression by type of prostaglandin and by gestational age (determined by enrollment of only postterm pregnancies versus mixed populations) found no significant interaction, with p-value >0.90. Subgroup analyses by study quality (excluding poor-quality RCTs), found very similar pooled estimates (Appendix F). Similarly, subgroup analysis of gestational age (7 studies including only postterm pregnancies versus 5 studies enrolling a mixed population, not specifically including or excluding postterm pregnancies) also found little difference in estimates of cesarean delivery (Appendix F).

Two RCTs (one good-quality of misoprostol and one fair-quality of dinoprostone) conducted within-study subgroup analysis of cesarean delivery frequency according to parity.[48,57] Although the studies were small (total N=118), and the subgroup analyses did not reach statistical significance, the direction of the effect in both studies varied according to parity. Nulliparous women had greater risk of cesarean delivery with a prostaglandin than placebo in the outpatient setting, while in multiparous women the risk was lower with a prostaglandin than placebo (Table 4).

Table 4. Risk of cesarean delivery with prostaglandin versus placebo in postterm pregnancies in the outpatient setting: subgroup analyses according to parity

Study Details	Population Baseline Characteristics	Overall Risk of CD Relative Risk (95% CI)	Nulliparous Risk of CD Relative Risk (95% CI)	Multiparous Risk of CD Relative Risk (95% CI)
McKenna 2004b[48] Good Misoprostol 25 µg Intravaginal single dose N=68	Bishop score < 9 (mean 4.5) Mean age: 29 years Nulliparous: 57%	All: 27.27% (9/33) vs. 25.71% (9/35) RR 1.06 (0.48 to 2.34)	Nulliparous: 40.00% (8/20) vs. 36.84% (7/19) RR 1.09 (0.49 to 2.41)	Multiparous: 7.69% (1/13) vs. 12.5% (2/16) RR 0.62 (0.06 to 6.05)
Sawai, 1991[57] Fair Dinoprostone gel 2 mg Intravaginal twice weekly N=50	Bishop score < 9 (mean 5 nulliparous, 4 multiparous) Mean age: NR Nulliparous: 60%	All: 25.00% (6/24) vs. 15.38% (4/26) RR 1.63 (0.52 to 5.07)	Nulliparous: 42.86% (6/14) vs. 18.75% (3/16) RR 2.29 (0.70 to 7.48)	Multiparous: 0% (0/10) vs. 10.00% (1/10) RR 0.33 (0.02 to 7.32)

CD = cesarean delivery; CI = confidence interval; NR = not reported; RR = relative risk

Secondary Birth Outcomes

All twelve RCTs reported at least one of the secondary birth outcomes, most commonly cesarean delivery for various reasons (failed induction) and cervical assessment at the time of admission (primarily Bishop score). The incidence of failed induction defined as cesarean delivery without fetal distress was similar between groups (10% vs. 11%) and the difference was not statistically significant (8 RCTs; RR 0.71, 95% CI 0.48 to 1.05, I^2=0%). There was a small, but not statistically significant, difference in the incidence of failed induction with fetal distress (4% vs. 6%; 7 RCTs; RR 0.81, 95% CI 0.37 to 1.89, I^2=0%). Bishop score at the time of admission was reported in ten RCTs.[28,33,37,41,42,46,48,53,57,60] The combined analysis found a higher score with prostaglandins versus placebo (10 RCTs; MD 0.48, 95% CI 0.07 to 0.95, I^2=24.7%). However, in a sensitivity analysis removing the poor-quality RCT,[28] the difference in mean Bishop score at admission was smaller and no longer significant (9 RCTs, MD 0.30, 95% CI –0.06 to 0.71). Subgroup analysis by gestational age (as indicated by inclusion of postterm pregnancies only versus mixed populations) found a smaller difference in mixed populations than postterm only populations, but again, the poor-quality study affected the results. One poor-quality study reported the incidence of delivery within 24 hours, but did not stratify by mode of delivery.[28] The incidence for any mode of delivery within 24 hours was 17 percent with dinoprostone and 0 percent with placebo.

Strength of evidence was not assessed for secondary outcomes; these findings are presented here to give additional insights into the evidence.

Fetal/Neonatal Harm Outcomes

Hypoxic-Ischemic Encephalopathy

A good-quality RCT (N=126) reported on "neonatal encephalopathy," not specifically defined as hypoxic-ischemic, with no cases in either the misoprostol or placebo group.[53] This is insufficient evidence to draw conclusions.

Infection (Confirmed Sepsis or Pneumonia)

Only one fair-quality RCT reported on confirmed sepsis, with one case of GBS sepsis in the dinoprostone group (3%; 1/32), and none in the placebo group (0/42); RR 3.91 (95% CI 0.16 to 92.91).[56] One other fair-quality RCT (N=143) reported on incidence of probable sepsis, with 11 percent in the dinoprostone group and 6 percent in the placebo group (RR 1.51, 95% CI 0.30 to 7.69). This evidence is insufficient to draw conclusions.

Meconium Aspiration Syndrome

Two fair-quality RCTs (N=134) reported on meconium aspiration syndrome, with both assessing dinoprostone.[41,57] The overall incidence was low (2% versus 4%), with no differences between groups in either study or when combined (RR 0.76, 95% CI 0.03 to 22.33, I^2=0%; Appendix F). In one of these studies, with two cases (of 26 infants) in the control group, it was noted that both were infants of multiparous women.[57] This evidence is insufficient to draw conclusions.

Birth Trauma

Three RCTs (N= 270, 1 good- and 2 fair-quality)[37,42,60] reported shoulder dystocia, with one trial reporting no events in either group and none of the RCTs finding the differences to be statistically significant. One of the other two trials reported a higher proportion of neonates with shoulder dystocia in the dinoprostone group (7.0% versus 2.1%), but there was also a difference in the proportion of neonates with birth weight >4000gm in the dinoprostone group (33% versus 15%).[42] Pooled analyses also did not find the difference to be statistically significant; the combined incidence was 3 percent (4/127) with prostaglandins versus 0.70 percent (1/143) with placebo. The risk difference was 0.01 (95% CI –0.02 to 0.04, I^2=0%)[37,42,60] (Appendix F). The pooled relative risk, in which the study with zero events was dropped,[37] is RR 3.40 (95% CI 0.55to 20.95), I^2=0%. This is low-strength evidence.

Secondary Fetal/Neonatal Outcomes

All twelve RCTs reported at least one secondary fetal harm outcome (Appendix E-2). Ten RCTs reported an outcome related to Apgar scores; three reported that there were no infants with a score of ≤3 or <7 at five minutes.[33,53,60] Four RCTs (N=293) reported at least one infant with a score <7 at five minutes, with a lower incidence in the prostaglandin groups (1/138, [0.73%] vs. 6/155 [4%]) that did not reach statistical significance in individual studies or in the pooled estimate (RR 0.40, 95% CI 0.09 to 1.81, I^2=0%).[42,46,48,56] Three other RCTs reported the mean Apgar score at 5 minutes, with no differences between groups (mean 9.1 in both groups).[28,37,41] A good-quality RCT (N=60) reported one case of persistent pulmonary hypertension, requiring extracorporeal membrane oxygenation therapy in the placebo group (1/33 [3%]) and none in the misoprostol group (0/27).[60] One fair-quality RCT (N=82) reported that the mean umbilical cord gas at delivery was identical between dinoprostone and placebo (mean 7.27 in both groups),[56] and no study reported the incidence of umbilical cord gas pH <7.0 or 7.1. Although admission to NICU was not a prespecified secondary outcome, since so few studies reported eligible outcomes, we noted that it was reported in 10 RCTs, with none finding a difference between groups.[31,33,37,41,46,48,53,56,57,60]

Strength of evidence was not assessed for secondary outcomes; these findings are presented here to give additional insights into the evidence.

Maternal Harm Outcomes

Uterine Infection

Seven RCTs (N=771) reported on the incidence of uterine infection (chorioamnionitis or endometritis).[31,33,41,42,48,53,56] While there was a small difference between groups favoring prostaglandins, the difference was not statistically significant (7% vs. 10%; RR 0.75, 95% CI 0.40 to 1.39, I^2=0%; Appendix F). This is low-strength evidence. Meta-regression analysis did not find significant interaction based on type of prostaglandin, or on gestational age (as determined by studies that enrolled only women with postterm pregnancies versus those with mixed populations). Sensitivity analysis, removing two RCTs that reported endometritis, resulted in similar findings. For this outcome we were also able to conduct an analyses of small sample size bias, finding no evidence of it (Egger test p=0.981; Appendix F).

Postpartum Hemorrhage

Four RCTs (N=339) reported on overall incidence of postpartum hemorrhage, but not by mode of delivery.[31,33,46,53] The pooled incidence with any delivery mode was 2 percent (3/173) in the prostaglandin groups and 0.60 percent (1/166) in the placebo groups (p=0.36) (Appendix F). No study reported on hemorrhage requiring transfusion. This evidence is insufficient to draw conclusions.

Other Maternal Outcomes

One good-quality RCT (N=126) reported no cases of uterine rupture.[53] This evidence is insufficient to draw conclusions.

Prostaglandin Versus Other Approaches

Seven RCTs compared prostaglandins for cervical ripening with various other approaches, including expectant management, membrane sweeping, and estradiol cream in the outpatient setting. Six RCTs,[31,43,44,50,51,54] involving 919 women, compared dinoprostone (3 trials, N=538)[44,51,54] or misoprostol (1 trial, N=77)[50] versus expectant management, and dinoprostone versus membrane sweeping (3 trials, N=339).[31,43,44] Four were conducted in the United States,[31,43,44,54] one in Israel,[51] and one in Nigeria.[50] One was funded by industry,[54] two by a nonprofit organization, and the remaining three trials did not report their funding sources.[31,50,51] An additional RCT[41] (N=85) conducted in the United States compared dinoprostone versus estradiol cream; it was funded by a nonprofit organization. Five were rated fair quality[31,41,43,50,54] and two were rated poor quality[44,51] due to lack of assessor blinding, poor reporting of patient characteristics, failure to report intent-to-treat (ITT) analysis, and high attrition.

Dinoprostone (PGE2) and Misoprostol (PGE1) Versus Expectant Management

Four RCTs, involving 615 women, compared prostaglandins with expectant management for cervical ripening in the outpatient setting (Appendix E). Two trials (1 fair-[54] and 1 poor-quality[44]) administered intracervical dinoprostone gel 0.5 mg, with repeat doses given either daily[44] or weekly[54] as necessary. One poor-quality trial[51] administered an intravaginal dinoprostone tablet 3 mg, with women returning 3 to 4 days later for a second dose. A fourth fair-quality trial[50] administered a single dose of an intravaginal misoprostol tablet 25 mcg. Only one trial[54] reported that the mean number of doses used was 1.5. Treatment protocols for

expectant management varied across the studies, but generally included a vaginal examination, either daily, weekly, or bi-weekly until spontaneous labor or the need for induction occurred. All of the trials required a period of continuous FHR monitoring prior to discharge for those women who received prostaglandins (2 hours in one, 1 hour in one, and 2 did not specify the duration). In one trial,[54] it was noted that if a second dose of study drug was required, FHR monitoring was only completed if clinically indicated. None of the trials reported the type of provider inserting the prostaglandin or conducting examinations.

Characteristics of the women enrolled are in Appendix E-1. Across the trials, the weighted mean age was 27 years, and the weighted mean gestational age was 39.8 weeks. One trial enrolled only multiparous women[54] with a history of prior cesarean delivery and another trial did not specify parity by groups but did report that mean gravidity was 2.3.[51] Two trials enrolled 58 percent nulliparous women (weighted mean).[44,50] One trial excluded women with prior cesarean delivery[50] and two trials[44,51] did not report on previous cesarean delivery. One trial[54] excluded women with insulin-dependent diabetes and pregnancy-induced hypertension (no additional information provided). No other trials reported on diabetes or hypertension and none of the trials reported BMI. Reason for induction was elective (to prevent postterm pregnancy) in two trials,[50,51] postterm pregnancy (>41 weeks) in one trial,[44] and unclear in the final trial (main objective of this trial was to increase the rate of vaginal birth after prior cesarean delivery).[54] Weighted mean baseline Bishop score was 4.8 (across 3 trials);[44,50,51] median Bishop score was 2.0 in the fourth trial.[54]

Across all outcomes reported, differences between groups were small and did not reach statistical significance. The only primary birth outcome reported was cesarean delivery, with little to no difference between groups (SOE: low). Primary harms as prespecified for this review were infrequently reported; there was little to no difference in uterine infection between groups (SOE: low). Evidence on other harms outcomes was insufficient to draw conclusions, primary due to small sample sizes and lack of detailed reporting.

Birth Outcomes

Cesarean Delivery

The incidence of cesarean delivery was similar for prostaglandins (27%) versus expectant management (26%) across four trials (pooled RR 0.95, 95% CI 0.68 to 1.33, I^2=0%)[44,50,51,54] (Figure 6). Exclusion of the two poor-quality trials[44,51] resulted in a somewhat lower incidence of cesarean delivery with any prostaglandin, though an increased incidence overall (35.4% vs. 39.5%; pooled RR 0.92, 95% CI 0.45 to 1.30, I^2=0%), but the difference was not statistically significant (Appendix F). When stratified by type of prostaglandin, the incidence of cesarean delivery was similar between dinoprostone (29%) and expectant management (27%) across three trials (1 fair- and 2 poor-quality; pooled RR 0.98, 95% CI 0.73 to 1.54, I^2=0%; Appendix F)[44,51,54] but was lower with misoprostol in one fair-quality trial (8% vs. 18%; RR 0.44, 95% CI 0.12 to 1.58).[50] Again, none of the differences were statistically significant. This evidence is low strength.

Secondary Birth Outcomes

Except for Bishop score, authors did not report secondary birth outcomes as specified for this review.

One poor-quality trial reported that women who received dinoprostone compared with expectant management were five times more likely to deliver (vaginal or cesarean) within 24 hours from *entry* into the trial (66% vs. 13%; RR 4.88, 95% CI 2.91 to 8.18).[51]

Two fair-quality trials reported the incidence of failed induction, defined as cesarean delivery due to and excluding fetal distress. Cesarean delivery due to fetal distress was less common with prostaglandins across both trials (7% vs. 8%; pooled RR 0.79, 95% CI 0.25 to 2.05, I^2= 0%)[50,54] but the difference did not reach statistical significance. For cesarean delivery excluding fetal distress, results were inconsistent across the trials with the larger RCT reporting a higher incidence with dinoprostone (23% vs. 16%; RR 1.45, 95% CI 0.90 to 2.33)[54] and the other reporting a lower incidence with misoprostol (5% vs. 13%; RR 0.41, 95% CI 0.08 to 1.99)[50] versus expectant management, although neither reached statistical significance. In addition to the difference in the specific prostaglandin used, the study populations varied. Only multiparous women with a history of prior cesarean delivery[54] enrolled in the dinoprostone trial; the misoprostol trial enrolled 53 percent nulliparous women and excluded those with prior cesarean delivery. An additional trial[44] evaluating dinoprostone stated that there were no cases of cesarean delivery for failed induction (not further defined) in either group.

Two fair-quality trials[50,54] reported mean Bishop scores at time of admission which were similar between prostaglandins and expectant management (pooled difference –0.08, 95% CI -0.70 to 0.87, I^2=0%). A third, poor-quality trial[44] noted that the Bishop score on admission was significantly more favorable among those who received dinoprostone versus expectant management ($p<0.001$; data not reported).

Strength of evidence was not assessed for secondary outcomes; these findings are presented here to give additional insights into the evidence.

Fetal/Neonatal Harm Outcomes

Perinatal Mortality

One fair-quality trial evaluating misoprostol reported a single case of stillborn birth which occurred in the expectant management group (0% [0/38] vs. 2.6% [1/39]; RR 0.34, 95% CI 0.01 to 8.14); no information regarding the timing or circumstances surrounding the death was reported.[50] This evidence is insufficient to draw conclusions

Infection

One fair-quality trial (N=294) evaluating dinoprostone indicated that neonates in both groups had prolonged nursery stays for the same reasons, which included suspected sepsis; no other information was provided.[54]

Secondary Fetal/Neonate Harm Outcomes

Secondary outcomes were reported as specified for this review only for Apgar scores at 5 minutes and umbilical artery pH <7.0. A fair-quality RCT (N=294) reported a single neonate in the dinoprostone group had an Apgar score ≤3 at 5 minutes (0.70% [1/143] vs. 0% [0/151] with expectant management). The frequency of neonates with Apgar scores ≤7 at 5 minutes was similar between dinoprostone (7%) and expectant management (8%) across two trials (pooled RR 0.90, 95% CI 0.31 to 2.74).[44,54] The other two trials (1 dinoprostone[51] and 1 misoprotol[50]) reported mean Apgar score at 5 minutes which was also similar between groups (pooled difference 0.04, 95% CI –0.03 to 0.11), with scores ranging from 9.2 to 9.5 across all groups.[50,51]

One poor-quality trial[44] reported that 20 percent (7/35) of neonates in both the dinoprostone and expectant management group had an umbilical artery pH <7.2.

One fair-quality trial reported that breathing complications that resulted in prolonged nursery stays occurred in both groups. No other information was provided.[54] This same trial reported that 12 percent (17/143) versus 8 percent (11/151) of neonates in the dinoprostone and expectant management groups, respectively, required resuscitation (no further information provided) with no significant difference between groups (RR 1.63, 95% CI 0.79 to 3.36).

Strength of evidence was not assessed for secondary outcomes; these findings are presented here to give additional insights into the evidence.

Maternal Harm Outcomes

Postpartum Hemorrhage

One fair-quality trial reported two cases of postpartum hemorrhage (undefined, mode of delivery not reported), one (3%) in each group (misoprostol [1/38] vs. expectant management [1/39]; RR 1.03, 95% CI 0.07 to 15.82).[50] This evidence is insufficient to draw conclusions

Uterine Infection

Endometritis occurred with similar frequency in the dinoprostone (6% [8/143]) versus the expectant management group (5% [7/151]) in one fair-quality trial (RR 1.21, 95% CI 0.45 to 3.24);[54] this trial also reported no cases of uterine rupture in either group. A second fair-quality trial evaluating misoprostol reported the frequency of "infectious morbidity" which was also similar between groups, respectively (5% [2/38] vs. 8% [3/39]; RR 0.68, 95% CI 0.12 to 3.87).[50] This is low-strength evidence.

Dinoprostone (PGE2) Versus Membrane Sweeping

Three RCTs,[31,43,44] involving 339 women, compared dinoprostone versus membrane sweeping for cervical ripening in the outpatient setting (Appendix E-1). The routes of administration and dosages for dinoprostone varied across the trials and included intravaginal gel 2 mg (1 fair-quality trial),[31] intracervical gel 0.5 mg (one poor-quality trial),[44] and a intravaginal insert 10 mg (1 fair-quality trial).[43] In two trials,[43,44] both treatments were administered in clinic on a daily basis until spontaneous labor or rupture of membranes; if women achieved a Bishop score of ≥8 or reached 42 weeks gestation, they were admitted for labor induction. In the third trial,[31] if necessary, repeat doses/sweepings were administered 1 week after the first administration and then 3 to 4 days thereafter to a maximum gestational age of 43 weeks, at which time they were admitted. None of the RCTs reported the type of provider administering either treatment. In one trial,[31] approximately 34 percent of women required more than one dose/sweep (number of administrations not reported in the other trials). One trial[31] administered a placebo gel in addition to membrane sweeping. Two trials[43,44] performed fetal monitoring (nonstress test and amniotic fluid index) daily in the dinoprostone groups; in one of these trials, identical testing was performed every 3 days in the membrane sweeping group[44] while the second trial did not specify their fetal monitoring protocol in this group. A third trial performed FHR monitoring continuously for a minimum of 1 hour after treatment; women were instructed to perform daily kick counts and repeat fetal testing was performed at 42 weeks and then every 3 to 4 days until 43.9 weeks gestation.[31]

Characteristics of the women enrolled are in Appendix E-1. Across the trials, the weighted mean age of women enrolled was 26 years and 57 percent were nulliparous. Gestational age was

similar across all trials (weighted mean 41 weeks in 2 trials,[43,44] median 41 weeks in 1 trial).[31] Women with prior cesarean delivery were excluded by one trial[31] and not reported in the others.[43,44] None of the studies reported BMI or proportion with comorbidities such as diabetes or hypertension. Reason for induction as an eligibility criterion was postterm pregnancy (≥41 weeks) in all three trials.[31,43,44] For enrollment, women had to have Bishop scores of <4 in two trials (weighted mean 2.8);[43,44] the third trial[31] did not have a required Bishop score for enrollment, though 66 percent of women had a Bishop <6 at baseline. There were no between-group differences in Bishop scores at enrollment.

Few of the prespecified outcomes were reported. There was low-strength evidence that the risk of cesarean delivery did not differ between groups. Other outcomes were generally similar between groups, and mostly deemed insufficient to draw conclusions due to small sample sizes and imprecision.

Birth Outcomes

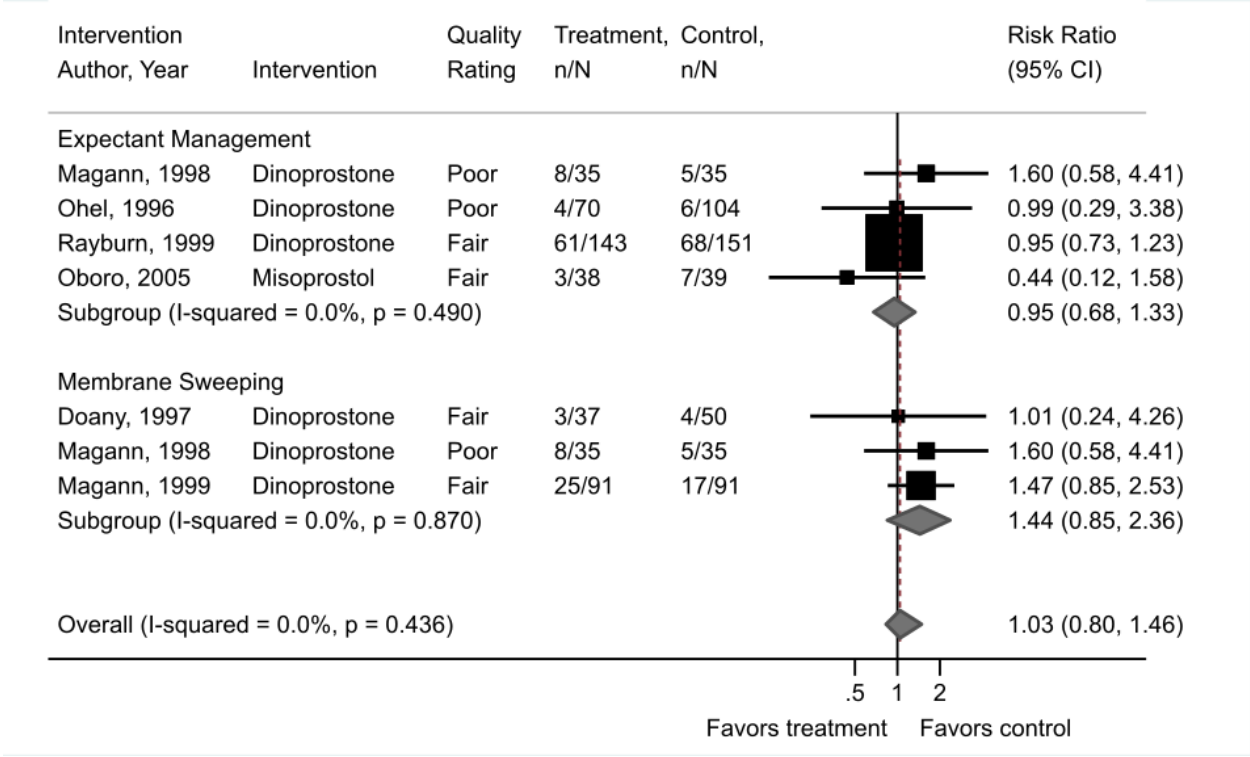
Cesarean Delivery

The incidence of cesarean delivery was greater with dinoprostone (22%) compared with membrane sweeping (15%) across three RCTs, however the difference did not reach statistical significance (pooled RR 1.44, 95% CI 0.85 to 2.36, I^2=0%; Figure 6).[31,43,44] Exclusion of the poor-quality trial[44] resulted in a similar estimate (2 RCTs, pooled RR 1.40, 95% CI 0.64 to 2.65, I^2=0%; Appendix F).[31,43] This evidence is low strength.

Total Time From Admission to Vaginal Birth

Two fair-quality trials reported the time interval from admission to delivery for any mode of delivery, not the prespecified outcome of vaginal birth; therefore, the strength of evidence was not assessed for this outcome. Including cesarean deliveries, it was significantly longer in the dinoprostone versus the membrane sweeping group across the trials (pooled difference 2.64 hours, 95% CI 0.47 to 4.88, I^2=0%).[31,43]

Figure 6. Meta-analysis of cesarean delivery with prostaglandins versus expectant management and membrane sweeping for cervical ripening in the outpatient setting



CI = confidence interval

Secondary Birth Outcomes

Two of the trials reported on secondary birth outcomes, however neither reported the outcomes as they were specified for this review (see Appendix E-2). A fair-quality trial[43] reported that failed induction due to fetal distress requiring operative delivery (i.e., cesarean or forceps) was twice as frequent with dinoprostone (12%) than membrane sweeping (6%), but the difference was not statistically significant (RR 2.20, 95% CI 0.80 to 6.08). The frequency of operative delivery excluding fetal distress (i.e., cephaplelux disproportion or transverse arrest) was identical in both groups (18%). The second, poor-quality, trial[44] stated that there were no cases of cesarean delivery for failed induction (not further defined) in either group. Both trials reported Bishop score at time of admission; one reported a statistically significant difference between groups which favored membrane sweeping (mean 6.6 vs. 8.6; MD –1.93, 95% CI –2.66 to –1.20)[43] while the other simply stated that there was no difference between groups ($p>0.05$).[44]

Strength of evidence was not assessed for secondary outcomes; these findings are presented here to give additional insights into the evidence.

Fetal/Neonate Harm Outcomes

No trial reported primary fetal harms as specified for this report; therefore, the strength of evidence was not assessed for this outcome. The frequency of probable or suspected infection (i.e., sepsis) was similar in the dinoprostone and membrane sweeping groups across two fair-quality trials (2 RCTs; 4% vs. 2%; pooled RR 1.96, 95% CI 0.39 to 11.80). A fair-quality trial[43] also reported NICU admission due to meconium ("syndrome" not specified), which occurred in one neonate (1%) each group.

Two trials[43,44] reported on secondary fetal harms of interest to this report, none of which differed statistically between groups. In both trials, the incidence of neonates with Apgar scores <7 at 5 minutes was low, and not significantly different between groups (none in one study, and one in each group in the other). The incidence of umbilical artery pH <7.2 was identical between groups (24%) across both trials (RR 1.0, 95% CI 0.56 to 1.69, I^2=0%).

Maternal Harm Outcomes

In one fair-quality trial there were no cases of postpartum hemorrhage (undefined) in either group.[31] The frequency of uterine infection (chorioamnionitis or endometritis) was similar, and not statistically significantly different between groups in two fair-quality trials (4.7% vs. 4.3%; RR 1.22, 95% CI 0.56 to 2.75, I^2=0%; Appendix F).[31,43] This is low-strength evidence.

Dinoprostone (PGE2) Versus Estradiol Cream

One fair-quality RCT[41] (N=85) compared intracervical dinoprostone gel 0.5 mg versus intravaginal estradiol cream 4 mg. The study also had a placebo arm and is included in the section above. Women received doses on a weekly basis until the onset of spontaneous labor, rupture of membranes, or an indication for delivery arose. Authors did not report the type of provider administering the treatments or the mean number of doses received. Reason for induction of labor was unclear; women with ≥37 weeks gestation and Bishop score ≤6, and an uncomplicated pregnancy (no comorbidities) were enrolled. The first 20 women underwent 2 hours of FHR monitoring following drug administration (discontinued because no abnormalities or significant uterine activity were noted in any of the 20 women). The study was conducted in the United States and had funding from a nonprofit organization. Characteristics of women enrolled are in Appendix E-1. Mean maternal age was 22 years, 19 percent were nulliparous, mean gestational age was 37.2 weeks, and mean Bishop score at baseline was 2.9.

Primary outcomes, as specified for this review, were cesarean delivery and uterine infection. However, although the incidence of both were lower with dinoprostone, as the sample size was very small (41 to 43 per group), the differences were not statistically significant and the evidence is insufficient to draw conclusions for all primary outcomes reported.

Birth Outcomes

The cesarean delivery rate was lower with dinoprostone (12%) versus estradiol cream (31%); however, the difference did not reach statistical significance (RR 0.41, 95% CI 0.16 to 1.06). Regarding secondary birth outcomes, failed induction was not reported as specified for this review and was defined as cesarean delivery for fetal distress (2% in both groups) and cesarean delivery excluding fetal distress (e.g., dystocia, abnormal presentation) (7% vs. 23%, respectively; RR 0.32, 95% CI 0.10 to 1.09). The mean Bishop score at the time of admission was similar (7.9 vs. 8.0). Strength of evidence was not assessed for secondary outcomes; these findings are presented here to give additional insights into the evidence.

Fetal/Neonate Harm Outcomes

The trial did not report primary and secondary fetal harms as specified for this review. One case of meconium aspiration ("syndrome" not specified) occurred in the dinoprostone group (1/41 vs. 0/44; RR 3.21, 95% CI 0.13 to 76.74). The frequency of secondary fetal harm outcomes was similar between groups: mean Apgar score at 5 minutes (9.4 vs. 9.2) and mean arterial cord blood pH (7.32 vs. 7.35).

Maternal Harm Outcomes

The incidence of uterine infection was somewhat lower following dinoprostone versus estradiol cream, but the differences were not statistically significant (and SOE was insufficient to draw conclusions): chorioamnionitis (2.4% vs. 9.1%; RR 0.27, 95% CI 0.03 to 2.30) and endomyometritis (4.9% vs. 6.8%; RR 0.72, 95% CI 0.13 to 4.07). No secondary maternal harms were reported.

Dinoprostone Versus Single-Balloon Catheter

One fair-quality, retrospective cohort study (n=153)[67] compared intravaginal, controlled-release dinoprostone 10 mg inserts versus intracervical single-balloon catheters filled to 30 to 60 ml for cervical ripening in the outpatient setting. The study did not specify the type of provider inserting the cervical ripening agent or conducting examinations. After insertion and before discharge home, women in both groups were required to undergo a nonstress test; additionally, women in the dinoprostone group were required to complete one hour of FHR monitoring and one hour of walking sequentially. Over the course of the study, four (5.6%) women in the dinoprostone group required more than one dose and 20 (28%) had a catheter inserted, while in the catheter group, one (1.2%) was also given dinoprostone. Enrollment criteria did not specify reasons for induction; prior cesarean delivery or multiple pregnancies were excluded. The study was conducted in Canada and funding was not reported.

Characteristics of women enrolled are in Appendix E-1. Mean maternal age was 31 years, mean BMI was 26.3, 65 percent were nulliparous, and gestational age was 41 weeks or greater in 80% (37–40 weeks in the remainder). Nineteen percent of women were GBS positive and 2 percent each had gestational diabetes and hypertension. The primary indication for induction was postdate pregnancy (84%), followed by medically indicated (10%). Cervical dilation at baseline was 1 centimeter or less in 73 percent and greater than 1 centimeter in the rest. The latter was the only characteristic that varied significantly between groups, with the catheter group more dilated at the time of insertion than the dinoprostone group. The authors controlled for this variable in their primary analyses (i.e., time from insertion to delivery and time from admission to delivery).

Statistically significant differences were not found between groups in the few outcomes reported that were prespecified primary outcomes for this report (cesarean delivery, shoulder dystocia or postpartum hemorrhage; Appendix E-2). The strength of evidence is insufficient to draw conclusions for all primary outcomes.

Birth Outcomes

The cesarean delivery rate was higher with dinoprostone (32%) versus single-balloon catheter (22%) however, the difference was not statistically significant (RR 1.48, 95% CI 0.87 to 2.50). Though not reported as specified for this review, time from admission to delivery (vaginal or cesarean) did not differ statistically between groups (median 11.9 vs. 11.3 hours; adjusted HR 1.05, 95% CI 0.74 to 1.51, for dinoprostone vs. catheter). Regarding secondary birth outcomes, cervical dilation improved less following dinoprostone compared with a catheter (MD –1.0 cm, 95% CI –1.44 to –0.60) and fewer women who received dinoprostone were considered favorable (i.e., modified Bishop score >6 or noted to be “favorable for induction” in patient records) at removal of the first ripening agent (48% vs. 97%; RR 0.49, 95% CI 0.75 to 0.64). However, the catheter group was significantly more dilated than the dinoprostone group at the time of insertion of the cervical ripening agent which was not controlled for in the analysis.

Fetal/Neonatal Harm Outcomes

The incidence of shoulder dystocia did not differ statistically between the dinoprostone (2.82%) and catheter groups (6.10%), RR 0.46 (95% CI 0.09 to 2.31). Authors indicated "meconium" as a birth complication, with no difference between groups (28.17% vs. 23.17%, respectively; RR 1.22, 95% CI 0.71 to 2.09), but did not specify the syndrome. Secondary fetal harms did not differ statistically for dinoprostone versus catheter and included Apgar score less than 7 at 5 minutes (5.63% vs. 2.44%; RR 2.31, 95% CI 0.47 to 12.24) and NICU admission (7.04% vs. 6.10%; RR 1.15, 95% CI 0.35 to 3.83).

Maternal Harm Outcomes

The risk of postpartum hemorrhage (not defined) was 1.41 percent with dinoprostone versus 6.10 percent with a single-balloon catheter and did not differ statistically between groups (RR 0.23, 95% CI 0.03 to 1.93). Two women (2.82%) in the dinoprostone group and none in the catheter group had a fever over 38.5 degrees Celsius but no further details were provided.

Single-Balloon Silicone Versus Latex Catheter

A fair-quality RCT (n=534) compared single-balloon catheters made of silicone with those made of latex for cervical ripening in the outpatient setting.[45] Catheters were inserted by "trained obstetric and midwifery staff," and women were asked to return the following day for induction. If insertion with the assigned catheter failed, the other could be tried, and if that failed, a medication method could be implemented. As a result, 97 percent of those assigned to the silicone single-balloon and 91 percent of those assigned to the latex single-balloon received the assigned intervention. Analyses were conducted based on intention-to-treat assumptions. Enrollment criteria were not specific to reason for induction, but Bishop score <7 and gestational age ≥36 weeks were required, and prior cesarean delivery or multiple pregnancies were not excluded. A 2-hour period of FHR monitoring was required after catheter insertion. The study was locally funded.

Characteristics of women enrolled are in Appendix E-1. Seventy-one percent enrolled were 25 to 35 years old, 59 percent were nulliparous, 30 percent were categorized as overweight and 22 percent as obese. The median gestational age was 39 weeks and 6 days. At baseline, the proportion of women with diabetes or hypertension were not reported, 5 percent had a prior cesarean delivery, and 6 percent received antibiotics for GBS prophylaxis. Postterm pregnancy was the reason for induction in 31 percent, and medically indicated in 65 percent of women. Cervical dilation at baseline was less than 1 centimeter in 65 percent, and 1 to 2 centimeters in the rest; Bishop scores were ≤4 in 35 percent and 5 to 6 in the rest.

The only primary birth outcome reported was cesarean delivery, with the primary fetal harm outcome of infection, and maternal harms of infection and hemorrhage reported. Overall, differences between groups were small and not found to be statistically significant (Appendix E-2). The strength of evidence was low for cesarean delivery and insufficient to draw conclusions neonatal infection, chorioamnionitis and postpartum hemorrhage.

Birth Outcomes

The cesarean delivery rate was 39 percent versus 40 percent with silicone versus latex single-balloon catheters (RR 0.98, 95% CI 0.80 to 1.22).[45] This is low-strength evidence. The secondary birth outcome of the mean Bishop score at the time of admission (removal of catheter) was 5.9 in

both groups. Strength of evidence was not assessed for secondary outcomes; these findings are presented here to give additional insights into the evidence.

Fetal/Neonatal Harm Outcomes

Although the study did not report any of the primary fetal harm outcomes for this review, admission to NICU due to "infection risk" was reported, with little to no difference in incidence between groups (1.87% vs. 1.47%; RR 1.27, 95% CI 0.35 to 4.69).[45] Secondary fetal harm outcomes included respiratory distress with high lactate level, requiring NICU admission (10% vs. 7%; RR 1.32, 95% CI 0.76 to 2.31) and incidence of umbilical cord artery lactate level ≥ 6.0 mmol/L (10% vs. 10%; RR 1.06, 95% CI 0.63 to 1.76) for silicone versus latex catheters. Strength of evidence was not assessed for secondary outcomes; these findings are presented here to give additional insights into the evidence.

Maternal Harm Outcomes

This trial reported on the incidence of intrapartum antibiotics for suspected chorioamnionitis (14% vs. 10%; RR 1.35, 95% CI 0.85 to 2.16), but this evidence is insufficient to draw conclusions in part due to not reporting confirmed infections.[45] Postpartum hemorrhage was reported by volume of blood loss, but not according to mode of delivery (vaginal versus cesarean). The differences between the catheters was small and not statistically significant for any of the three categories of blood loss. For the most severe category (>1500 ml) there were 1.89 percent in the silicone and 1.12 percent in the latex group (RR 1.69, 95% CI 0.41 to 7.01). The strength of evidence is insufficient to draw conclusions.

The primary outcome specified for this RCT was accidental ROM at the time of catheter insertion. This outcome was not one prespecified for this review, but the study conducted subgroup analyses on parity. Overall, accidental ROM occurred more frequently with the silicone catheter (7% vs. 2%; RR 4.8; 95% CI 1.7 to 14.0). Subgroup analyses found increased risk in nulliparous women (RR 5.4, 95% CI 1.6 to 18.1), but not in parous women (RR 3.1, 95% CI 0.3 to 29.3), although this subgroup was small (N=163, vs. N=371 for nulliparous). No other subgroup analyses were conducted. Strength of evidence was not assessed for secondary outcomes; these findings are presented here to give additional insights into the evidence.

Key Question 4. Fetal Surveillance During Cervical Ripening With Prostaglandins in Any Setting

No studies comparing different methods and protocols for fetal surveillance during cervical ripening with prostaglandins in any setting that met inclusion criteria were identified.

Summary Tables: Evidence for Efficacy/Effectiveness and Harms

The key findings of this review, including strength of evidence ratings, are summarized for each Key Question in Tables 5-7.

Table 5. Primary birth-related efficacy/effectiveness outcomes: cesarean delivery

Key Question	Intervention	Findings[a]	Studies	Incidence	Relative Risk (95% CI) I^2 for Pooled Analyses[b]
Key Question 1: Prostaglandin Outpatient vs. Inpatient	Dinoprostone outpatient vs. inpatient	Low-strength evidence of little or no difference	2 RCTs (n=1,120)	23% vs 23%	RR 0.97 (0.75 to 1.25)
	Dinoprostone outpatient vs. inpatient	Low-strength evidence of little or no difference	4 Cohort studies (n=2,511)	33% vs. 33%	RR 0.79 (0.67 to 0.98)
Key Question 2: Mechanical Method Outpatient vs. Inpatient	Single-balloon catheter outpatient vs. inpatient	Low-strength evidence of a small, but nonsignificant, difference	3 RCTs (n=370)	12% vs. 20%	RR 0.59 (0.21 to 1.03)
	Single-balloon catheter outpatient vs. inpatient	Low-strength evidence of a small, but nonsignificant, difference	2 Cohort studies (n=1,057)	33% vs. 30%	RR 0.95 (0.72 to 1.22)
	Outpatient catheter vs. inpatient dinoprostone	Low-strength evidence of a small, but nonsignificant, difference	2 RCTs (n=549)	33% vs. 26%	RR 1.24 (0.88 to 1.70)
Key Question 3: Outpatient Comparison of Methods	Dinoprostone gel 2.5 mg vs. 5.0 mg	Low-strength evidence of little or no difference	1 RCT (n=116)	20% vs. 19%	RR 1.07 (0.51 to 2.22)
	Prostaglandin vs. placebo	Low-strength evidence of a small, but nonsignificant, difference	12 RCTs (n=924)	16% vs. 21%	RR 0.80 (0.58 to 1.09), I^2=4.3%
	Prostaglandin vs. expectant management	Low-strength evidence of little or no difference	4 RCTs (n=615)	27% vs. 26%	RR 0.95 (0.68 to 1.33)
	Dinoprostone vs. membrane sweeping	Low-strength evidence of a small, but nonsignificant, difference	3 RCTs (n=339)	22% vs. 15%	RR 1.44 (0.85 to 2.36)
	Silicone vs. latex single-balloon catheters	Low-strength evidence of little or no difference	1 RCT (n=534)	39% vs. 40%	RR 0.98 (0.80 to 1.22)

CI = confidence interval; RCT = randomized controlled trial; RR = relative risk

[a] Difference of < 5% = little or no difference; 5% to 10% = small difference; 11% to 20% = moderate difference; >20% = large difference.

[b] I^2=0% unless otherwise indicated.

Table 6. Primary fetal harms outcomes

Key Question	Intervention	Outcome	Findings[a]	Studies	Incidence	Relative Risk (95% CI) I^2 for Pooled Analyses[b]
Key Question 1: Prostaglandin Outpatient vs. Inpatient	Dinoprostone outpatient vs. inpatient	Infection	Low-strength evidence of little or no difference	2 RCTs (n=1,120)	4% vs. 3%	RR 1.39 (0.67 to 3.03)
Key Question 2: Mechanical Method Outpatient vs. Inpatient	Single-balloon catheter outpatient vs. inpatient	Birth Trauma[c]	Low-strength evidence of little or no difference	1 RCT (n=129)	2% vs. 3%	RR 0.49 (0.05 to 5.30)
	Single-balloon catheter outpatient vs. inpatient	Shoulder dystocia	Low-strength evidence of a moderate, but nonsignificant, difference	1 RCT (n=129)	3% vs. 11%	RR 0.28 (0.06 to 1.30)
Key Question 3: Outpatient Comparison of Methods	Dinoprostone vs. placebo	Meconium Aspiration Syndrome[d]	Low-strength evidence of a small, but nonsignificant, difference	2 RCTs (n=134)	2% vs. 4%	RR 0.76 (0.03 to 22.33)
	Prostaglandins vs. placebo	Shoulder dystocia	Low-strength evidence of a small, but nonsignificant, difference	3 RCTs (n=270) 2 RCTs (n=150)	3% vs. 0.70% 6% vs. 1%	RD 0.01 (–0.02 to 0.04)[e] RR 3.40 (0.55 to 20.95)

CI = confidence interval; RCT = randomized controlled trial; RD = risk difference; RR = relative risk

[a] Difference of ≤1% = little or no difference; >1% to 3% = small difference; >3% to 8% = moderate difference; >8% = large difference

[b] I^2=0% unless otherwise indicated.

[c] There were 3 cases total (1 in the outpatient and 2 in the inpatient group) which included 1 case each of brachial plexus injury, cephalohematoma, and scalp laceration plus cephalohematoma; authors did not report which specific injuries occurred in which group)

[d] Neonatal intensive care unit (NICU) admission required, not specified as the Syndrome

[e] RD analysis is presented because one RCT reported no events and would not be included in a RR analysis. Of note, one of the other two trials reported a higher proportion of neonates with shoulder dystocia in the dinoprostone group (7.0% vs. 2.1%), but there was also a difference in the proportion of neonates with birth weight >4000 gm in the dinoprostone group (33% vs. 15%).

Table 7. Primary maternal harms outcomes

Key Question	Intervention	Outcome	Findings[a]	Studies	Incidence	Relative Risk (95% CI) I^2 for pooled analyses[b]
Key Question 2: Mechanical Method Outpatient vs. Inpatient	Single-balloon catheter outpatient vs. inpatient	Uterine Infection	Low-strength evidence of little or no difference	2 RCTs (n=259)	5% vs. 5%	RR 0.99 (0.31 to 3.19)
	Outpatient catheter vs. inpatient dinoprostone	Postpartum Hemorrhage	Low-strength evidence of a small, but nonsignificant, difference	2 RCTs (n=549)	28% vs. 25%	RR 1.10 (0.62 to 1.56)
Key Question 3: Outpatient Comparison of Methods	Prostaglandins vs. placebo	Uterine Infection	Low-strength evidence of a small, nonsignificant, difference	7 RCTs (n=771)	7% vs. 10%	RR 0.75 (0.40 to 1.39)
	Prostaglandins vs. expected management	Uterine Infection	Low-strength evidence of little or no difference	1 RCT (n=294)	6% vs. 5%	RR 1.21 (0.45 to 3.24)
	Prostaglandins vs. membrane sweeping	Uterine Infection	Low-strength evidence of a small, but nonsignificant, difference	2 RCTs (n=269)	7% vs. 4%	RR 1.22 (0.56 to 2.75)

CI = confidence interval; RCT = randomized controlled trial; RR = relative risk

[a] Difference of <1% = little or no difference; >1% to 3% = small difference; >3% to 8% = moderate difference; >8% = large difference

[b] I^2=0% unless otherwise indicated.

Insufficient Evidence

For this report, there were several instances where the evidence was insufficient to draw conclusions (see Appendix H). It is important to note these instances for clarity. The Summary Tables (above) include only evidence for which there was at least low-strength evidence. Other important outcomes where evidence was insufficient to draw conclusions included outcomes related to time from admission to vaginal delivery, time in labor and delivery, fetal/neonatal harm outcomes (e.g., hypoxic-ischemic encephalopathy, intracranial/subgaleal hemorrhage), and maternal harm outcomes (e.g., hemorrhage requiring transfusion, postpartum hemorrhage by mode of delivery, confirmed chorioamnionitis). For the harm outcomes, the main reason for the evidence being insufficient was inadequate sample sizes for determining rare events. This reason is combined with other issues that reduced the strength of evidence (e.g., study limitations, lack of consistency or directness). For the benefit outcomes, the main reason is that very few studies reported the outcomes prespecified for this report, such that when they were reported the evidence was indirect (i.e., using a different definition). See Appendix H for details of our assessments of the strength of evidence.

Discussion

Findings in Relation to the Decisional Dilemmas

The key decisional dilemmas identified for this review were – when cervical ripening is indicated, what methods can be recommended as effective, but without increased risks, in the outpatient setting, and what surveillance best serves women having cervical ripening using a prostaglandin setting. More specifically, there was a need to assess the benefits of outpatient versus inpatient cervical ripening, without increasing risk (rise in cesarean delivery rate, adverse neonatal outcomes), framed within considerations of cost, patient autotomy, and satisfaction. The findings of this review can inform an update of guidance from American College of Obstetricians and Gynecologists (ACOG), as the prior guidance (a 2009 Practice Bulletin on induction of labor) was unable to make recommendations on outpatient cervical ripening due to too few studies (one each on prostaglandins and catheters).[14] An even more recent Cochrane review from 2017 found the evidence on outpatient versus inpatient cervical ripening to be insufficient to draw conclusions on key outcomes.[15] While current use of outpatient cervical ripening in the United States is not well documented, controversy over its use centers around interpretation of risk. Hence, the findings of this review are useful for informing choices by clinicians and pregnant women by providing better information on the benefits (birth outcomes), and risk of harms (fetal/neonatal and maternal), and some insight into women's preferences. Although many of the included studies on the outcomes of outpatient cervical ripening reported on the fetal heart rate (FHR) monitoring protocols used in the trials, we did not find evidence examining the benefits and harms of different protocols for FHR during cervical ripening with prostaglandins in any setting.

Across the primary outcomes prioritized for this review, there was only low-strength evidence, with many gaps where the evidence was insufficient to draw conclusions. However, for some interventions and outcomes, the evidence was more robust than was available at the time of the prior ACOG guidance, or in the 2017 Cochrane review. The first category of outcomes to consider are the effectiveness outcomes related to birth. For these, we found low-strength evidence that outpatient cervical ripening with dinoprostone or single-balloon catheters did not increase the risk of cesarean delivery relative to inpatient cervical ripening. Similarly, outpatient single-balloon catheter use did not increase the risk of cesarean delivery compared with inpatient dinoprostone. While there was not a clear difference in findings based on variables such as type of dinoprostone (gel or insert) or study quality, there are too few studies and participants to draw conclusions on the impact of these factors. Comparisons in the outpatient setting also did not indicate increased risk of cesarean delivery with dinoprostone gel at 2.5 versus 5 mg, latex versus silicone single-balloon catheter, or prostaglandins (either type) versus placebo, expectant management, or membrane sweeping. Analysis of type of prostaglandin, study quality, or of women with postterm pregnancy versus study populations that also included women with other indications for cervical ripening were possible for placebo comparisons and did not alter these findings. Most studies reported on cesarean delivery, but few reported on the time from admission to vaginal delivery. Many studies instead reported time from administration of cervical ripening method to delivery (of any mode). Additionally, much of the evidence for direct comparisons of different interventions in the outpatient setting was insufficient.

Evidence on fetal/neonatal harms was incomplete because some key outcomes were not reported or evidence was insufficient. Because fetal/neonatal harms are rare events, studies with inadequate sample sizes are unlikely to identify statistically significant differences, particularly

where the differences are small. With low-strength evidence, our findings suggest no signal of differences in risk of hypoxic-ischemic encephalopathy, infection, or meconium aspiration syndrome with dinoprostone used for cervical ripening in the outpatient setting compared with the inpatient setting. Our findings on single-balloon catheters suggest no signal for increased risk for infection, shoulder dystocia and birth trauma when used for outpatient cervical ripening versus inpatient cervical ripening. Comparing interventions in the outpatient setting, we did not find important differences in the risk of meconium aspiration syndrome with a prostaglandins versus placebo, however, while not statistically significant the absolute risk for shoulder dystocia was slightly greater in the prostaglandin group. The low-strength evidence for these conclusions leads to a need for future studies to confirm this finding. Outcomes where evidence was found, but was deemed insufficient, include perinatal mortality and fetal/neonatal infection with the double-balloon catheter (outpatient versus inpatient) and dinoprostone versus expectant management in the outpatient setting. The limited evidence on these outcomes did not suggest obvious increased risk for cervical ripening in the outpatient setting. More evidence is needed to draw firm conclusions. Analysis of effect modifiers such as type of prostaglandin, or study quality were not possible for these outcomes due to too few studies.

For maternal harms, again the findings are incomplete because most key outcomes were not reported, or evidence was insufficient. Low-strength evidence suggests that outpatient cervical ripening with dinoprostone did not increase the risk of hemorrhage requiring transfusion compared with use in the inpatient setting. This outcome was not reported for other comparisons. There was not a clearly increased risk of postpartum hemorrhage with single-balloon catheter sin the outpatient setting compared to the inpatient setting or compared with dinoprostone in the inpatient setting. Across three small randomized controlled trials (RCTs), although we found a slightly greater incidence of postpartum hemorrhage with prostaglandins than placebo in the outpatient setting, it was not statistically significant leading to a conclusion that prostaglandins are not associated with increased risk. The low strength of evidence for this conclusion leads to a need for future studies to confirm this finding. A caution in interpreting the evidence on postpartum hemorrhage is that the preferred outcome would be stratified by mode of delivery, so that hemorrhage associated with cesarean delivery could be separated from vaginal births, but the studies did not report the outcome this way. Evidence on double-balloon catheters (outpatient versus inpatient), prostaglandins versus expectant management or membrane sweeping (outpatient), or latex versus silicone single-balloon catheters was insufficient, but did not suggest obvious increased risk for cervical ripening in the outpatient setting. More evidence is also needed for this topic. The evidence on uterine infection (either chorioamnionitis or endometritis) was a bit more robust. Low strength evidence indicated little to no difference uterine infection risk with single-balloon catheters in the outpatient versus inpatient setting. In the outpatient setting, low strength evidence found small, nonsignificant, differences between prostaglandins and placebo, expectant management or membrane sweeping. Evidence on the risk of chorioamnionitis with silicone versus latex single-balloon catheters in the outpatient setting was insufficient, but the use of antibiotics for suspected cases was greater in the silicone group. Evidence for the double-balloon catheter was also insufficient, but did not indicate an obvious increase in risk of uterine infection. Analysis by type of prostaglandin, study quality, or of women with postterm pregnancy versus populations of women with this and other indications for cervical ripening were possible for placebo comparisons and did not alter these findings.

Reasons for insufficient evidence were multifactorial, but were largely driven by the small numbers of studies and participants for less common outcomes, where more events are required

for statistical power and precise estimates of effect. In addition, for some interventions there was only one RCT and thus, no corroborating evidence to assess consistency of the findings. However, for adverse outcomes, where there was insufficient evidence to draw firm conclusions for guidance, it is important to recognize that we also did not find early signals (i.e., much greater incidence, although not statistically significant) of increased risk with the outpatient cervical ripening interventions.

We anticipated heterogeneity in the way that outcomes would be defined and reported, and as noted above. For the secondary outcomes, listed in the Methods section, we found that they were often not reported as specified for this review, or with a great deal of heterogeneity, making it more difficult to draw conclusions about them across studies. Failed induction (as evidence by cesarean delivery) was reported in many trials, but most did not describe or define the criteria used to diagnose "failed induction." Across the Key Questions, differences between groups in incidence of failed induction were small in RCT evidence. One exception was an RCT of single-balloon catheters, where the incidence was lower in the outpatient group, while a cohort study found the opposite. Vaginal birth within 24 hours was not reported, while some studies reported any delivery within 24 hours. For dinoprostone, RCT evidence indicated similar incidence in outpatient and inpatient groups, and slightly higher incidence than placebo in the outpatient setting. Bishop score or cervical dilation on admission was reported in a few studies, favoring outpatient dinoprostone in one RCT, with inconsistent findings with single-balloon catheters (outpatient versus inpatient), and was similar for other comparisons. Secondary fetal/neonatal harm outcomes reported included Apgar scores (mainly <7) at 5 minutes, various outcomes related to respiratory problems that typically required support, and umbilical cord artery gas pH. None of the comparisons were significantly different for these outcomes. Unfortunately, secondary maternal harm outcomes were very infrequently reported, and not as defined in the protocol for this report.

In order to best use evidence on outpatient cervical ripening, adequate information is needed to determine if there is variation in outcomes for specific subgroups. The subgroups identified a priori for this review were parity, maternal age, Group B Streptococcus (GBS) status, diabetes (pregestational, gestational), and hypertension (chronic, preeclampsia without severe features, gestational). Important fetal subgroups were fetal growth restriction, and gestational age (by category). No RCT data were available to evaluate differential effectiveness or harms (i.e., effect modification, heterogeneity of treatment effect) for subgroups specified in our protocol based on outpatient versus inpatient status. To effectively evaluate this, data from well-powered high-quality (preferably RCTs) studies that report the outcomes for all treatment groups (e.g., outpatients and inpatients) for all strata of a given subgroup (e.g., for nulliparous and multiparous women) are needed. The limited information available is less than ideal, based on meta-regressions and subgroup analyses within our own meta-analyses (where we had at least 7 studies), and subgroup analyses conducted by the studies we included. These findings are hypothesis-generating and are only appropriate to guide future studies. In comparing outpatient and inpatient dinoprostone use, subgroup analyses of a cohort study suggested that postterm pregnancies had similar outcomes compared with the overall study population.[30] Subgroup analysis of women with Bishop score >3 at enrollment in an RCT comparing outpatient double-balloon catheters with inpatient dinoprostone found a slightly higher incidence of cesarean delivery in the catheter group, though this difference was not statistically significant. In outpatient comparisons of prostaglandins and placebo for cervical ripening, meta-regression by type of prostaglandin and by gestational age (determined by enrollment of only postterm

pregnancies versus mixed populations), and analysis of study quality did not find significant subgroup effects on the risk for cesarean delivery. Subgroup analyses conducted by two RCTs (Table 4) of outpatient cervical ripening found that nulliparous women had higher frequency of cesarean delivery with a prostaglandin than with placebo (2.4% and 3.2% greater), while multiparous women had a lower frequency of cesarean delivery with a prostaglandin versus placebo (4% to 10% lower). Within the subgroups, differences in risk of cesarean delivery between prostaglandin and placebo did not reach statistical significance.

Strengths and Limitations

The evidence base on outpatient cervical ripening has multiple important limitations, but there are strengths to be recognized as well. Clearly, the evidence comparing interventions in the outpatient and inpatient settings suffers from too few RCTs with too small of sample sizes (range 48 to 827; mean 172), particularly when assessing harms that are rare. More and better-quality evidence is needed on specific interventions, including misoprostol and double-balloon catheters, direct comparisons of double- and single-balloon catheters, and the various formulations and routes of administration of dinoprostone or misoprostol. The studies are limited by the narrowness of the populations enrolled and inadequate reporting on or analysis of important subgroups such as women over 30 or 35, the effect of GBS status, diabetes, hypertension, fetal growth restriction, and gestational age categories. The studies generally either excluded women with such characteristics, or failed to report on them in detail. RCTs are needed to help address issues of imbalance in characteristics such as these in observational studies. There was variation in how outcomes were defined and reported across the studies. Few studies reported the outcomes as they were specified for this review, based on input from experts. For example, the primary birth outcome of time from admission to vaginal birth was rarely reported as such. More often, studies reported on time from admission to any delivery mode, time from placement of the intervention to delivery (any mode), or placement to the onset of active labor. Input from experts indicates that, in addition to establishing similar efficacy and risk of harm, when comparing outpatient and inpatient cervical ripening, there is interest in reducing the amount of time in the labor and delivery ward. Hence, these other outcomes are not as relevant, but are frequently reported. There were also numerous primary harm outcomes that failed to meet the criteria set by the experts. These outcomes include meconium aspiration (rather than the syndrome), neonatal encephalopathy (not specifically hypoxic-ischemic), infection (typically suspected, rather than confirmed), postpartum hemorrhage (not according to mode of delivery), and uterine infection (again, typically not reported as confirmed infections). Secondary outcomes also suffered from similar lack of specificity, with most not consistent with the definitions for this review and for the comparison of interventions in the outpatient setting versus each other; we were looking for longer-term outcomes related to breastfeeding, maternal mood, and mother-baby attachment, but no study reported these. In addition to these specifics, the studies were limited by inadequate reporting on many characteristics of the populations, interventions, comparators, and outcomes that limited our ability to analyze their impact. For example, women's cervical dilation when synthetic oxytocin was initiated and the dose/timing of augmentation was not consistently noted in the included studies.

Subgroups analyses were infrequent, and few studies were conducted to directly examine the key subgroups of interest. Examples include race, provider type, parity, and maternal body mass index (BMI). A major limitation was the lack of studies evaluating fetal monitoring in the context of cervical ripening using a prostaglandin (in any setting).

Strengths of the evidence base included that the available evidence can shed light on the use of outpatient cervical ripening for younger women with singleton pregnancies, primarily nulliparous women either to prevent or for postterm pregnancy. The evidence was adequate to address the impact of dinoprostone and single-balloon catheters on cesarean delivery, and some fetal/neonatal harms in this population.

Limitations of the review process included our intention to undertake a "best evidence" approach. Initially, we proposed including cohort and case-control studies if RCT evidence was inadequate. Based on this, we included nine cohort studies, most of which were small (range 42 to 1343, mean 567). However, even after including these, we recognized that the evidence base was likely to provide inadequate information to guide recommendations or clinical practice, in particular related to the risk of important harms, and for fetal surveillance studies. After discussion with the Agency for Healthcare Research and Quality Task Order Officer and the review sponsor, we undertook an additional search for studies with much broader design criteria – single-arm studies of outpatient cervical ripening that reported on any of the harms prioritized for this review. However, this additional search did not identify any relevant studies. While the lack of identifying additional studies may be a limitation, we feel that the approach was a strength. Other limitations of our review process were that we excluded studies published in languages other than English, and were unable to conduct small sample size bias assessments for most outcomes due to small numbers of studies. We consider our approach to meta-analysis, using the profile-likelihood random effects models, to be a strength of our approach because we assumed that there was heterogeneity across the studies and knew we would have small numbers of studies for most outcomes.

Applicability

A number of factors could impact the applicability of our findings. Studies generally included women with singleton pregnancies with vertex presentations, without a history of a prior cesarean delivery or other uterine surgeries, premature rupture of membrane/rupture of membrane, comorbidities (e.g., diabetes, hypertension), uterine growth restriction, or other fetal problems. The exception is the evidence comparing prostaglandins in the outpatient setting, where 35 percent of women had a prior cesarean delivery. While studies did not often limit enrollment by parity, most women were nulliparous. The mean age of enrolled women was 26 to 28 years in the prostaglandin studies, and slightly older in studies of catheters (30 years). As such, the studies were not able to evaluate effects in women with older maternal age (e.g., >30 or 35 years). Gestational age was typically 40.6 weeks. The definition of "postterm" varied or was often not defined. However, using ACOG's 2014 definitions, 40.6 weeks is "late-term", rather than "post-term" (42 weeks and beyond).[76] Mean Bishop score at enrollment was 2.9 to 4 (weighted mean of 3.6). The evidence is most applicable to women with at 40 weeks gestation or greater, or to prevent a postterm pregnancy. The findings were less applicable to women with comorbidities, such as diabetes or hypertension, including those that developed during pregnancy. Some studies did not restrict enrollment of women with these comorbidities, but the small percentages of such women ultimately enrolled did not allow for subgroup analyses to inform on the applicability of the findings to these subgroups. There was too little, or no, information on other important characteristics of pregnant women that were identified a priori, including race, ethnicity, BMI, maternal prepregnancy health status (including mental health), and intangibles such as birth plan/philosophy and type of provider to understand implications for outcomes or applicability of the findings. Applicability to low-income patients, or those with low

access to healthcare is unclear. Although a small number of studies required that women have had prenatal care, or that they live within 30 minutes of the hospital, and most of the studies did not have such restrictions, other factors, such as comorbidities (diabetes, hypertension) need to be considered. These problems with applicability did not vary by the type of cervical ripening method. None of the studies reported other information relevant for assessing applicability, such as the description of the source of potential study participants and the number of women randomized relative to the number of women enrolled.

Intervention-related factors that may limit applicability include dose, route of administration, and re-administration schedule variation with medications, and balloon-fill volume variation with catheters. Across the studies, we found little variation in prostaglandin dose, within the specific drug and formulations or routes of administration. For example, the evidence for misoprostol applies to a 25 mcg intravaginal dose, or a 100 mcg oral dose, and dinoprostone doses and application were consistent with the specific product (i.e., the gel or the insert). All prostaglandin studies reported FHR monitoring following administration, but the duration ranged from 40 minutes to 2 hours. Reapplication criteria and schedules for prostaglandins were most often not well reported, and while a small number of studies limited to a single dose, most were either silent on reapplication or did not report the actual number of doses women received. Additionally, we noted that the applicability of the findings to misoprostol (PGE1) is limited, particularly for the inpatient versus outpatient comparison. Single- and double-balloon catheter fill volumes were consistent across the studies, according to the specific catheter, but monitoring procedures prior to discharge were inconsistently reported.

Outcomes related to time from admission to delivery often included cesarean as well as vaginal delivery. Inclusion of cesarean delivery reduces the applicability of the findings from individual studies, due to variation in clinical practice, policy, and preferences across provider, patient, health system or country, and across time (as temporal trends for cesarean delivery have changed).[77]

Information relevant for assessing applicability of the care setting such as details on the type of outpatient setting (e.g., home, home birthing center) or inpatient setting (e.g., hospital, clinic) was poorly reported. Other limitations to our ability to assess applicability include the lack of information on variation in provider type (e.g., midwife, nurse, or generalist obstetrician), rural versus metropolitan, planned home birth versus planned inpatient birth, and country. While many studies reported that the interventions were applied by a midwife or a physician, none limited to a specific provider type or stratified results by this variable. Although 60 percent of studies were conducted in the United States, we were unable to assess the impact of country of study or other geographic location characteristics (e.g., rural, metropolitan) on the applicability of specific results.

A number of evidence gaps or limitations in evidence potentially impacted the applicability of our findings. Lack of evidence on misoprostol, double-balloon catheters, hygroscopic dilators, direct comparison of interventions, type of provider applying the intervention, reapplication criteria and schedules, and protocols for clinician contact/monitoring in outpatient cervical ripening may limit applicability to common obstetrical practice. Inadequate reporting of maternal and fetal factors such as parity, maternal age, GBS status, diabetes, hypertension, fetal growth restriction, and gestational age made it difficult to access applicability of our findings to subgroups of patients with these factors.

Implications for Clinical Practice, Education, Research, or Health Policy

Considerations for Clinical Practice

The implications of the findings of this report include the ability to provide more guidance to clinicians and pregnant women on the relative benefits and harms of outpatient cervical ripening. This report finds low strength of evidence that outpatient cervical ripening with dinoprostone and single-balloon catheters does not impose increased risk of cesarean delivery and does not indicate that there are important signals of increased risk of fetal/neonatal and maternal harms, with the limitation that not all such harms were adequately studied or reported. The findings apply most directly to women under age 30, with singleton fetuses with vertex presentation, and no major comorbidities. The question of the characteristics of pregnant women and fetuses that will benefit most or have the lowest risk of harm is not addressed by this evidence. Similarly, there is less information to guide the use of double-balloon catheters, hygroscopic dilators, misoprostol, or to compare doses and routes of administration of prostaglandins.

Women's preferences for the setting for cervical ripening (inpatient versus outpatient), and satisfaction with outpatient cervical ripening are important factors in applying the results of this systematic review. Our assessment of studies pertaining to these issues suggest a preference for outpatient cervical ripening and that women are willing to make tradeoffs based on their personal circumstances, however the decision-making process is complex. Commonly weighed factors included support at home, proximity to the hospital and perceived safety. Overall, women who had cervical ripening in the outpatient setting seemed to be more satisfied with their experience compared with women who had cervical ripening in an inpatient setting. These findings are based on qualitative studies of women undergoing cervical ripening in the United States and Australia, or surveys of women participating in trials of outpatient cervical ripening in Canada and Australia.[68-75] These studies included women with low-risk pregnancies. Most were being induced for postterm pregnancies and over half were nulliparous. These were identified as a "contextual question" for this report, and more detailed information on these studies is available upon request.

Research Recommendations

- Additional RCTs are needed to corroborate findings for all comparisons, particularly where there is only a single small study available currently (e.g. outpatient misoprostol, double-balloon catheters, dilators). Preference is for more studies in the United States.
- Larger RCTs, with sample sizes large enough to evaluate important harm outcomes are needed. Sample size calculations should be based on discussion with clinical experts on minimally important differences in risk for key rare harm outcomes.
- Quality improvement studies and registry studies, employing the power of electronic medical records, may be utilized to evaluate rare harms and explore process questions.
- Also needed are RCTs with sufficient sample size to evaluate differential effectiveness and harms of outpatient cervical ripening in important subgroups of the population: parity, maternal age, GBS status, diabetes (pregestational, gestational), hypertension (chronic, preeclampsia without severe features, gestational), fetal growth restriction, gestational age (<39 weeks, 39 to 41 weeks, >41 weeks).

- Future studies should evaluate the effects of important subgroups (e.g. race, maternal BMI) and additional factors not considered here (e.g. augmentation of labor with synthetic oxytocin, epidural anesthesia).
- While we acknowledge that there can be challenges in enrolling pregnant women in RCTs, we do not recommend additional retrospective cohort studies. Large, prospective, cohort studies that use strong methods to control for variation in baseline risk of women studied (e.g., propensity score matching) may be helpful. Large, well-conducted case-control studies may be useful to evaluate the risk of rare harms.
- Evidence comparing methods of fetal surveillance (e.g., intermittent heart rate auscultation versus electronic monitoring) during cervical ripening with prostaglandins is needed, as we found no studies of different approaches that might be useful in outpatient cervical ripening.

Conclusions

In women with low-risk pregnancies, incidence of cesarean delivery, fetal/neonatal infection or birth trauma, or maternal uterine infection were not significantly different with dinoprostone or single-balloon catheter for cervical ripening in the outpatient versus inpatient setting. Prostaglandins compared with placebo, expectant management, or membrane sweeping in the outpatient setting did not significantly change the incidence of cesarean delivery, meconium aspiration, shoulder dystocia, or maternal uterine infection . Evidence for these findings was low strength; evidence for other comparisons or outcomes was insufficient.

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Abbreviations and Acronyms

Abbreviation	Definition
ACOG	American College of Obstetricians and Gynecologists
AHRQ	Agency for Healthcare Research and Quality
BMI	body mass index
CI	confidence interval
CQ	Contextual Question
DCE	discrete choice experiment
EHC	Effective Health Care
FHR	fetal heart rate
GA	gestational age
GBS	Group B Streptococcus
GDM	gestational diabetes
IOL	induction of labor
ITT	intent-to-treat
KQ	Key Question
MD	mean difference
NA	not applicable
NHS	National Health Service
NICU	Neonatal Intensive Care Unit
NR	not reported
NS	not significant
OHSU	Oregon Health & Science University
OR	odds ratio
PCORI	Patient-Centered Outcomes Research Institute
PICO	Population, Intervention, Comparator, Outcome
PRISMA	Preferred Reporting Items for Systematic Reviews
PROM	premature rupture of membrane
RCT	randomized controlled trial
ROM	rupture of membrane
RR	relative risk
SEADS	Supplemental Evidence and Data for Systematic review
SOE	strength of evidence
TEP	Technical Expert Panel

Appendix A. Introduction

Table A-1. Details of commonly used pharmacologic interventions for cervical ripening[1]

Cervical Ripening Agent	Formulations Available	Dose or Description	Frequency/ Duration of Application	Application	Recommended Monitoring	Contraindications
Dinoprostone (PGE2)	Endocervical gel (Prepidil®)[2] Frozen, bring to room temperature before use	0.5 mg/ 3 g	Repeat with 0.5 mg every 6 hours, max 1.5 mg in 24 hours	Applied to the cervical canal just below the level of the internal os	Remain recumbent for 30 minutes. Monitor fetal heart rate and uterine activity continuously starting 15 to 30 minutes before gel introduction and continuing for 30 to 120 minutes after insertion	• Patients in whom oxytocic drugs are generally contraindicated or where prolonged contractions of the uterus are considered inappropriate, such as: o History of cesarean section or major uterine surgery o Presence of cephalopelvic disproportion o History of difficult labor and/or traumatic delivery o Grand multiparae (≥6 previous term pregnancies) with non-vertex presentation o Hyperactive or hypertonic uterine patterns o Fetal distress where delivery is not imminent o Obstetric emergencies where the benefit-to-risk ratio for either the fetus or the mother favors surgical intervention • Patients with hypersensitivity to prostaglandins or constituents of the gel • Patients with placenta previa or unexplained vaginal bleeding during this pregnancy • Patients for whom vaginal birth is not indicated (e.g., vasa previa, active herpes genitalia)

Cervical Ripening Agent	Formulations Available	Dose or Description	Frequency/ Duration of Application	Application	Recommended Monitoring	Contraindications
Dinoprostone (PGE2)	Extended release insert (Cervidil®)[3] Frozen until use	10 mg (0.3 mg/hour over 12 hours)	Remove upon onset of labor or after 12 hours.	Placed transversely in the posterior fornix of the vagina	Remain recumbent for 2 hours. Monitor fetal heart rate and uterine activity continuously, starting 15 to 30 minutes before introduction of the insert, continue until 15 minutes after removal.	• Patients with hypersensitivity to prostaglandins • Patients with clinical suspicion or definite evidence of fetal distress where delivery is not imminent • Patients with unexplained vaginal bleeding during this pregnancy • Patients in whom there is evidence or strong suspicion of marked cephalopelvic disproportion • Patients in whom oxytocic drugs are contraindicated or when prolonged contraction of the uterus may be detrimental to fetal safety or uterine integrity (e.g., previous cesarean section, major uterine surgery) • Patients already receiving intravenous oxytocic drugs • Multipara with 6 or more previous term pregnancies
Misoprostol (PGE1)	Tablet (Cytotec®)[4]	25 mcg (1/4 of a 100 mcg tablet)	Every 4 to 6 hours	Placed intravaginally, without gel	Remain recumbent for 30 minutes after application. Monitor fetal heart rate and uterine activity continuously for at least 3 hours after application.	• Cytotec should not be taken by anyone with a history of allergy to prostaglandins • Cytotec should not be used in cases where uterotonic drugs are generally contraindicated or where hyperstimulation of the uterus is considered inappropriate (e.g., cephalopelvic disproportion, grand multiparity, hypertonic, or hyperactive uterine patterns, or fetal distress where delivery is not imminent, or when surgical intervention is more appropriate)

PGE1 = prostaglandin E1; PGE2 = prostaglandin E2

Table A-2. Details of commonly used nonpharmacologic interventions for cervical ripening[1]

Cervical Ripening Agent	Formulations Available	Dose or Description	Frequency/ Duration of Application	Application	Recommended Monitoring	Contraindications
Single balloon catheter	Foley catheter	The balloon reservoir is inflated with 30 to 50 mL of normal saline	Remove after 6 hours, or rupture of membranes. If spontaneous expulsion occurs do not re-insert.	The catheter is introduced into the endocervix, into the potential space between the amniotic membrane and the lower uterine segment. The balloon is retracted so that it rests on the internal os	None	None[a]
Double balloon catheter	Cook® Catheter[5]	Both balloon reservoirs are inflated with 80 mL of normal saline	Remove after 6 hours, or rupture of membranes. If spontaneous expulsion occurs do not re-insert.	After completing the single balloon steps noted above, the second balloon is inflated. This balloon places mechanical pressure on the external cervical os	None	Patients receiving or planning to undergo exogenous prostaglandin administration Placenta previa, vasa previa, or placenta percreta Transverse fetal orientation Prolapsed umbilical cord Prior hysterectomy, classic uterine incision, myomectomy or any other full-thickness uterine incision Pelvic structural abnormality Active genital herpes infection Invasive cervical cancer Abnormal fetal heart-rate patterns Breech presentation Maternal heart disease Multiple gestational pregnancy Polyhydramnios Presenting part above the pelvic inlet Severe maternal hypertension Any contraindication to labor induction Ruptured membranes

Cervical Ripening Agent	Formulations Available	Dose or Description	Frequency/ Duration of Application	Application	Recommended Monitoring	Contraindications
Hygroscopic dilator	Dilapan[6]	Available in 3 dimensions: 4 x 65 mm, 4 x 55 mm, and 3 x 55 mm. More than one dilator can be inserted	Up to 24 hours	Insert the Dilapan rod through the cervix, up to the handle, so that the collar rests on the external os. Use a gauze pad to keep in place if needed	None	Presence of clinically apparent genital tract infection
Laminaria tent	Dilateria[7]	60 mm long; available in 4 thicknesses: 3 mm (thin); 4 mm (medium); 5 mm (thick); 6 mm (extra thick)	Up to 24 hours	Gradually insert Dilateria in the endocervical canal using long forceps so that it traverses the internal and external os. Dilateria should extended outside the cervical canal a minimum of 10 mm; attached string should rest in the vaginal vault.	None	Presence of vaginal, cervical, or pelvic infection A “non-compliant” patient – patient must return within 24 hours for removal of Dilateria Incidence of infectious complication is possible

[a] Foley catheters are not approved for cervical ripening or induction of labor by the Food and Drug Administration. General contraindications for the medical device include active genital tract infection, pelvic structure abnormality that prevents passage of the device, and invasive cervical cancer.[8,9]

Appendix B. Methods

Details of Study Selection

Search Strategy

Literature Databases: Ovid® MEDLINE®, Embase®, CINAHL®, Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews were searched. Detailed search strategies are listed below.

Publication Date Range: Searches were conducted across all Key Questions, with study dates reaching back to the inception of each database up to October 2019, with an updated search done through July 2020. Searches were deduplicated and screened for inclusion.

Supplemental Evidence and Data for Systematic review (SEADS): Manufacturers and other stakeholders of included drugs and devices were informed about submitting information relevant to this review using a Federal Register notification. A portal about the opportunity to submit information was made available on the Effective Health Care (EHC) website. We received two submissions, one from the review sponsor, ACOG, and one from Ferring Pharmaceuticals. While both were supportive of this research effort, neither included citations for evidence to consider. Additionally, after the public review period closed, we received another submission from Medicem, Inc. which included citations for Dilapan-S; all citations were reviewed and none met the inclusion criteria for this report.

Hand Searching: Reference lists of included articles were reviewed for includable studies.

Medline Search

Databases: Ovid MEDLINE® and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions® 1946 to October 9, 2019; updated search to July 27, 2020

Key Questions 1 – 3

Randomized Controlled Trials and Systematic Reviews

1 Pregnant Women/
2 pregnancy/ or labor, obstetric/ or pregnancy outcome/
3 pregnan*.ti,ab,kf.
4 Labor, Induced/
5 Cervical Ripening/
6 ((cervi* or labor or labour) adj3 (induction or induce* or ripening or priming)).ti,ab,kf.
7 ((foley or cook or balloon) adj3 catheter).ti,ab,kf.
8 ((foley or cook) adj3 balloon).ti,ab,kf.
9 7 or 8
10 Misoprostol/
11 Dinoprostone/

12 (misoprostol or dinoprostone or "prostaglandin E1" or "prostaglandin E2" or PGE1 or PGE2 or "hygroscopic dilator*" or dilapan or "laminaria tent*").ti,ab,kf.
13 Outpatients/
14 (outpatient* or "out of hospital").ti,ab,kf.
15 or/1-3
16 or/4-6,9-12
17 or/13-14
18 16 and 17
19 15 and 16
20 randomized controlled trial.pt.
21 (random* or control* or placebo or sham or trial).ti,ab,kw.
22 (systematic or "meta analysis" or metaanalysis or review or cochrane).ti,ab,kf.
23 20 or 21 or 22
24 19 and 23
25 limit 24 to english language
26 (animal* or mouse or mice or rat* or dog* or canine or cow* or bovine or horse* or mare* or pig* or porcine or rabbit* or llama* or sheep or ewe*).ti.
27 25 not 26

Cohort and Case-Control Studies

1 Pregnant Women/
2 pregnancy/ or labor, obstetric/ or pregnancy outcome/
3 pregnan*.ti,ab,kf.
4 Labor, Induced/
5 Cervical Ripening/
6 ((cervi* or labor or labour) adj3 (induction or induce* or ripening or priming)).ti,ab,kf.
7 ((foley or cook or balloon) adj3 catheter).ti,ab,kf.
8 ((foley or cook) adj3 balloon).ti,ab,kf.
9 7 or 8
10 Misoprostol/
11 Dinoprostone/
12 (misoprostol or dinoprostone or "prostaglandin E1" or "prostaglandin E2" or PGE1 or PGE2 or "hygroscopic dilator*" or dilapan or "laminaria tent*").ti,ab,kf.
13 Outpatients/
14 (outpatient* or "out of hospital").ti,ab,kf.
15 or/1-3
16 or/4-6,9-12
17 or/13-14
18 16 and 17
19 15 and 16
20 (animal* or mouse or mice or rat* or dog* or canine or cow* or bovine or horse* or mare* or pig* or porcine or rabbit* or llama* or sheep or ewe*).ti.
21 19 not 20
22 exp cohort studies/
23 (cohort* or prospective or observational).tw.
24 controlled clinical trial.pt.
25 epidemiologic methods/

26 limit 25 to yr=1966-1989
27 exp case-control studies/
28 (case$ and control$).tw.
29 or/22-24,26-28
30 21 and 29
31 30 not (abortion or terminate or termination).ti.
32 limit 31 to english language

Key Question 4

Randomized Controlled Trials and Systematic Reviews

1 Fetal Monitoring/
2 ((fetal or foetal or fetus or foetus or infant*) and (surveillance or monitor*)).ti,ab,kf.
3 1 or 2
4 Labor, Induced/
5 Cervical Ripening/
6 ((cervi* or labor or labour) and (induction or induce* or ripening or priming)).ti,ab,kf.
7 ((foley or cook or balloon) adj3 catheter).ti,ab,kf.
8 ((foley or cook) adj3 balloon).ti,ab,kf.
9 Misoprostol/
10 Dinoprostone/
11 (misoprostol or dinoprostone or "prostaglandin E1" or "prostaglandin E2" or PGE1 or PGE2 or "hygroscopic dilator*" or dilapan or "laminaria tent*").ti,ab,kf.
12 or/6-11
13 3 and 12
14 randomized controlled trial.pt.
15 (random* or control* or cohort or case* or placebo or sham or trial).ti,ab,kw.
16 (systematic or "meta analysis" or metaanalysis or review or cochrane).ti,ab,kf.
17 or/14-16
18 13 and 17
19 limit 13 to (clinical study or clinical trial or comparative study or controlled clinical trial or meta analysis or randomized controlled trial or "systematic review" or systematic reviews as topic)
20 18 or 19
21 limit 20 to english language
22 (animal* or mouse or mice or rat* or dog* or canine or cow* or bovine or horse* or mare* or pig* or porcine or rabbit* or llama* or sheep or ewe*).ti.
23 21 not 22

Cohort and Case Control Studies

1 Fetal Monitoring/
2 ((fetal or foetal or fetus or foetus or infant*) and (surveillance or monitor*)).ti,ab,kf.
3 1 or 2
4 Labor, Induced/
5 Cervical Ripening/
6 ((cervi* or labor or labour) and (induction or induce* or ripening or priming)).ti,ab,kf.
7 ((foley or cook or balloon) adj3 catheter).ti,ab,kf.

8 ((foley or cook) adj3 balloon).ti,ab,kf.
9 Misoprostol/
10 Dinoprostone/
11 (misoprostol or dinoprostone or "prostaglandin E1" or "prostaglandin E2" or PGE1 or PGE2 or "hygroscopic dilator*" or dilapan or "laminaria tent*").ti,ab,kf.
12 or/6-11
13 3 and 12
14 limit 13 to english language
15 exp cohort studies/
16 (cohort* or prospective or observational).tw.
17 controlled clinical trial.pt.
18 epidemiologic methods/
19 limit 18 to yr=1966-1989
20 exp case-control studies/
21 (case$ and control$).tw.
22 or/15-17,19-21
23 14 and 22

Highly Relevant Journals Search

1 "obstetrics & gynecology".jn.
2 "american journal of obstetrics and gynecology".jn.
3 "british journal of obstetrics and gynaecology".jn.
4 "international Journal of Gynaecology & Obstetrics".jn.
5 "journal of midwifery & women's health".jn.
6 "midwifery".jn.
7 "birth".jn.
8 Cervical Ripening/
9 (cervi* adj3 ripe*).ti,ab,kf.
10 Labor, Induced/
11 ((labor or labour) adj3 induc*).ti,ab,kf.
12 Outpatients/
13 outpatient*.ti,ab,kf.
14 8 or 9
15 (10 or 11) and (12 or 13)
16 14 or 15
17 or/1-7
18 16 and 17

Cochrane Central Register of Controlled Trials Search

Database: EBM Reviews - Cochrane Central Register of Controlled Trials to September 2019; updated search to July 27, 2020

Key Questions 1 – 3

1 Pregnant Women/

2 pregnancy/ or labor, obstetric/ or pregnancy outcome/
3 pregnan*.ti,ab.
4 Labor, Induced/
5 Cervical Ripening/
6 ((cervi* or labor or labour) adj3 (induction or induce* or ripening or priming)).ti,ab.
7 ((foley or cook or balloon) adj3 catheter).ti,ab.
8 ((foley or cook) adj3 balloon).ti,ab.
9 7 or 8
10 Misoprostol/
11 Dinoprostone/
12 (misoprostol or dinoprostone or "prostaglandin E1" or "prostaglandin E2" or PGE1 or PGE2 or "hygroscopic dilator*" or dilapan or "laminaria tent*").ti,ab.
13 Outpatients/
14 (outpatient* or "out of hospital").ti,ab.
15 or/1-3
16 or/4-6,9-12
17 or/13-14
18 15 and 16 and 17
19 limit 18 to (journal article or meta analysis or randomized controlled trial)
20 limit 19 to english language

Key Question 4

1 Fetal Monitoring/
2 Abortion, Spontaneous/ (403)
3 Perinatal Death/ (44)
4 Pregnancy Outcome/ (2796)
5 exp Fetal Death/ (213)
6 ((fetal or foetal or fetus or foetus or infant*) and (surveillance or monitor* or death or mortality or demise)).ti,ab. (8448)
7 (miscarriage* or stillbirth).ti,ab. (2380)
8 (pregnancy adj2 (loss or failure)).ti,ab. (820)
9 or/1-8 (13560)
10 Labor, Induced/ (1099)
11 Cervical Ripening/ (331)
12 ((cervi* or labor or labour) and (induction or induce* or ripening or priming)).ti,ab. (4850)
13 ((foley or cook or balloon) adj3 catheter).ti,ab. (1293)
14 ((foley or cook) adj3 balloon).ti,ab. (140)
15 13 or 14 (1330)
16 Misoprostol/ (1460)
17 Dinoprostone/ (1099)
18 (misoprostol or dinoprostone or "prostaglandin E1" or "prostaglandin E2" or PGE1 or PGE2 or "hygroscopic dilator*" or dilapan or "laminaria tent*").ti,ab. (5996)
19 or/10-12,15-18 (10102)
20 9 and 19 (1081)
21 limit 20 to (journal article or meta analysis or randomized controlled trial) (702)

22 limit 21 to english language (661)

Cochrane Database of Systematic Reviews Search

Database: EBM Reviews - Cochrane Database of Systematic Reviews 2005 to October 9, 2019; updated search to July 27, 2020

Key Questions 1–4

1 ((cervi* or labor or labour) adj3 (induction or induce* or ripening or priming)).ti.
2 ((foley or cook or balloon) adj3 catheter).ti,ab.
3 (misoprostol or dinoprostone or "prostaglandin E1" or "prostaglandin E2" or PGE1 or PGE2 or "hygroscopic dilator*" or dilapan or "laminaria tent*").ti.
4 ((foley or cook or balloon) and (pregnan* or labor or labour or cervi*)).ti,ab.
5 or/1-4
6 limit 5 to full systematic reviews

CINAHL Search

Database: CINAHL Plus with Full Text to October 9, 2019; updated search to July 27, 2020

Key Questions 1–4

S1 (MH "Labor, Induced")
S2 (MH "Cervix Dilatation and Effacement")
S3 (MH "Misoprostol")
S4 (MH "Dinoprostone")
S5 cervi OR cervical
S6 ripening
S7 S5 AND S6
S8 misoprostol OR dinoprostol OR prostaglandin E1 OR prostaglandin E2 OR PGE1 OR PGE2 OR hygroscopic dilator or dilapan or laminaria tent
S9 foley OR cook OR balloon
S10 catheter*
S11 S9 AND S10
S12 S1 OR S2 OR S3 OR S4
S13 S7 OR S8 OR S11
S14 S12 OR S13
S15 pregnan* OR labor OR labour
S16 S11 AND S15
S17 S7 OR S8 OR S16
S18 S12 OR S17
S19 S12 OR S17
Limiters - English Language; Exclude MEDLINE records; Human

Embase Search

Database: Elsevier Embase to October 9, 2019; updated search to July 2020

Key Questions 1–4

('labor induction'/exp AND ('misoprostol'/exp OR 'prostaglandin e2'/exp OR 'foley balloon catheter'/exp) OR 'uterine cervix ripening'/exp OR 'cervical ripening':ab,ti) AND [english]/lim AND ('article'/it OR 'article in press'/it) AND [embase]/lim NOT ([embase]/lim AND [medline]/lim)

Inclusion and Exclusion Criteria

Criteria for Inclusion/Exclusion of Studies in the Review

The criteria for inclusion and exclusion of studies for the systematic were based on the Key Questions and on the specific criteria listed in Table B-1. Population, interventions, comparators, outcomes, timing, and settings (PICOTS) for each key question. Outcomes prioritized as primary outcomes for this systematic review are footnoted and listed in **bold** below.

Table B-1. PICOTS

PICOTS	Inclusion Key Question 1: Prostaglandin Inpatient vs. Outpatient	Inclusion Key Question 2: Mechanical Method Inpatient vs. Outpatient	Inclusion Key Question 3: Outpatient Comparison of Methods	Inclusion Key Question 4: Fetal Surveillance	Exclusion
Population	Pregnant women ≥37 weeks undergoing cervical ripening in the outpatient setting Important maternal subgroups: parity, maternal age, GBS status, diabetes (pre-gestational, gestational), hypertension (chronic, preeclampsia without severe features, gestational) Important fetal subgroups: fetal growth restriction, gestational age (<39 weeks, 39 to 41 weeks, >41 weeks)	Pregnant women ≥37 weeks undergoing cervical ripening in the outpatient setting Important maternal subgroups: parity, maternal age, GBS status, diabetes (pre-gestational, gestational), hypertension (chronic, preeclampsia without severe features, gestational) Important fetal subgroups: fetal growth restriction, gestational age (<39 weeks, 39 to 41 weeks, >41 weeks)	Pregnant women ≥37 weeks undergoing cervical ripening in the outpatient setting Important maternal subgroups: parity, maternal age, GBS status, diabetes (pre-gestational, gestational), hypertension (chronic, preeclampsia without severe features, gestational) Important fetal subgroups: fetal growth restriction, gestational age (<39 weeks, 39 to 41 weeks, >41 weeks)	Pregnant women ≥37 weeks undergoing cervical ripening with a prostaglandin Important maternal subgroups: parity, maternal age, GBS status, diabetes (pre-gestational, gestational), hypertension (chronic, preeclampsia without severe features, gestational) Important fetal subgroups: fetal growth restriction, gestational age (<39 weeks, 39 to 41 weeks, >41 weeks)	Women with contraindications to cervical ripening in the outpatient setting: a multiple pregnancy, prior uterine rupture and breech presentation of the fetus.
Intervention	Pharmacologic agents (prostaglandins) given in outpatient setting	Mechanical methods (balloon catheters, laminaria tents) used in outpatient setting	Mechanical methods (balloon catheters, laminaria tents) or pharmacologic agents (prostaglandins)	Any method of fetal surveillance	Catheters not available in the U.S. Pharmacy-compounded prostaglandin products Other cervical ripening methods: Castor oil, nipple stimulation, membrane stripping, sexual intercourse, acupuncture/pressure, transcutaneous nerve stimulation, herbal compounds

PICOTS	Inclusion Key Question 1: Prostaglandin Inpatient vs. Outpatient	Inclusion Key Question 2: Mechanical Method Inpatient vs. Outpatient	Inclusion Key Question 3: Outpatient Comparison of Methods	Inclusion Key Question 4: Fetal Surveillance	Exclusion
Comparator	Mechanical (i.e., balloon catheters, laminaria tents) and/or pharmacologic (i.e., prostaglandins) methods in the inpatient setting	Mechanical (i.e., balloon catheters, laminaria tents) and/or pharmacologic (i.e., prostaglandins) methods in the inpatient setting	Any comparator including alternative mechanical device or protocol, alternative pharmacologic agent or dose, combination mechanical and pharmacologic, placebo, and other cervical ripening methods excluded as intervention (e.g., Castor oil, acupuncture)	Another method of fetal surveillance Another protocol for fetal surveillance with the same method No monitoring	Catheters not available in the U.S. Pharmacy-compounded prostaglandin products
Outcomes Effectiveness (birth-related)	**Total time admission to vaginal birth; total L&D length of stay**[c] **Cesarean delivery rate overall**[c] Vaginal birth within 24 hours Failed induction rate, defined as: Cesarean delivery in patient at <6cm dilation excluding fetal distress (labor dystocia, failure to progress, etc.) Cesarean delivery in patient at <6 cm dilation for fetal distress Cervical assessment at time of admission (e.g., latent vs. active phase, Bishop score, cervical dilation) Time from ROM to delivery	**Total time admission to vaginal birth; total L&D length of stay**[c] **Cesarean delivery rate overall**[c] Vaginal birth within 24 hours Failed induction rate, defined as: Cesarean delivery in patient at <6cm dilation excluding fetal distress (labor dystocia, failure to progress, etc.) Cesarean delivery in patient at <6 cm dilation for fetal distress Cervical assessment at time of admission (e.g., latent vs. active phase, Bishop score, cervical dilation) Time from ROM to delivery	**Total time admission to vaginal birth; total L&D length of stay**[c] **Cesarean delivery rate overall**[c] Vaginal birth within 24 hours Failed induction rate, defined as: Cesarean delivery in patient at <6cm dilation excluding fetal distress (labor dystocia, failure to progress, etc.) Cesarean delivery in patient at <6 cm dilation for fetal distress Cervical assessment at time of admission (e.g., latent vs. active phase, Bishop score, cervical dilation) Time from ROM to delivery Breastfeeding[b] Maternal mood[b] Mother-baby attachment[b]	**Total time admission to vaginal birth; total L&D length of stay**[c] **Cesarean delivery rate overall**[c] Vaginal birth within 24 hours Failed induction rate, defined as: Cesarean delivery in patient at <6cm dilation excluding fetal distress (labor dystocia, failure to progress, etc.) Cesarean delivery in patient at <6 cm dilation for fetal distress Cervical assessment at time of admission (e.g., latent vs. active phase, Bishop score, cervical dilation) Time from ROM to delivery	Outcomes not listed in inclusion criteria

PICOTS	Inclusion Key Question 1: Prostaglandin Inpatient vs. Outpatient	Inclusion Key Question 2: Mechanical Method Inpatient vs. Outpatient	Inclusion Key Question 3: Outpatient Comparison of Methods	Inclusion Key Question 4: Fetal Surveillance	Exclusion
Outcomes Fetal Harms	**Perinatal Mortality**[c] **Hypoxic-ischemic encephalopathy**[c] **Seizure**[c] **Infection** (confirmed sepsis or pneumonia)[c] **Meconium aspiration syndrome**[c] **Birth trauma** (e.g., bone fracture, neurologic injury, or retinal hemorrhage)[c] **Intracranial or subgaleal hemorrhage**[c] Need for respiratory support within 72 hours after birth Apgar score ≤3 at 5 minutes[a] Hypotension requiring vasopressor support Umbilical cord gas < pH 7.0 or 7.10	**Perinatal Mortality**[c] **Hypoxic-ischemic encephalopathy**[c] **Seizure**[c] **Infection** (confirmed sepsis or pneumonia)[c] **Meconium aspiration syndrome**[c] **Birth trauma** (e.g., bone fracture, neurologic injury, or retinal hemorrhage)[c] **Intracranial or subgaleal hemorrhage**[c] Need for respiratory support within 72 hours after birth Apgar score ≤3 at 5 minutes[a] Hypotension requiring vasopressor support Umbilical cord gas < pH 7.0 or 7.10	**Perinatal Mortality**[c] **Hypoxic-ischemic encephalopathy**[c] **Seizure**[c] **Infection** (confirmed sepsis or pneumonia)[c] **Meconium aspiration syndrome**[c] **Birth trauma** (e.g., bone fracture, neurologic injury, or retinal hemorrhage)[c] **Intracranial or subgaleal hemorrhage**[c] Need for respiratory support within 72 hours after birth Apgar score ≤3 at 5 minutes[a] Hypotension requiring vasopressor support Umbilical cord gas < pH 7.0 or 7.10	**Perinatal Mortality**[c] **Hypoxic-ischemic encephalopathy**[c] **Seizure**[c] **Infection** (confirmed sepsis or pneumonia)[c] **Meconium aspiration syndrome**[c] **Birth trauma** (e.g., bone fracture, neurologic injury, or retinal hemorrhage)[c] **Intracranial or subgaleal hemorrhage**[c] Need for respiratory support within 72 hours after birth Apgar score ≤3 at 5 minutes[a] Hypotension requiring vasopressor support Umbilical cord gas <pH 7.0 or 7.10	Outcomes not listed in inclusion criteria

PICOTS	Inclusion Key Question 1: Prostaglandin Inpatient vs. Outpatient	Inclusion Key Question 2: Mechanical Method Inpatient vs. Outpatient	Inclusion Key Question 3: Outpatient Comparison of Methods	Inclusion Key Question 4: Fetal Surveillance	Exclusion
Outcomes Maternal Harms	**Hemorrhage requiring transfusion**[c] **Postpartum hemorrhage by mode** (vaginal, cesarean delivery)[c] **Uterine infection** (i.e., choriamnionitis, administration of antibiotics in labor other than GBS prophylaxis)[c] Placental abruption Uterine rupture Umbilical cord prolapse Duration of time between hospital admission to birth that is insufficient to enable complete GBS prophylaxis antibiotics administration per CDC guidelines	**Hemorrhage requiring transfusion**[c] **Postpartum hemorrhage by mode** (vaginal, cesarean delivery)[c] **Uterine infection** (i.e., choriamnionitis, administration of antibiotics in labor other than GBS prophylaxis)[c] Placental abruption Uterine rupture Umbilical cord prolapse Duration of time between hospital admission to birth that is insufficient to enable complete GBS prophylaxis antibiotics administration per CDC guidelines	**Hemorrhage requiring transfusion**[c] **Postpartum hemorrhage by mode** (vaginal, cesarean delivery)[c] **Uterine infection** (i.e., choriamnionitis, administration of antibiotics in labor other than GBS prophylaxis)[c] Placental abruption Uterine rupture Umbilical cord prolapse Duration of time between hospital admission to birth that is insufficient to enable complete GBS prophylaxis antibiotics administration per CDC guidelines	**Hemorrhage requiring transfusion**[c] **Postpartum hemorrhage by mode** (vaginal, cesarean delivery)[c] **Uterine infection** (i.e., choriamnionitis, administration of antibiotics in labor other than GBS prophylaxis)[c] Placental abruption Uterine rupture Umbilical cord prolapse Duration of time between hospital admission to birth that is insufficient to enable complete GBS prophylaxis antibiotics administration per CDC guidelines	Outcomes not listed in inclusion criteria
Timing	Maternal outcomes From cervical ripening initiation to within 1 week following delivery Infant outcomes Immediately following delivery	Maternal outcomes From cervical ripening initiation to within 1-week following delivery Infant outcomes Immediately following delivery.	Maternal and additional outcomes (i.e., breastfeeding, maternal mood, mother-baby attachment) From cervical ripening initiation to 1-year postpartum Infant outcomes Immediately following delivery	Maternal outcomes From cervical ripening initiation to within 1-week following delivery Infant outcomes Immediately following delivery	KQ 1,2,4: Outcomes occurring after 1-week post delivery KQ3: Outcomes for breastfeeding, mother-infant attachment, and maternal mood occurring after 1 year post-delivery.
Setting	Inpatient versus outpatient settings	Inpatient versus outpatient settings	Outpatient setting	Inpatient and outpatient settings	

PICOTS	Inclusion Key Question 1: Prostaglandin Inpatient vs. Outpatient	Inclusion Key Question 2: Mechanical Method Inpatient vs. Outpatient	Inclusion Key Question 3: Outpatient Comparison of Methods	Inclusion Key Question 4: Fetal Surveillance	Exclusion
Study design	RCTs; recent high-quality SRs; if RCT evidence for benefits is insufficient, include large, high quality cohort studies comparing inpatient and outpatient setting. Include high quality cohort and case-control studies for harms.	RCTs; recent high-quality SRs; if RCT evidence for benefits is insufficient, include large, high quality cohort studies comparing inpatient and outpatient setting. Include high quality cohort and case-control studies for harms.	RCTs; recent high-quality SRs; if RCT evidence for benefits is insufficient, include large, high quality cohort studies comparing inpatient and outpatient setting. Include high quality cohort and case-control studies for harms.	RCTs; recent high-quality SRs; if RCT evidence for benefits is insufficient, include large, high quality cohort studies comparing inpatient and outpatient setting. Include high quality cohort and case-control studies for harms.	Case series, pre-post studies, case reports

KQ = Key Question; ROM = rupture of membrane; CDC = Centers for Disease Control and Prevention; L&D = labor and delivery; RCT = randomized controlled trial; SR = systematic review

[a] Allowed higher thresholds from older studies if inadequate evidence with this threshold

[b] Specific to Key Question 3

[c] **(Bolded) items indicate Primary Outcomes**

Study Design: For all Key Questions, we included RCTs for benefits and harms, and additionally comparative cohort or case-control studies to further evaluate harms. Our plan in the protocol was to consider observational studies (cohort and case-control designs) if RCT evidence on benefits was inadequate. Ultimately, we felt it was necessary to include such evidence where available and only those that attempted to control for confounding. We had also planned to consider including recent, good quality systematic reviews, but ultimately did not find any that would be useful.

Non-English Language Studies: We restricted to English-language articles, but reviewed English language abstracts of non-English language articles that might identify studies that would otherwise meet inclusion criteria. We did not identify any such studies.

Process for Selecting Studies

In accordance with the *Methods Guide for Effectiveness and Comparative Effectiveness Review*,[10] we used the pre-established criteria above to screen citations (titles and abstracts) identified through our searches or SEADS submissions to determine eligibility for full-text review. After de-duplication, we imported all references to DistillerSR to assist with abstract and full-text review. To ensure accuracy, any citation deemed not relevant for full-text review was reviewed by a second researcher. All citations deemed potentially eligible for inclusion by at least one of the reviewers were retrieved for full-text screening. Each full-text article was independently reviewed for eligibility by two team members. Any disagreements were resolved by consensus. A flow diagram of study screening and inclusion is below in Appendix C, and a record of studies included in the review and those excluded at the full-text level with reasons for exclusion are listed below in Appendix D and H, respectively.

Data Extraction

After studies were selected for inclusion, data were abstracted into evidence tables. We abstract study and patient characteristics into one table (study design, year, setting, country, sample size, eligibility criteria, population and clinical characteristics, intervention characteristics, funding), and study results relevant to each Key Question as outlined in the previous PICOTS section in another Evidence Table. Information relevant for assessing applicability include the description of the source of potential study participants, number of patients randomized relative to the number of patients enrolled, and characteristics of the population, intervention (including process details such as monitoring prior to discharge to the outpatient setting, timing or factors determining re-admission, etc.), and care setting such as outpatient or inpatient, details on the type of outpatient setting (e.g., home, home birthing center) or inpatient setting (e.g., hospital, clinic). All study data were verified for accuracy and completeness by a second team member.

Risk of Bias Assessment of Individual Studies

Methods from the *Methods Guide for Effectiveness and Comparative Effectiveness Review* were used in concordance with the approach recommended in the chapter, Assessing the Risk of Bias of Individual Studies When Comparing Medical Interventions.[10,11] RCTs were assessed based on criteria established in the *Cochrane Handbook for Systematic Reviews of Interventions*,[12] and principles for appraisal as developed by the Cochrane Back and Neck

Group.[13] Cohort or case control studies were evaluated using appropriate criteria developed by the U.S. Preventive Services Task Force.[14] Based on the risk of bias assessment, individual included studies were rated as being "good," "fair," or "poor" quality.

Studies rated "good" were considered to have the least risk of bias, and their results were considered valid. Good-quality studies include clear descriptions of the population, setting, interventions, and comparison groups; a valid method for allocation of patients to treatment; low dropout rates and clear reporting of dropouts; appropriate means for preventing bias; and appropriate measurement of outcomes. Studies rated "fair" were susceptible to some bias, though not enough to invalidate the results. These studies may not meet all the criteria for a rating of good quality, but no flaw is likely to cause major bias. The study may be missing information, making it difficult to assess limitations and potential problems. The fair-quality category is broad, and studies with this rating vary in their strengths and weaknesses. The results of some fair-quality studies are likely to be valid, while others may be only possibly valid.
Studies rated "poor" have significant flaws that imply biases of various types that may invalidate the results. They have a serious or "fatal" flaw in design, analysis, or reporting; large amounts of missing information; discrepancies in reporting; or serious problems in the delivery of the intervention. The results of these studies were as likely to reflect flaws in the study design as the true difference between the compared interventions.

Data Synthesis and Analysis

As an initial part of synthesizing the evidence, we constructed evidence tables, as described above, and summary tables to highlight the main findings. Results were presented in the report as structured by the Key Questions, and the prioritized (primary) outcomes were presented first. We reviewed and highlighted studies by using a hierarchy-of-evidence approach, where the best evidence is the focus of our synthesis for each Key Question (i.e., RCT evidence preferred over observational study evidence). Data were qualitatively summarized in the text, using ranges and descriptive analysis and interpretation of the results.

Meta-analyses, using profile-likelihood random effects models,[15] were conducted to summarize data and obtain more precise estimates where there are at least two studies reporting outcomes that were homogeneous enough to provide a meaningful combined estimate. Risk ratio (RR) was the effect measure of the binary screening outcomes. Adjusted RRs or odds ratios (OR) were used in the meta-analysis if reported (an adjusted OR was first converted to an adjusted RR) (reference).[16] Otherwise, the RR was calculated from the reported raw numbers. Mean difference was the effect measure for the continuous outcomes. Statistical heterogeneity was assessed using the χ^2 test, and the magnitude of heterogeneity using the I^2 statistic.[17]

Studies of different designs were pooled separately (RCTs vs. observational studies). Meta-analysis results for similar outcomes across study designs were compared and discussed where applicable, see section below for evaluation of bodies of evidence with mixed study designs. To determine whether meta-analysis could be meaningfully performed, we considered the quality of the studies and the heterogeneity among studies in design, patient population, interventions, and outcomes. The Key Questions were designed to assess the comparative effectiveness and harms by patient demographics, patient characteristics (such as gestational age, parity, uncomplicated pregnancy, prior cesarean delivery, etc.), and cervical ripening process details. Given the available evidence, we had limited possibilities to examine the impact of subgroups. Ultimately, we evaluated study quality, the reason for cervical ripening being a post-date pregnancy (versus any other reason), parity (% nulliparous), and for drug therapies, the specific prostaglandin

(dinoprostone versus misoprostol). Few of the RCTs conducted subgroup analyses, but where they did, we summarized those alongside our subgroup analyses to address the subquestions on whether patient characteristics affected outcomes. Small study effects (potential publication bias) was assessed using funnel plots and the Egger test when there were at least 10 studies that could be combined in meta-analysis. Only two outcomes (cesarean delivery, uterine infection) for one comparison (prostaglandins vs. placebo) had enough studies to evaluate publication bias. The forest plots for meta-analyses are included in Appendix F for primary outcomes. Forest plots for secondary outcomes are available upon request.

All analyses were performed by using STATA® 16.1 (StataCorp, College Station, TX), and all results were provided with 95 percent confidence intervals (CI).

Grading the Strength of the Body of Evidence

Table B-2. Definitions of the grades of overall strength of evidence[18]

Grade	Definition
High	We are very confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has few or no deficiencies. We believe that the findings are stable (i.e., another study would not change the conclusions).
Moderate	We are moderately confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has some deficiencies. We believe that the findings are likely to be stable, but some doubt remains.
Low	We have limited confidence that the estimate of effect lies close to the true effect for this outcome. The body of evidence has major or numerous deficiencies (or both). We believe that additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect.
Insufficient	We have no evidence, we are unable to estimate an effect, or we have no confidence in the estimate of effect for this outcome. No evidence is available, or the body of evidence has unacceptable deficiencies, precluding reaching a conclusion.

Outcomes assessed for strength of evidence (SOE) were prioritized based on input from the Technical Expert Panel, these are footnoted and listed in bold in the PICOTS table above. Based on this prioritized list, the strength of evidence for comparison-outcome pairs within each Key Question was initially assessed by one researcher for each clinical outcome (see PICOTS) by using the approach described in the *Methods Guide for Effectiveness and Comparative Effectiveness Review*.[10] To ensure consistency and validity of the evaluation, the grades were reviewed by the entire team of investigators for:

- Study limitations (low, medium, or high level of study limitations)
    - Rated as the degree to which studies for a given outcome are likely to reduce bias with study design and study conduct, based on risk of bias assessments.
- Consistency (consistent, inconsistent, or unknown/not applicable)
    - Rated by degree to which studies find similar magnitude of effect (i.e., range sizes are similar) or same direction (i.e., effect sizes have the same sign)
    - Where there was only one study of a given design, we assessed consistency as "unknown" and downgraded the SOE.
- Directness (direct or indirect)
    - Rated by degree to which evidence assesses a) comparison of interest, b) in the population of interest, and measures the specific outcome of interest.
- Precision (precise or imprecise)
    - Degree of certainty surrounding an effect estimate as it relates to a specific outcome. This may be based on sufficiency of sample size and number of events,

and if these are adequate, the interpretation of the confidence interval. We used thresholds of 400 analyzed patients for continuous outcomes, and 300 events for dichotomous outcomes to determine whether the Optimal Information Size (OIS) had been met. If the OIS was met, the 95% confidence interval was evaluated according to the criteria in the *Methods Guide*. The SOE was downgraded if either assessment indicated imprecision.

- Publication bias (suspected or undetected)
    - Whether selective publishing of research findings based on favorable direction or magnitude of effects was identified using funnel plots or statistical methods, however, only one analysis included enough studies to conduct this assessment, so the majority of SOE assessments rated this domain as "unknown".

The bodies of evidence were assigned an overall SOE grade of high, moderate, low, or insufficient according to a four-level scale by evaluating and weighing the combined results of the above domains:

- High—we are very confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has few or no deficiencies. We believe that the findings are stable, i.e., another study would not change the conclusions.
- Moderate—we are moderately confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has some deficiencies. We believe that the findings are likely to be stable, but some doubt remains.
- Low—we have limited confidence that the estimate of effect lies close to the true effect for this outcome. The body of evidence has major or numerous deficiencies (or both). We believe that additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect. Single-study bodies of evidence with >100 patients analyzed and of at least fair quality were allowed to be rated as Low SOE, even if consistency was unknown and it was imprecise.
- Insufficient—we have no evidence, we are unable to estimate an effect, or we have no confidence in the estimate of effect for this outcome. No evidence is available, or the body of evidence has unacceptable deficiencies, precluding reaching a conclusion.

For observational study evidence, the strength started at moderate for harms outcomes, and low for benefit outcomes. Although the Agency for Healthcare and Quality (AHRQ) Methods Guidance allows this evidence to be upgraded under specific circumstances, none of the included observational studies were good quality, so no upgrading was considered. In cases where there were both RCTs and observational studies included for a given intervention-outcome pair, we followed the additional guidance on how to weight RCTs over observational studies, how to assess consistency across the two bodies of evidence, and how to come to a final rating.[19] In this case, we mainly used the SOE assigned to the RCT evidence as the observational evidence was lower strength, with the exception of cesarean delivery in Key Question 1, where there were six cohort studies and only one RCT. In this case the bodies of evidence were given equal weight.

Assessing Applicability

Applicability was assessed in accordance with the AHRQ's Methods Guide,[10,20] which is based on the PICOTS framework. Applicability addresses the extent to which outcomes associated with an intervention are likely to be similar across the individual studies, bodies of

evidence, and individual patients in clinical practice based on different populations, interventions, comparisons, and outcome measures in various settings.[21] For example, lack of inclusion of low-income patients, or those with low access to healthcare, reduces applicability to many clinical practices where an outpatient cervical ripening. Inclusion of only very low-risk pregnancies also reduces applicability to women with moderate risk, who may be candidates for cervical ripening depending on the specific risk, method of cervical ripening, and monitoring available.

We evaluated factors that may affect applicability, which were identified a priori, such as narrowly defined eligibility criteria and resulting characteristics of included patients, such as demographics (including maternal age, gestational age, race and ethnicity), pregnancy risk factors (such as diabetes, high blood pressure, pre-eclampsia), obstetric factors (e.g., parity), maternal pre-pregnancy health status, including mental health, and intangibles such as birth plan/philosophy and type of provider. Intervention-related factors considered were dose and re-administration schedule variation with medications, and balloon-fill volume variation with catheters. In this review, the setting is the key comparison – inpatient versus outpatient – but other features of setting were considered as they may affect applicability of the findings. These included provider type (e.g., midwife, nurse, or generalist obstetrician), rural versus metropolitan, planned home-birth versus planned inpatient birth, and country. We used this information to assess the situations in which the evidence is most relevant to real-world clinical practice in typical U.S. settings, summarizing applicability assessments qualitatively, according to the PICOTS framework.

Contextual Question

We followed the methods of the US Preventive Services Task Force (USPSTF) to evaluate the contextual question.[14] A targeted search was designed by a medical librarian with experience in searching for contextual question evidence for USPSTF reviews, including searching for systematic and narrative reviews. The team also identified any information relevant to this question opportunistically, while reviewing comprehensive literature searches for Key Questions. The information on the contextual question was summarized in the introduction of the report, and discussed in relation to the systematic review evidence on the Key Questions in the Discussion sections.

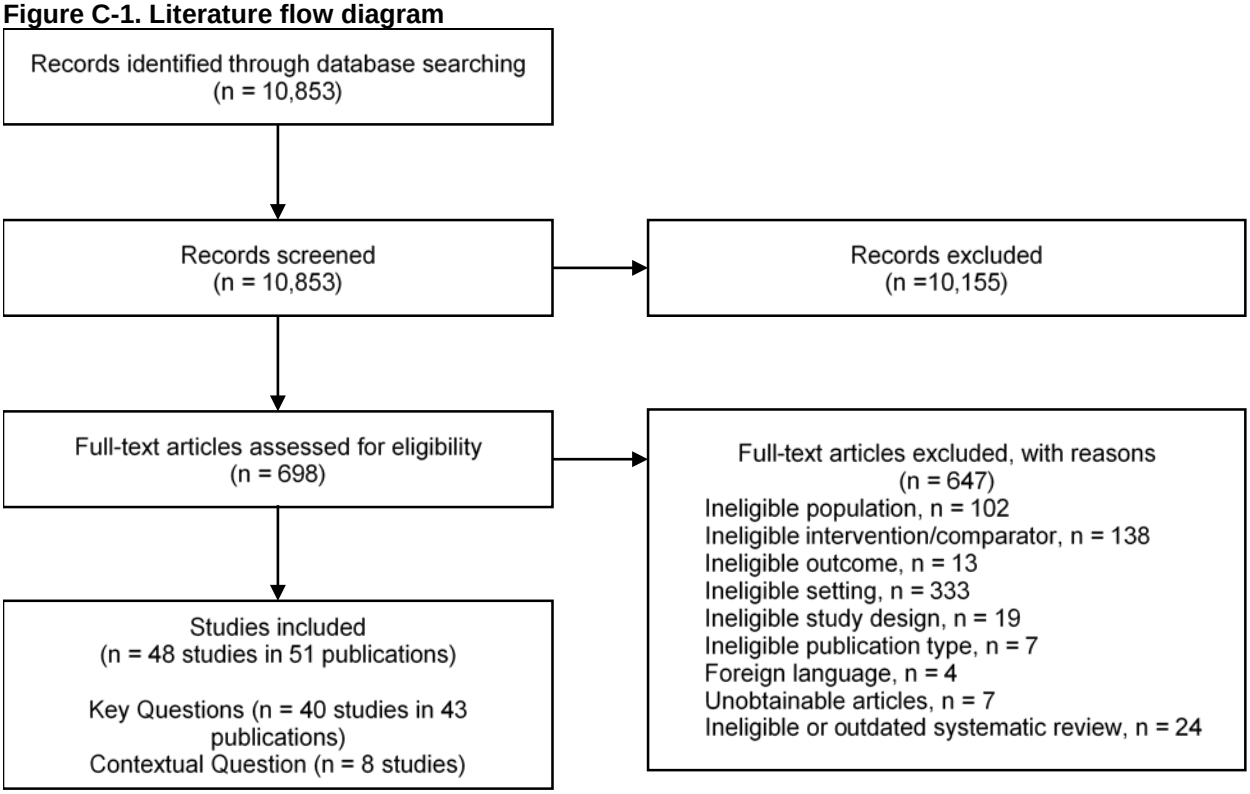
Peer Review and Public Commentary

Experts in obstetrics and midwifery fields and individuals representing stakeholder and user communities were invited to provide external peer review of this systematic review; AHRQ and an associate editor also provided comments. The draft report was posted on the AHRQ website for 4 weeks (beginning August 13, 2020) to elicit public comment. A disposition of comments table of public comments will be posted on the EHC website 3 months after the Agency posts the final systematic review.

Appendix C. Results Overview

Results of Literature Searches

Figure C-1. Literature flow diagram



A total of 10,853 references were identified from electronic database searches. After dual review of abstracts, 698 articles were evaluated for inclusion. A total of 48 studies (in 51 publications)[22-72] were included for efficacy/effectiveness and safety and Table C-1 shows breakdown of included studies by Key Question and study design. Four studies rated good quality, 29 fair quality, and seven poor quality. In addition, eight studies were included for the Contextual Question.[22,24,47,53,68-71] Search results and selection of studies are summarized in the literature flow diagram above (Figure C-1). A list of included studies appears in Appendix D and excluded studies with reason for exclusion in Appendix I.

Table C-1. Number of studies by Key Question and study design

Key Question	RCTs	Observational Studies
KQ 1	2	6
KQ 2	6	3
KQ 3	22	1
KQ 4	0	0

KQ = Key Question; RCT = randomized controlled trial

Description of Included Studies

Majority of studies (65%) excluded women with prior cesarean delivery. Some studies excluded women with preexisting diabetes (13%), gestational diabetes (10%), chronic hypertension (18%), or gestational hypertension (20%). Postterm pregnancy was the most frequently reported reason for cervical ripening (61% of all participants), followed by medical indication (23%) then elective/social reasons (14%). Majority of studies were conducted in the United States (60%). Less than half of the studies (45%) reported funding source and nonprofit organization was the most prevalent source (50% of studies that reported funding source).

Participants' weighted mean age was 28.8 years and weighted body mass index (BMI) was 26.7. Majority of participants were nulliparous (65%) though mean parity was only reported by five studies (weighted mean 0.25). One trial limited recruitment to women with prior vaginal birth[50] while another trial only recruited women with prior cesarean delivery.[37] A very small proportion of women reported gestational diabetes (GDM, 6%), though one trial reported 69 percent of participants had GDM.[49] Weighted mean Bishop score at baseline was 3.4 and mean gestational age (GA) was 40.6 weeks (some studies reported at GA while others reported GA at delivery). Further baseline patient characteristics by Key Question and study design are shown in Table C-2.

Table C-2. Weighted average and proportion of baseline characteristics by Key Question and study design

Weighted Means	KQ 1 RCTs	KQ 1 Cohort Studies	KQ 2 RCTs	KQ 2 Cohort Studies	KQ 3 RCTs	KQ 3 Cohort Studies
Number of studies	2	6	6	3	22	1
N population	1127	3963	1214	1142	2741	153
Age (years)	28.2	30.5	29.8	24.2	26.1	30.5
Race, non-white (n studies)	NR	43.1% (2)	41.4% (3)	NR	63.7% (8)	NR
BMI (kg/m^2)	NR	25.8	27.3	NR	28.5	NR
Parity	NR	0.23	NR	0.5	0.81	NR
Baseline Bishop score	4[a]	3.3	2.9	NR	3.6	NR
Gestational age (weeks)	NR[b]	41.2	40.5	40.3	40.1	NR[c]
% Nulliparous	68.6%	79.1%	62.6%	54.4%	51.8%	64.7%
% with prior cesarean delivery	0%	0%	6.3%[d]	15.7%[d]	35.4%[e]	0%
% Elective IOL	10.1%	0.6%	24.0%	3.3%	43.6%	2%
% Postterm IOL	83.6%	72.3%	57.5%	51.8%	32.8%	84.3%
% Medically-indicated IOL	4.6%	26.6%	18.1%	39.5%	21.1%	13.1%
# Good-quality studies	0	0	0	0	4	0
# Fair-quality studies	2	5	6	1	14	1
# Poor-quality studies	0	1	0	2	4	0
# Conducted in United States	0	2	2	2	18	0

BMI = body mass index; IOL = induction of labor; KQ = Key Question; RCT = randomized controlled trial; NR = not reported

[a]Only 1 study reported the median Bishop score at baseline

[b]One RCT reported mean 40.71 weeks, the other RCT reported median 40.14 weeks

[c] Gestational age was ≥41 weeks in 80% and 37–40 weeks in 20% of women.

[d]Based on only one study. All other studies did not report percentage of participants with cesarean delivery or excluded them.

[e]Based on three trials that included participants with prior cesarean delivery. Twelve other trials excluded participants with prior cesarean delivery.

Table C-3. Intervention specifics for studies addressing Key Question 1

Author, Year Study Design	Intervention[a]	Type	Dose	Number of Doses	Route	Provider
Biem, 2003 RCT	Dinoprostone	Insert	10 mg (controlled-release)	1	Vaginal	Obstetrician
Wilkinson, 2015a (OPRA) RCT	Dinoprostone	Gel	2 mg (nulliparous) 1 mg (multiparous)	≥1: 51% (425/827)[b] 1: 36% (298/827) 2: 12% (103/827) 3: 3% (24/827)	Vaginal	Physician or Midwife
Awartani, 1999 Cohort	Dinoprostone	Gel	2 mg	1: 64% (64/100)[c] 2: 30% (30/100)[c] 3: 5% (5/100)[c]	Cervical	Physician
Cundiff, 2017 Cohort	Dinoprostone	Insert (Cervidil®)	10 mg (controlled-release)	*Oupatient vs. Inpatient:* mean 1.38 vs. 1.23 1: 70% (429/611) vs. 81% (462/568) 2: 23% (142/611) vs. 15% (83/568) 3: 5% (33/611) vs. 3% (19/568) 4 to 6: 1% (7/611) vs. 1% (4/568)	Vaginal	Obstetrician
Farmer, 1996 Cohort	Dinoprostone	Gel (Prepidil®)	0.5 mg	1	Cervical	NR
Salvador, 2009 Cohort	Dinoprostone	Insert (Cervidil®)	10 mg (controlled-release)	*Oupatient vs. Inpatient:* mean (SD): 1.38 (0.65) vs. 1.27 (0.56) 1: 69% (394/567) vs. 79% (611/776) 2: 24% (136/567) vs. 17% (129/776) 3: 6% (31/567) vs. 4% (32/776) 4 to 5: 0.2% (6/567) vs. 0.5% (4/776)	Vaginal	Obstetrician
Stock, 2014 Cohort	Dinoprostone	Insert (Gel)	1 mg	*Oupatient vs. Inpatient:* median (range): 1 (1-6) vs. median 1 (1-5)	Vaginal	NR
Chang, 2005 Cohort	Misoprostol	Tablet	50 µg	1	Vaginal	Obstetrician

µg = micrograms; mg = milligrams; NR = not reported; RCT = randomized controlled trial

[a] Outpatient and Inpatient groups received identical intervention unless otherwise specified.

[b] Per the article: "Approximately half (48% [196/411] outpatient vs. 49% [206/416] inpatient) of the women did not receive cervical ripening, largely because of spontaneous labor before induction or cervical change which resulted in ripening not being required." The proportion of patients in both groups that received ≥ one (52% [215/411] vs. 51% [210/416]); one (38% [157/411] vs. 34% [141/416]); two (11% [45/411] vs. 14% [58/416]); and three (3% [13/411] vs. 3% [11/416]) doses were similar.

[c] The proportion of patients in both groups that received one (62% [31/50] vs. 66% [33/50]); two (30% [15/50] vs. 30% [15/50]); three (6% [3/50] vs. 6% [3/50]) doses were similar.

Table C-4. Intervention specifics for studies addressing Key Question 2

Author, Year Study Design	Intervention[a]	Type	Dose	Number of Doses	Route	Provider
Wilkinson, 2015b (COPRA) RCT	Cook Catheter	Double balloon (Cook® Cervical Ripening Balloon J-CRBS-184000)	70-80 ml sterile water	1 (prostaglandin: 13% [6/48])	NA	Physician or Midwife
Policiano, 2017 RCT	Foley catheter	Single balloon (Covidian™ Dover™ Silicon Coated Latex Foley catheter 16Fr/Ch 5.3mm)	40 ml saline	1 (prostaglandin: 65% [84/130])	NA	NR
Sciscione, 2001 RCT	Foley catheter	Single balloon (16-French Foley)	30 ml sterile water	1	NA	NR
McKenna, 2004a Cohort	Foley catheter	Single balloon (16-French Foley)	30 ml saline	1	NA	NR
Kruit, 2016 Cohort	Foley catheter	Single balloon (Rüsch two-way single balloon Foley Couvelaire tip catheter size 22 Ch)	40-50 ml saline	1 (misoprostol: 8.9% [43/485])	NA	Obstetrician
Kuper, 2018 RCT	Foley catheter +/- concurrent infusion of oxytocin[b]	Single balloon (16-French Foley)	30 ml sterile water	1	NA	Physician
Beckmann, 2019 RCT	Outpatient: Cook catheter	Double balloon (CRB plus stylet)	80 ml saline	1	NA	Physician or Midwife
	Inpatient: Dinoprostone or tape (Cervidil)	Gel (Prostin) or controlled release tape (Cervidil)	2 mg gel; 10 mg tape	1: 72% (163/227) 2: 23% (53/227) 3: 5% (11/227)	Vaginal	Physician or Midwife
Henry, 2013 RCT	Outpatient: Foley catheter	Single balloon (16-F standard latex)	30 ml sterile water	1	NA	Resident trained in cervical cath insertion
	Inpatient: Dinoprostone	Gel	2 mg (nulliparous) 1 mg (multiparous)	1 (+2nd 1 mg dose regardless of parity if needed)	Vaginal	NR
Upadhyaya, 1999 Cohort	Dilapan	Stick (synthetic cervical dilator composed of a slender stick made from hydrophilic polymer of polyacrylonitrile)	NA	*OP vs. IP:* mean (SD): 6.0 (2.1) vs. 4.9 (1.0) sticks	Cervical	NR

mg = milligrams; ml = milliliter; NR = not reported; RCT = randomized controlled trial

[a] Outpatient and Inpatient groups received identical intervention unless otherwise specified.

[b] Oxytocin was infused concurrently during inpatient cervical ripening (Foley placement) as is the standard practice at this institution. For women in the outpatient group, if the transcervical catheter was in place on admission, oxytocin was initiated and the catheter was retaped on gentle traction. The transcervical catheter was allowed to remain in place for up to 24 hours from initial placement. Subsequently, the outpatient group was managed in a similar fashion to the inpatient group. Total oxytocin duration (10.4 ± 7.5 vs. 11.3 ± 6.6 hours) and maximum oxytocin rate (17.8 ± 9.6 vs. 16.4 ± 9.0 milliunits/min) were similar between outpatient and inpatient groups, respectively (p=0.50 and 0.42).

Table C-5. Intervention specifics for studies addressing Key Question 3

Author, Year Study Design	Intervention Comparator(s)[a]	Type	Dose	Number of Doses	Route	Provider
Herabutya, 1988 RCT	Dinoprostone	Tablets	0.5 mg	Hourly for 6 hours/day (total NR)	Oral	NR
	Dinoprostone	Gel	0.5 mg	≤3	Cervical	NR
Smith, 1996 RCT	Dinoprostone	Gel	2.5 mg	1: 38% (21/55); 2: 62% (34/55)	Vaginal	NR
	Dinoprostone	Gel	5.0 mg	1: 39% (25/64); 2: 61% (39/64)	Vaginal	NR
Kipkasa, 2005 RCT	Misoprostol	Tablet	25 µcg	1: 48% (11/23); 2: 22% (5/23); 3: 13% (3/23)	Oral	Clinical nurse
	Misoprostol	Tablet	50 µcg	1: 77% (20/26); 2: 12% (3/26); 3: 4% (1/26)	Oral	Clinical nurse
Meyer, 2005 RCT	Misoprostol	Tablet	25 µcg	NR	Vaginal	NR
	Dinoprostone	Gel (Prepidil®)	0.5 mg	NR	Cervical	NR
Gaffaney, 2009 RCT	Misoprostol	Capsule	100 µcg	1: 72% (31/43); 2: 21% (9/43); 3: 7% (3/43)	Oral	NR
	Placebo	Capsule	NA	1: 23% (10/44); 2: 55% (24/44); 3: 23% (10/44)	Oral	NR
Incerpi, 2001 RCT	Misoprostol	Tablet	25 µg	median 2 (range, 1-2)	Vaginal	NR
	Placebo	Tablet (lactose)	NA	median 2 (range, 1-2)	Vaginal	NR
McKenna, 2004b RCT	Misoprostol	Capsule (Cytotec)	25 µcg	NR	Vaginal	NR
	Placebo	Capsule (starch)	NA	NR	Vaginal	NR
PonMalar, 2017 RCT	Misoprostol (+ stretch and sweep)	Tablet	25 µg	NR [Full stretch/sweep: 65% (41/63) Partial stretch/sweep: 14% (9/63)]	Vaginal	NR
	Placebo (+ stretch and sweep)	Tablet	NA	NR [Full stretch/sweep: 78% (41/63) Partial stretch/sweep: 14% (9/63)]	Vaginal	NR
Stitely, 2000 RCT	Misoprostol	Tablet	25 µcg	mean (SE): 1.41 (0.1) 1: 46% (12/27) 2: 56% (15/27) (2nd dose on day 2)	Vaginal	NR
	Placebo	Tablet (dicalcium phosphate)	NA	mean (SE): 1.85 (0.1) 1: 9% (3/33) 2: 91% (30/33) (2nd dose on day 2)	Vaginal	NR

Author, Year Study Design	Intervention Comparator(s)[a]	Type	Dose	Number of Doses	Route	Provider
Buttino, 1990 RCT	Dinoprostone	Gel	0.5 mg in 2 ml	NR	Cervical	NR
	Placebo	Hydroxyethyl cellulose acetate + sesame oil	2 ml	NR	Cervical	NR
Doany, 1997 RCT	Dinoprostone	Gel	2 mg in 4 ml	NR (>1 visit: 35%)*	Vaginal	NR
	Placebo only	hydroxyethyl cellulose gel mixed with an inert emulsion	4 ml	>1 visit 61%*	Vaginal	NR
	Membrane sweeping (+ placebo)	see Placebo only	see Placebo only	NR (>1 visit: 34%)* successful strip with 3 sweeps: 86%	Vaginal	NR
Larmon, 2002 RCT	Dinoprostone	Gel (Prepidil®)	0.5 mg	NR (~mean 2.4 doses)*	Cervical	NR
	Placebo	Inert lubricant jelly	1 ml	NR (~mean 2.4 doses)*	Vaginal	NR
	Estradiol cream	Cream	4 mg	NR (~mean 2.2 doses)*	Vaginal	NR
Lien, 1998 RCT	Dinoprostone	Gel (Prepidil®)	0.5 mg	median (range): 2 (1-3)	Cervical	Physician or Midwife
	Placebo	NR	NA	median (range): 2 (1-3)	Cervical	Physician or Midwife
McKenna, 1999 RCT	Dinoprostone	Gel (Prostin E2®)	0.5 mg in 1.5 ml	NR	Cervical	NR ("an investigator")
	Placebo	inert hydroxyethyl cellulose gel	1.5 ml	NR	Cervical	NR ("an investigator")
Sawai, 1991 RCT	Dinoprostone	Gel (Prostin E2®)	2 mg in 2 ml	Median 2.0 (for both nulli- and multiparas)	Vaginal	NR
	Placebo	hydroxyethyl cellulose gel	2 ml	Nulliparas, median 2.0 Multiparas, median 1.0	Vaginal	NR
Sawai, 1994 RCT	Dinoprostone	Suppository Gel (Prostin E2®)	2 mg (in a fatty base)	median (±range): 4 (15)	Vaginal	Patient
	Placebo	Suppository containing a fatty base	NA	median (±range): 7 (17)	Vaginal	Patient
Magann, 1998 RCT	Dinoprostone	Gel (Prepidil®)	0.5 mg	Daily (total days NR)	Cervical	NR ("provider")
	Expectant management	gentle daily cervical examination	NA	Daily (total days NR)	NA	NR ("provider")
	Membrane sweeping	NA	NA	Daily (total days NR)	NA	NR ("provider")
Oboro, 2005 RCT	Misoprostol	Tablet (Cytotec®)	25 mg	NR	Vaginal	NR
	Expectant management	Gentle vaginal examination only with a Bishop score assigned	NA	NA	NA	NR

Author, Year Study Design	Intervention Comparator(s)[a]	Type	Dose	Number of Doses	Route	Provider
Ohel, 1996 RCT	Dinoprostone	Tablet	3 mg	NR (patients to return in 3-4 days for repeat testing and a further dose)	Vaginal	NR
	Expectant management	seen twice weekly; if passed 42 weeks of gestation admitted for induction	NA	NA	NA	NR
Rayburn, 1999 RCT	Dinoprostone	Gel (Prepidil®)	0.5 mg in 2.5 ml	mean 1.5	Cervical	NR
	Expectant management	1st assessment at 39 weeks; return at 40 and 41 weeks for routine reassessments	NA	NA	NA	NR
Magann, 1999 RCT	Dinoprostone	Suppository (Cervidil®)	NR	Daily (total days NR)	Vaginal	NR
	Membrane sweeping	NA	NA	Daily (total days NR)	NA	NR
Blair, 2020 Cohort study	Dinoprostone	Insert (Cervidil®)	10 mg (controlled-release)	1: 94% (67/71) ≥2: 6% (4/71) (20 [28%] switched to a catheter)	Vaginal	NR
	Foley catheter	Single balloon (single-lumen urethral catheter)_	30–60 ml sterile water	1: 100% (82/82) (1 [1%] switched to dinoprostone)	Cervical	NR
McGee, 2019 RCT	Foley catheter, silicone	Single balloon (18F, 100% silicone)	30 ml sterile water	1: 97% (258/265) 2: 3% (7/265) (received alternative Foley after failure to insert allocated Foley)	NA	Obstetrician or Midwife
	Foley catheter, latex	Single balloon (18F, silicone elastomer coated latex)	30 ml sterile water	1: 91% (244/269) 2: 9% (25/269) (received alternative Foley after failure to insert allocated Foley)	NA	Obstetrician or Midwife

µg/µcg = micrograms; mg = milligrams; ml = milliliter; NA = not applicable; NR = not reported; RCT = randomized controlled trial

[a]All interventions were given in the outpatient setting

Appendix D. Included Studies List

1. Awartani KA, Turnell RW, Olatunbosun OA. A prospective study of induction of labor with prostaglandin vaginal gel: ambulatory versus in-patient administration. Clin Exp Obstet Gynecol. 1999;26(3-4):162-5. PMID: 10668144.
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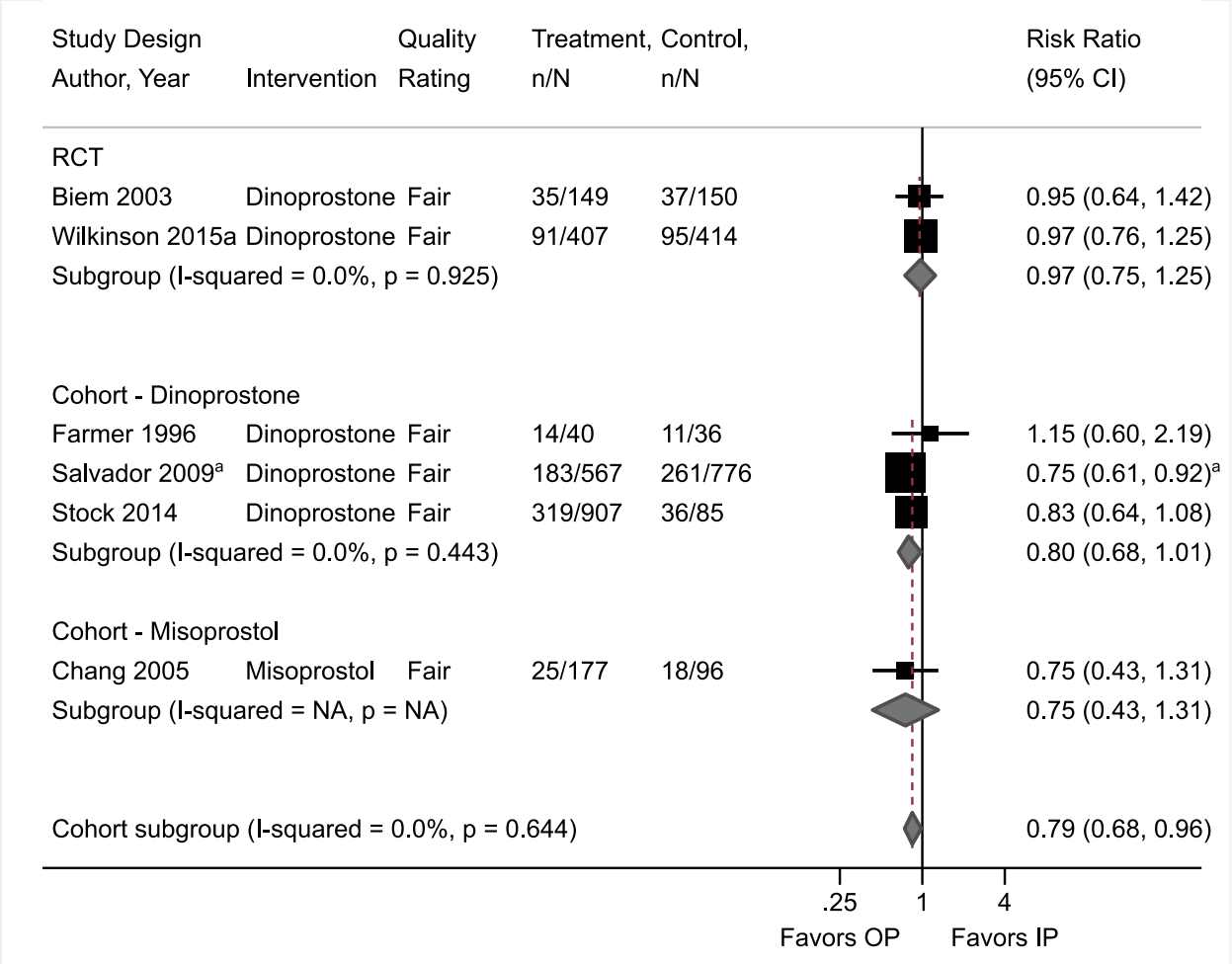
Appendix E. Evidence Tables

Shown in associated Excel file(s).

Appendix F. Forest Plots

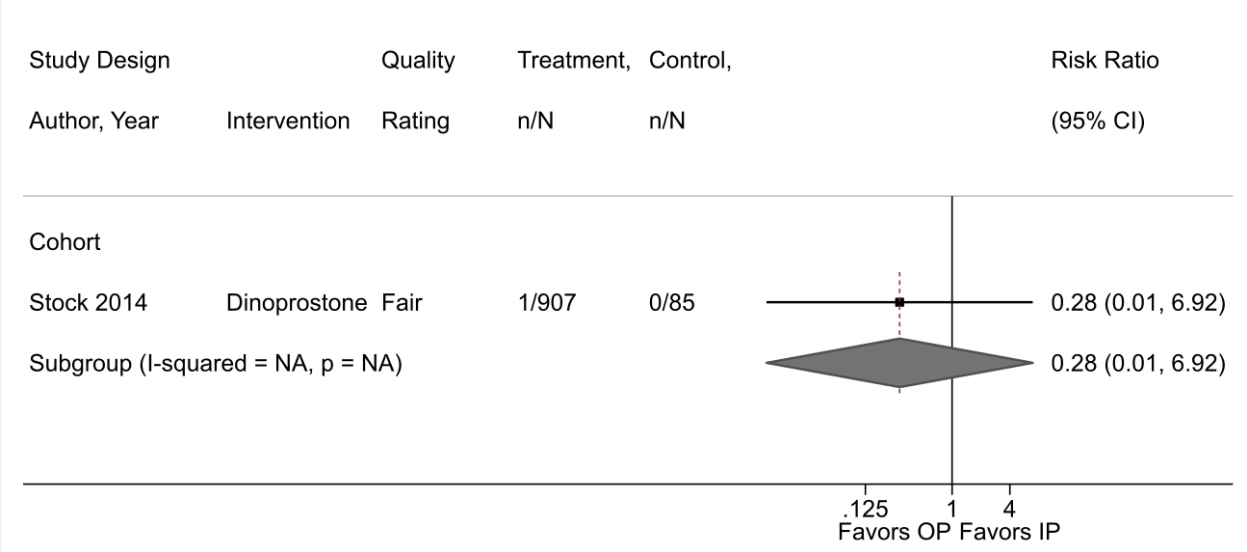
Key Question 1: Outpatient Prostaglandin Versus Any Inpatient Intervention

Figure F-1. Rate of cesarean delivery – excluding poor-quality study



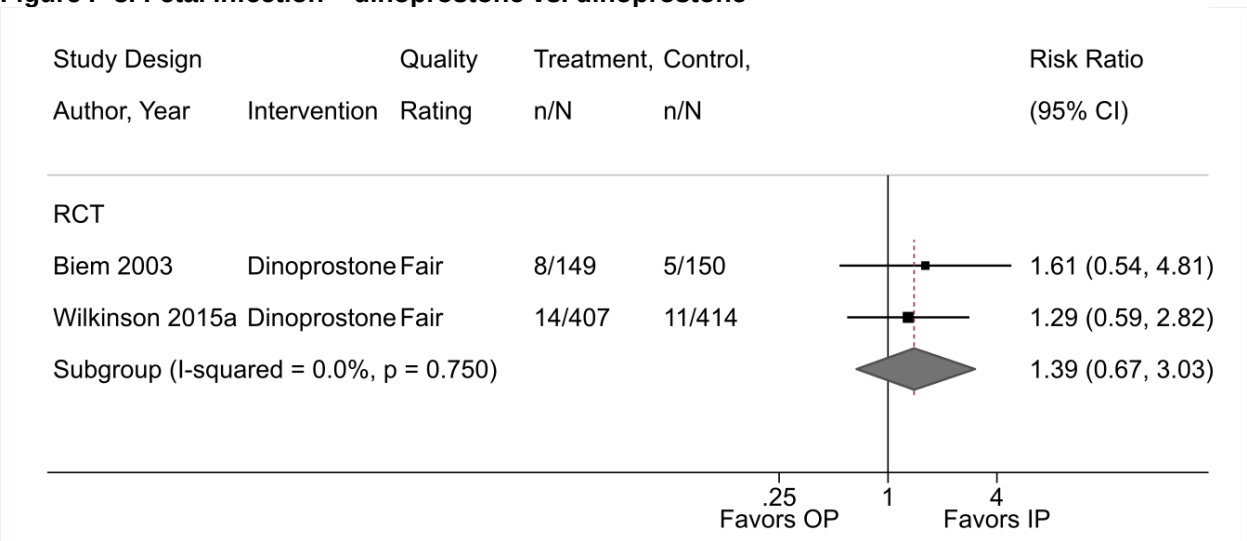
CI = confidence interval; IP = inpatient; NA = not applicable; OP = outpatient; RCT = randomized controlled trial.
[a] RR estimate calculated from author's adjusted odds ratio comparing outpatient with inpatient; adjusted for age, gestational age, reasons for induction, use of epidural, birth weight, parity.

Figure F-2. Perinatal mortality – dinoprostone vs. dinoprostone



CI = confidence interval; IP = inpatient; NA = not applicable; OP = outpatient.

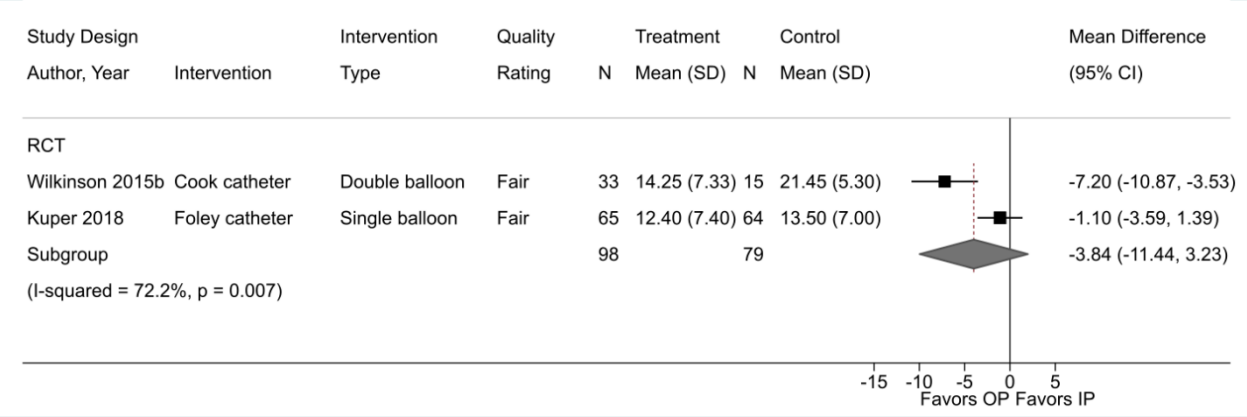
Figure F-3. Fetal infection – dinoprostone vs. dinoprostone



CI = confidence interval; IP = inpatient; OP = outpatient; RCT = randomized controlled trial.

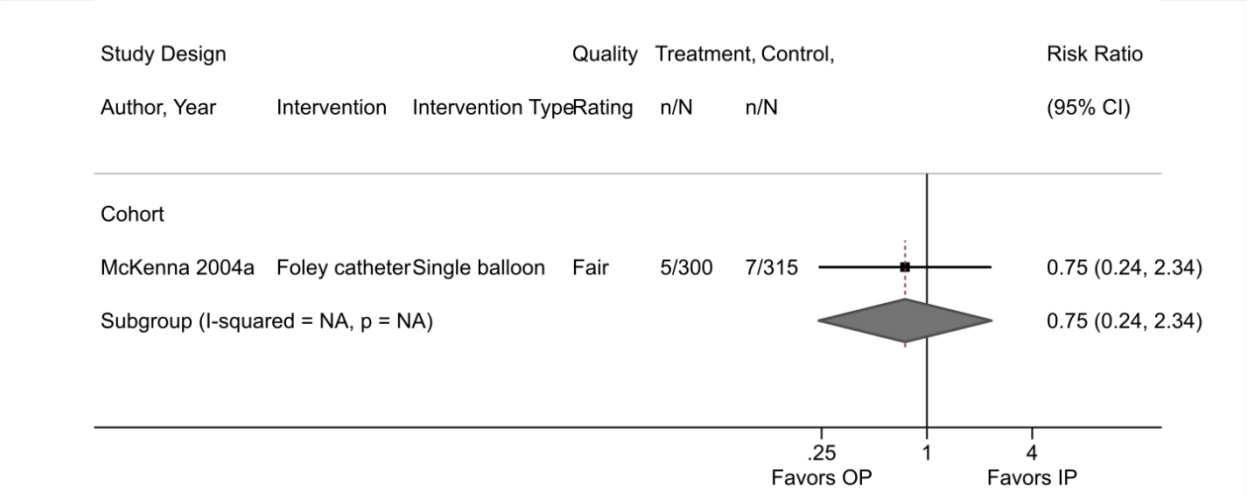
Key Question 2: Outpatient Mechanical Method Versus Any Inpatient Intervention

Figure F-4. Time from admission to delivery – catheter vs. catheter



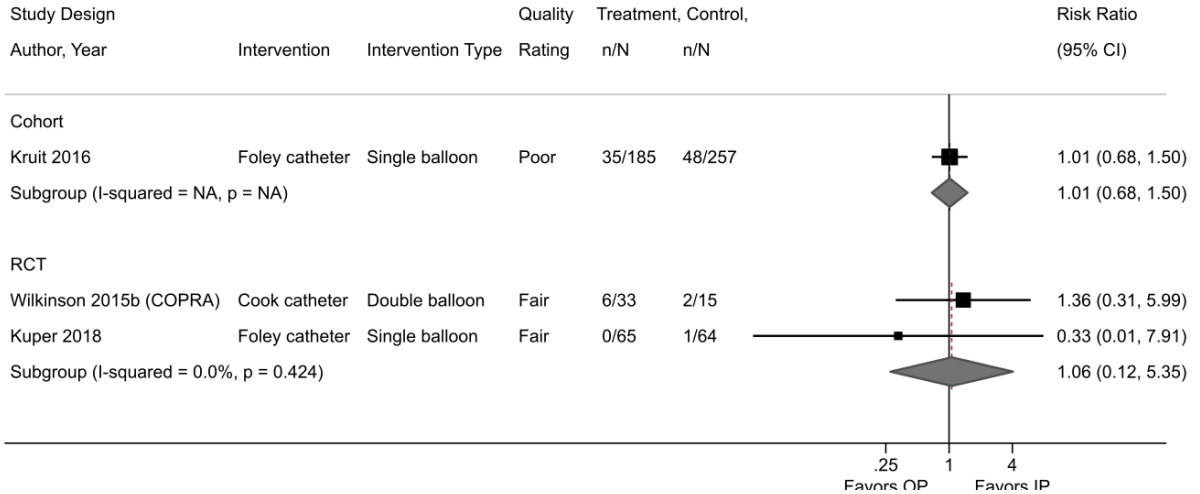
CI = confidence interval; IP = inpatient; OP = outpatient; RCT = randomized controlled trial; SD = standard deviation.

Figure F-5. Fetal infection – catheter vs. catheter



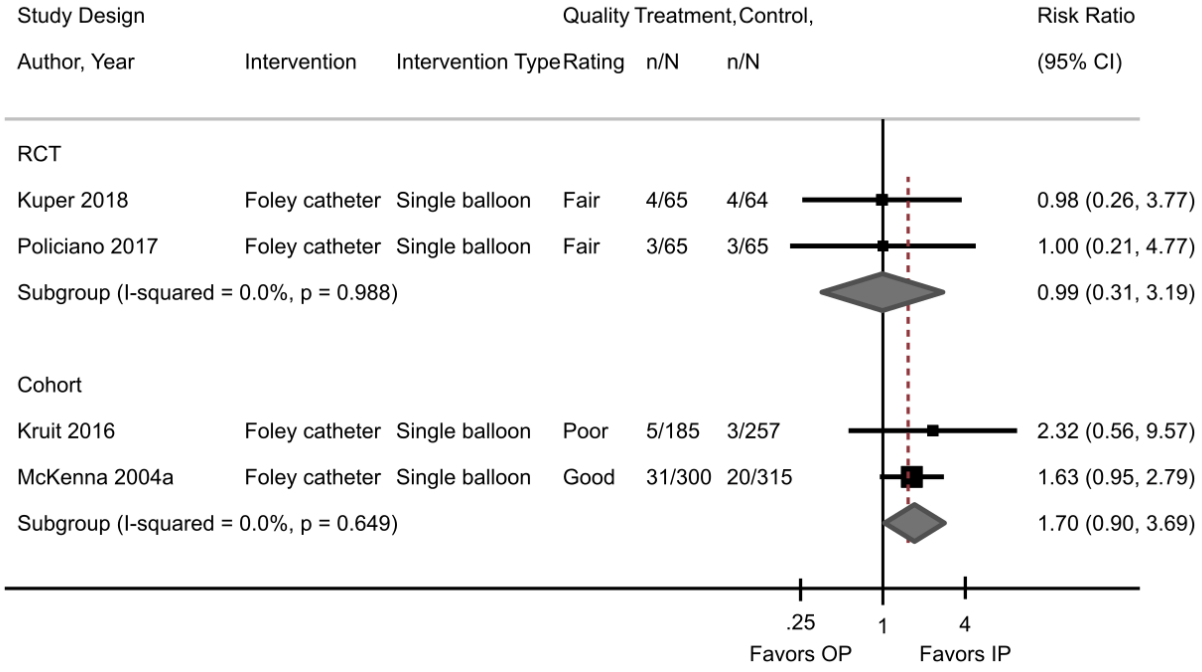
CI = confidence interval; IP = inpatient; NA = not applicable; OP = outpatient

Figure F-6. Postpartum hemorrhage – catheter vs. catheter



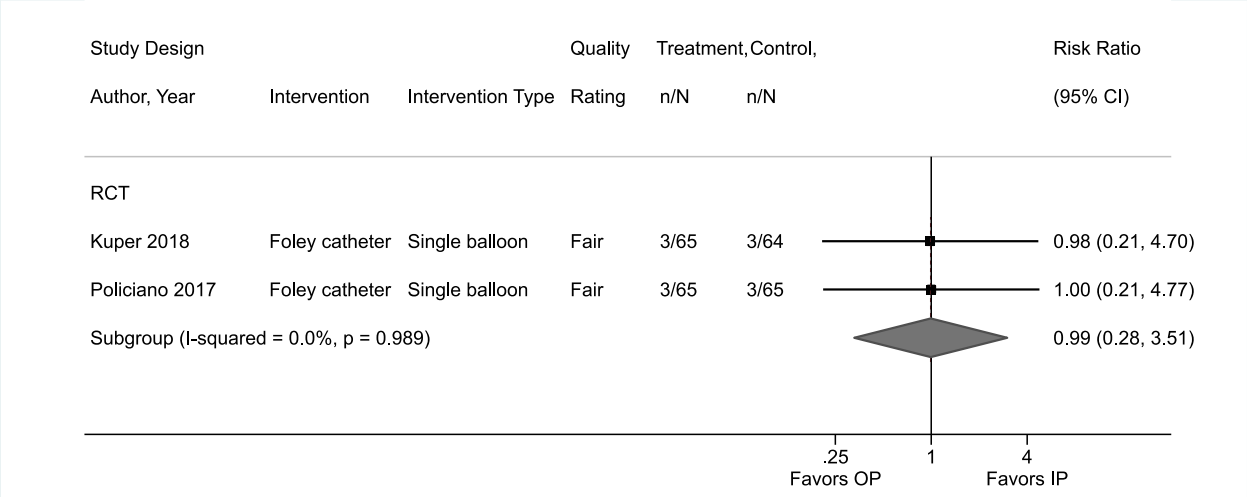
CI = confidence interval; IP = inpatient; NA = not applicable; OP = outpatient; RCT = randomized controlled trial.

Figure F-7. Uterine infection – catheter vs. catheter, any uterine infection



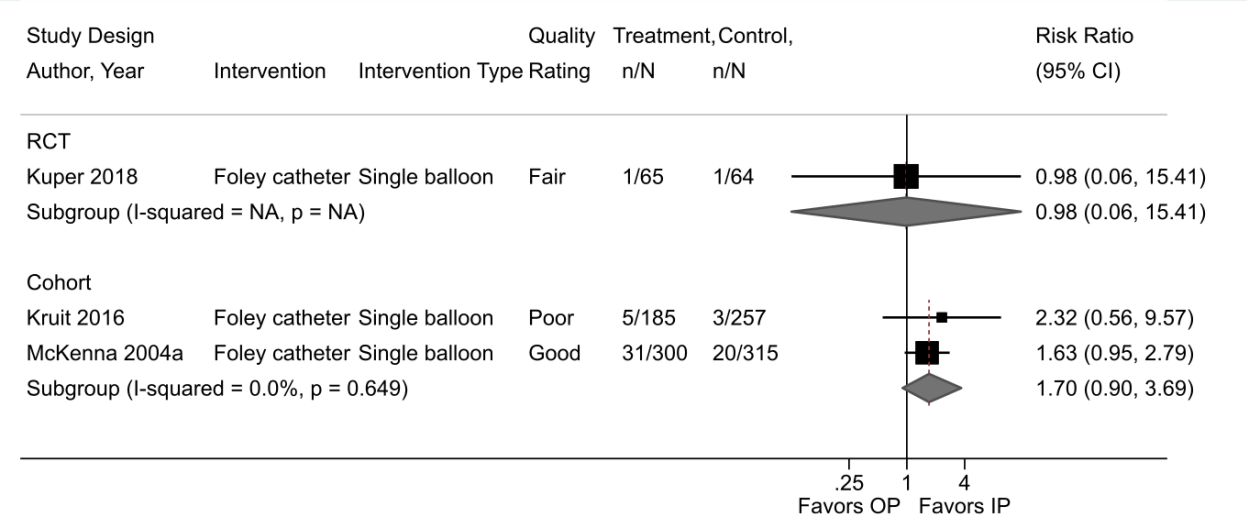
CI = confidence interval; IP = inpatient; OP = outpatient; RCT = randomized controlled trial.

Figure F-8. Uterine infection – catheter vs. catheter, chorioamnionitis



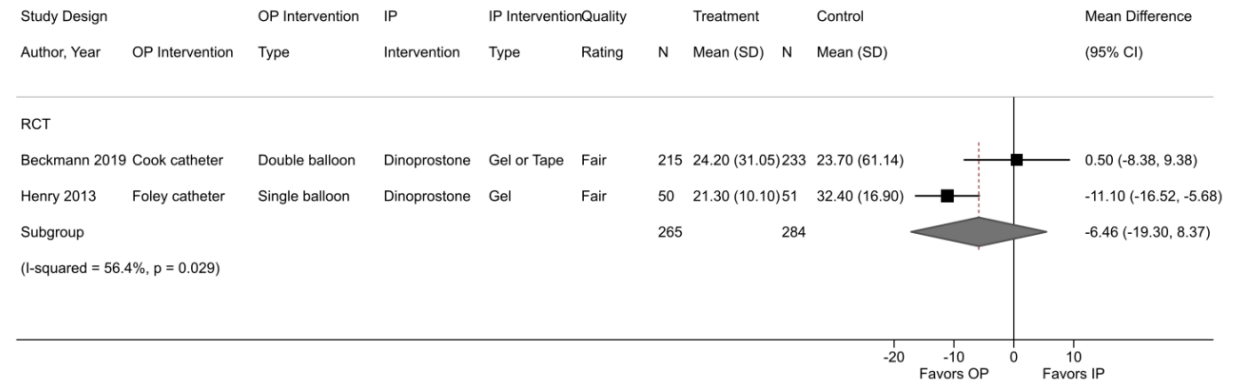
CI = confidence interval; IP = inpatient; NA = not applicable; OP = outpatient; RCT = randomized controlled trial.

Figure F-9. Uterine infection – catheter vs. catheter, endometritis



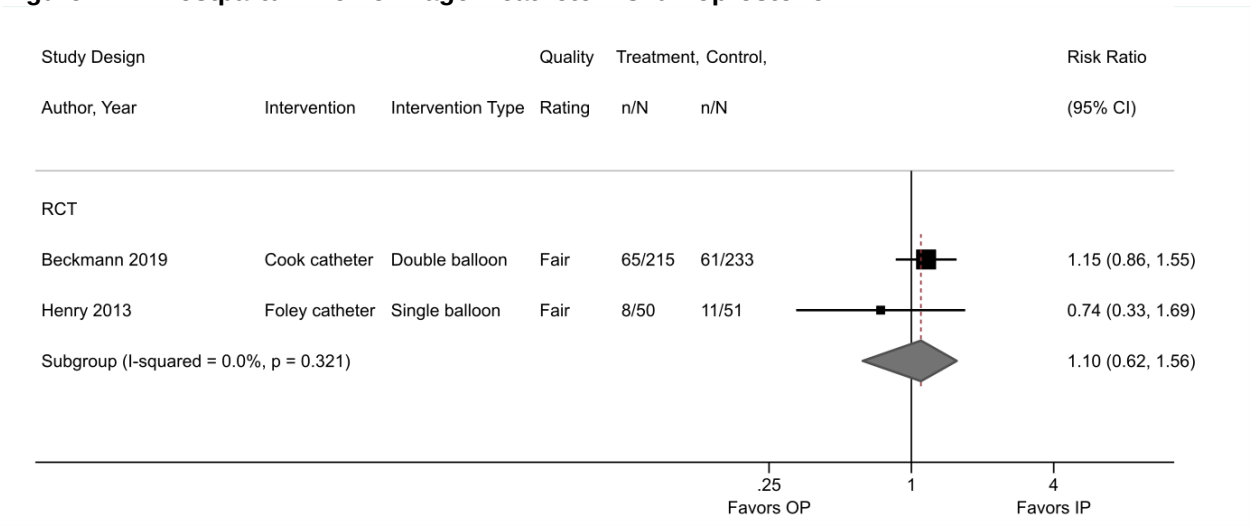
CI = confidence interval; IP = inpatient; NA = not applicable; OP = outpatient; RCT = randomized controlled trial.

Figure F-10. Time from admission to delivery – catheter vs. dinoprostone



CI = confidence interval; IP = inpatient; OP = outpatient; RCT = randomized controlled trial; SD = standard deviation.

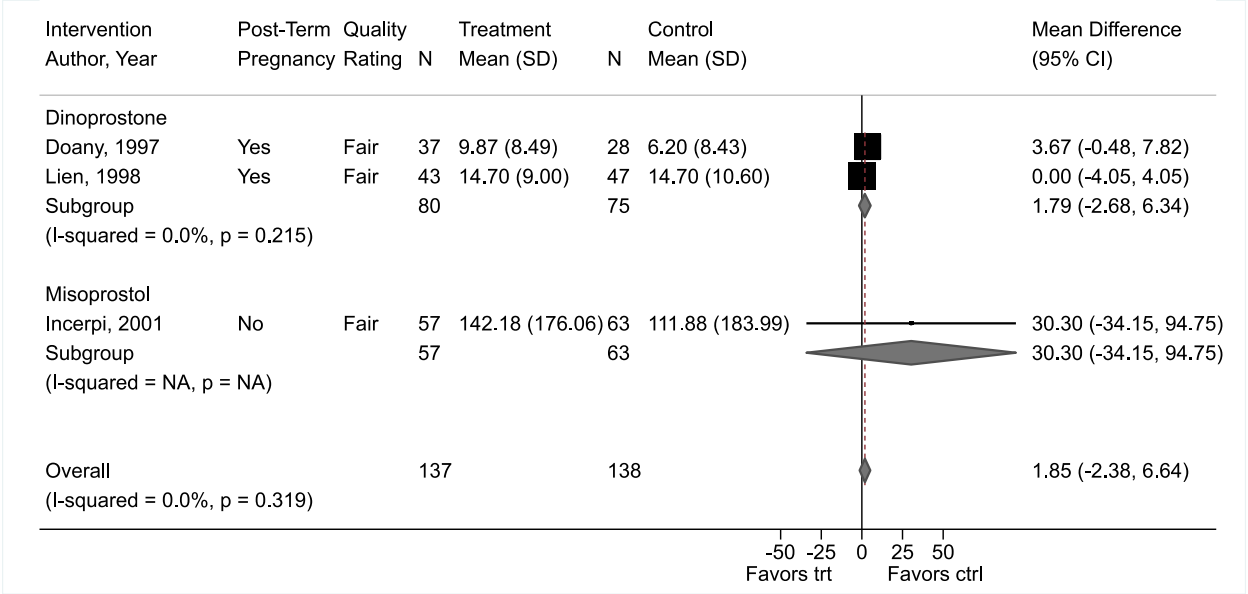
Figure F-11. Postpartum hemorrhage – catheter vs. dinoprostone



CI = confidence interval; IP = inpatient; OP = outpatient; RCT = randomized controlled trial.

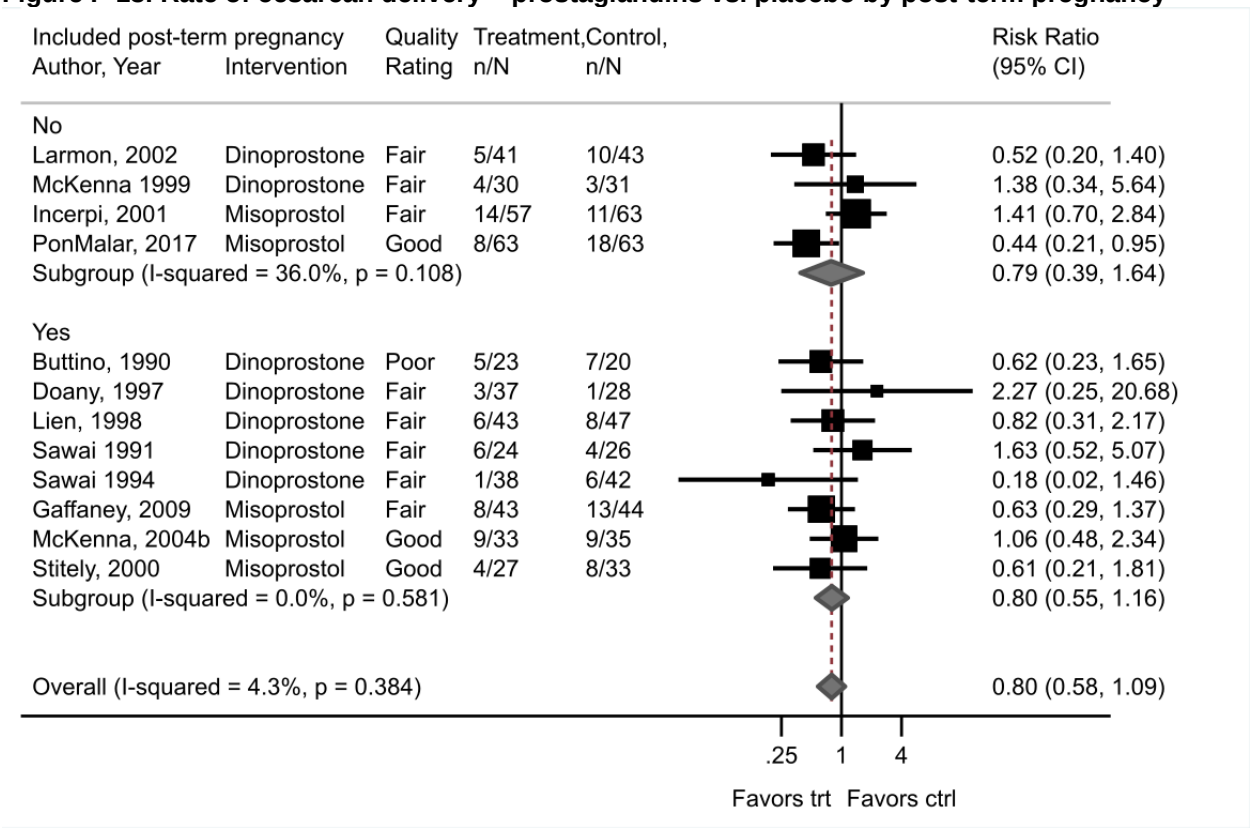
Key Question 3: Outpatient Versus Outpatient Intervention

Figure F-12. Time from admission to delivery – prostaglandins vs. placebo



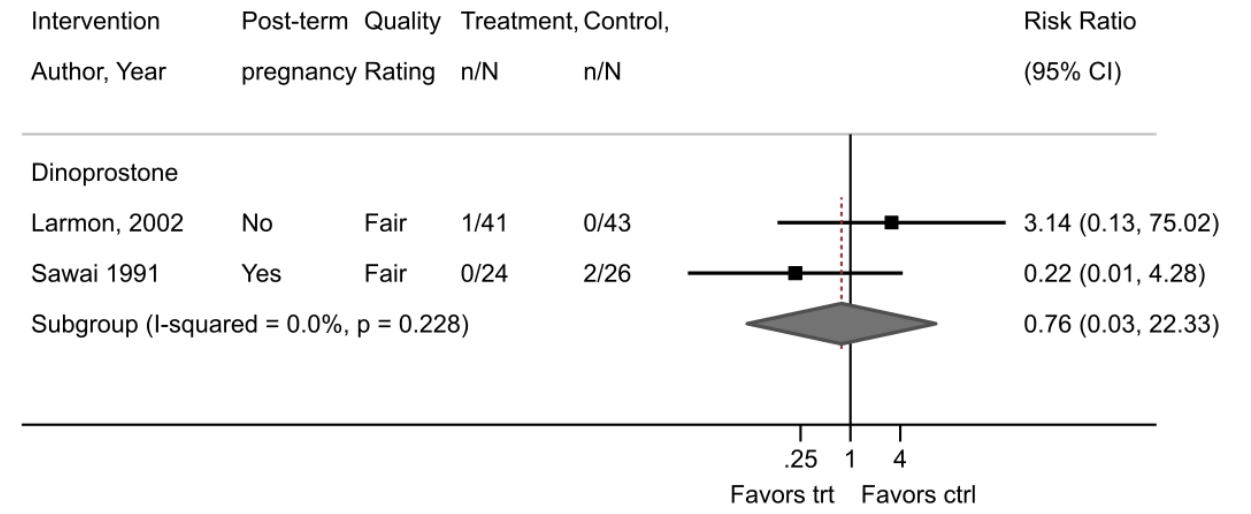
CI = confidence interval; ctrl = control; NA = not applicable; SD = standard deviation; trt = treatment.

Figure F-13. Rate of cesarean delivery – prostaglandins vs. placebo by post-term pregnancy



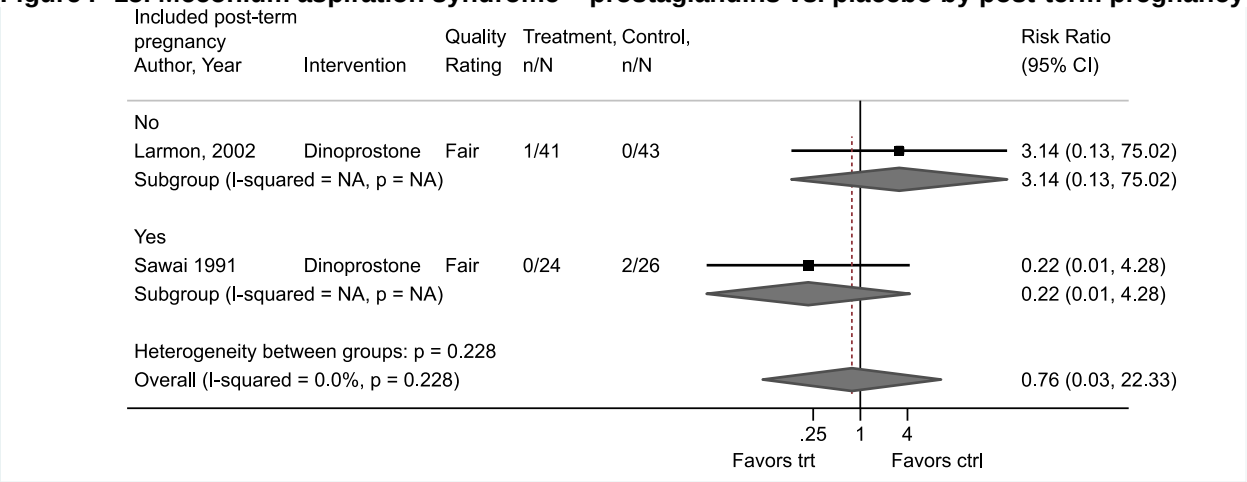
CI = confidence interval; ctrl = control; trt = treatment.

Figure F-14. Meconium aspiration syndrome – prostaglandins vs. placebo by intervention



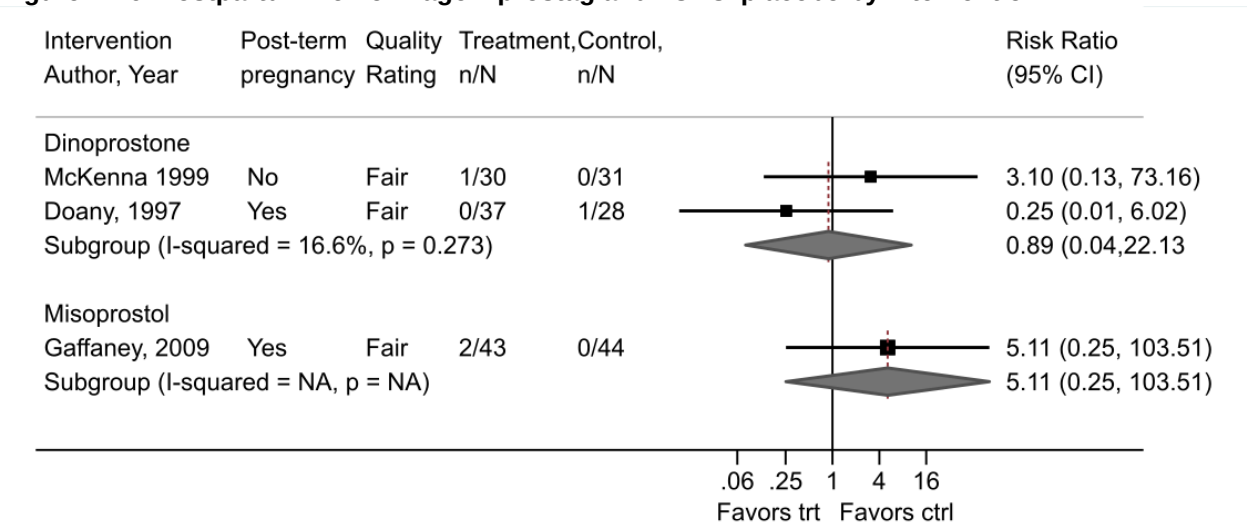
CI = confidence interval; ctrl = control; trt = treatment.

Figure F-15. Meconium aspiration syndrome – prostaglandins vs. placebo by post-term pregnancy



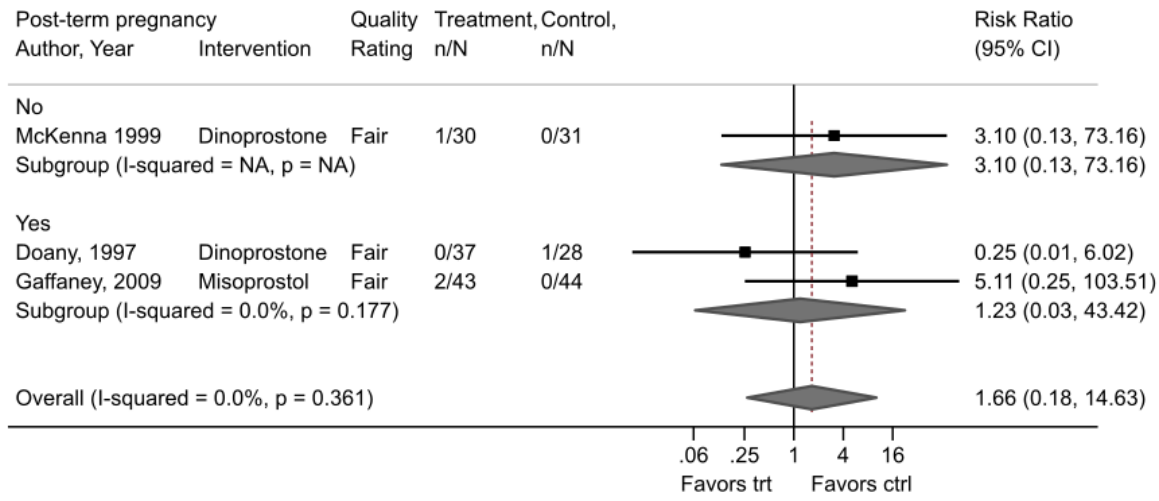
CI = confidence interval; ctrl = control; NA = not applicable; trt = treatment.

Figure F-16. Postpartum hemorrhage – prostaglandins vs. placebo by intervention



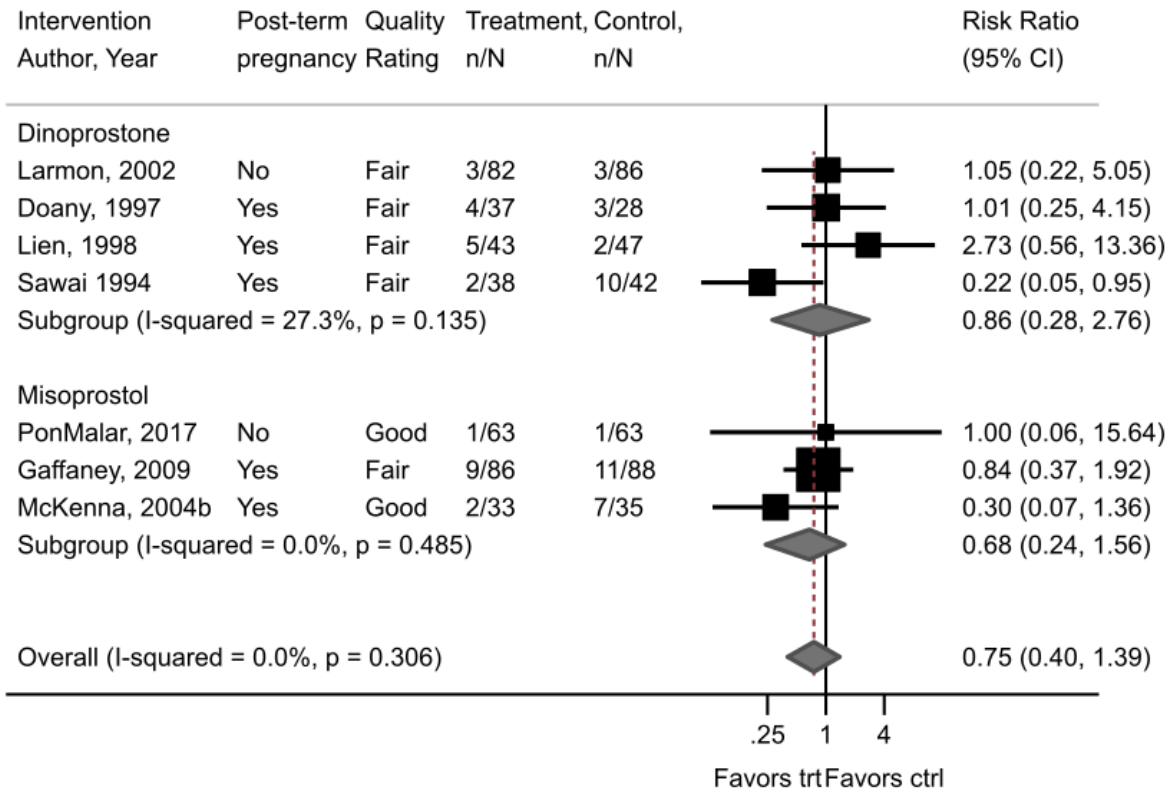
CI = confidence interval; ctrl = control; NA = not applicable; trt = treatment.

Figure F-17. Postpartum hemorrhage – prostaglandins vs. placebo by post-term pregnancy



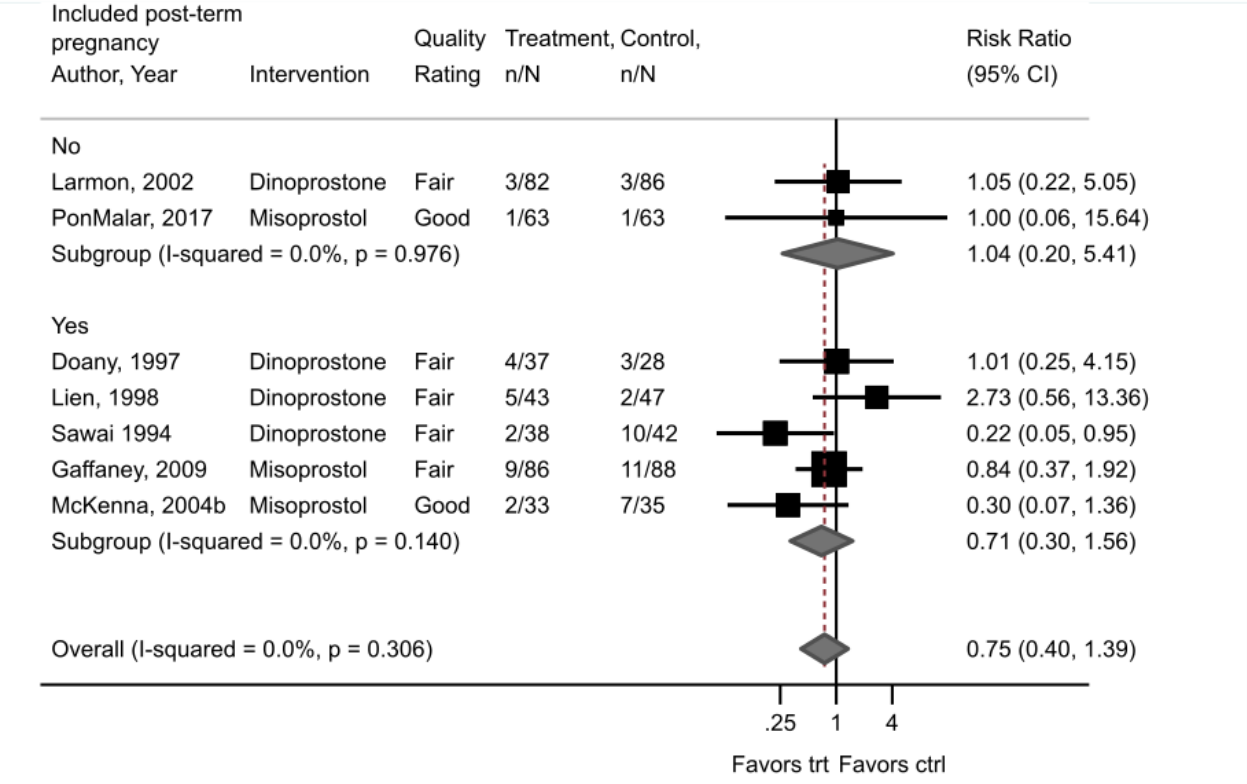
CI = confidence interval; ctrl = control; NA = not applicable; trt = treatment.

Figure F-18. Uterine infection – prostaglandins vs. placebo by intervention



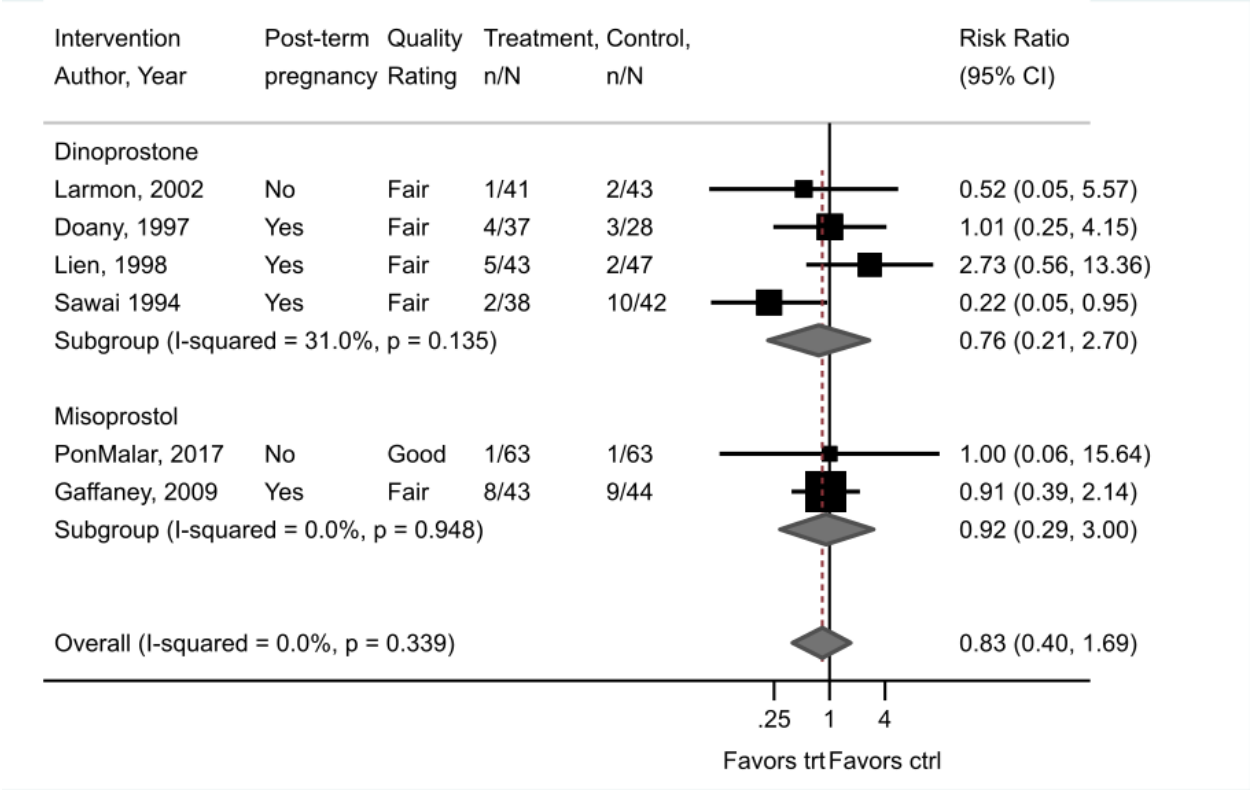
CI = confidence interval; ctrl = control; trt = treatment.

Figure F-19. Uterine infection – prostaglandins vs. placebo by post-term pregnancy



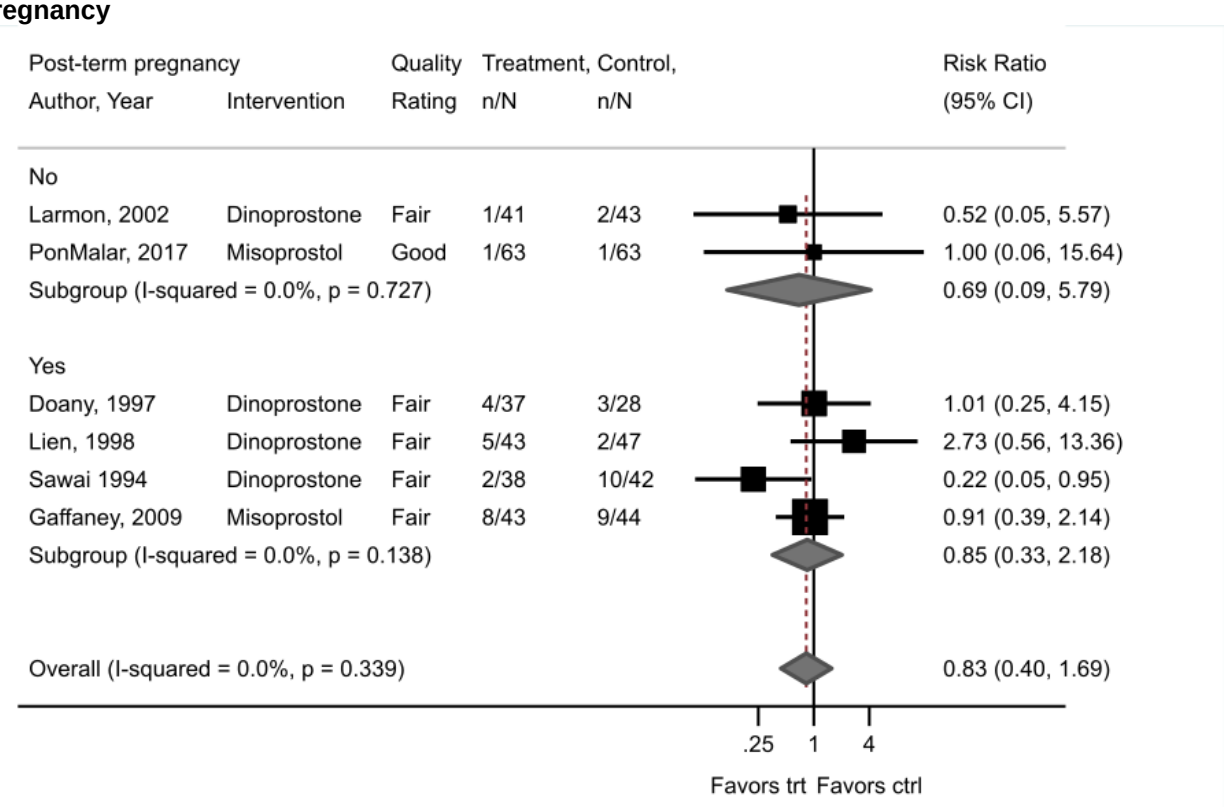
CI = confidence interval; ctrl = control; trt = treatment.

Figure F-20. Uterine infection – prostaglandins vs. placebo, chorioamnionitis by intervention



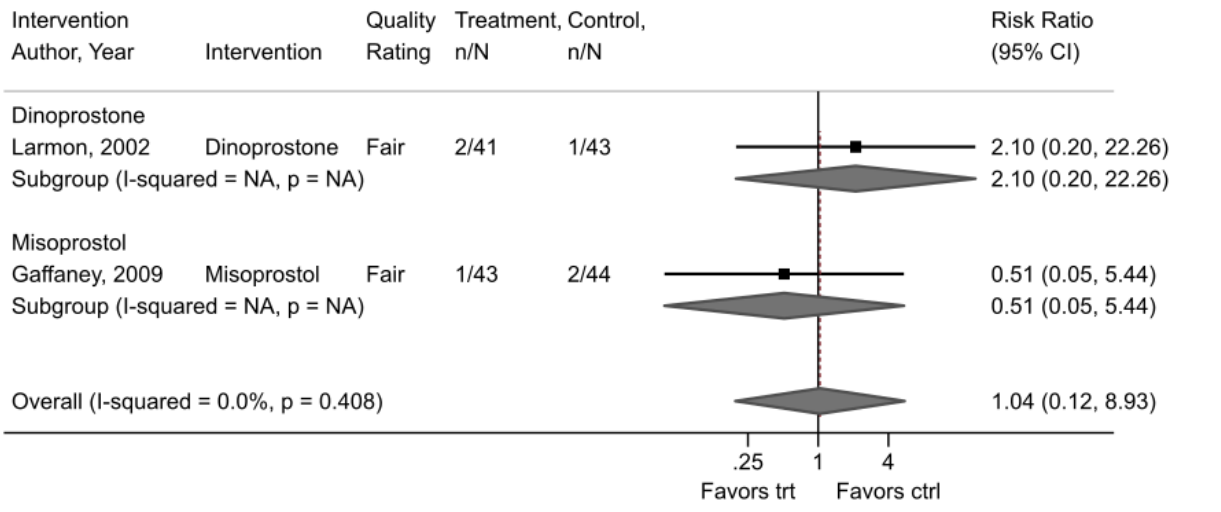
CI = confidence interval; ctrl = control; trt = treatment.

Figure F-21. Uterine infection – prostaglandins vs. placebo, chorioamnionitis by post-term pregnancy



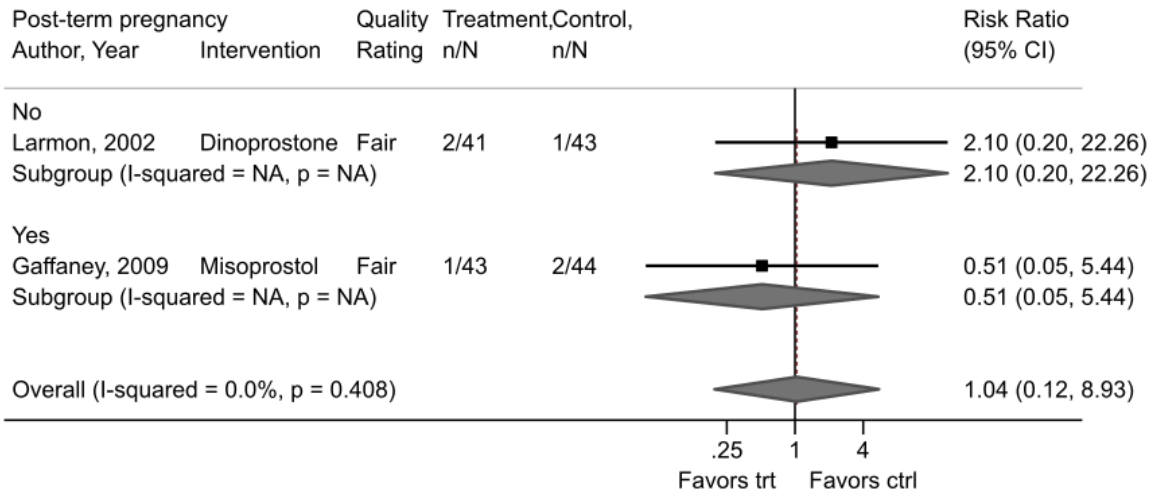
CI = confidence interval; ctrl = control; trt = treatment.

Figure F-22. Uterine infection – prostaglandins vs. placebo, endometritis by intervention



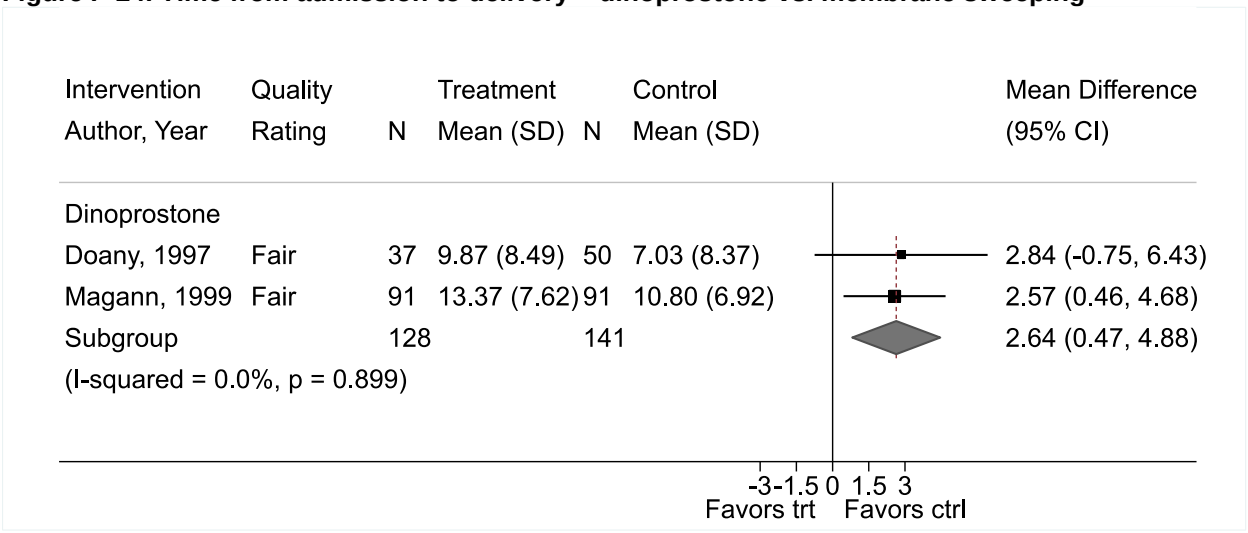
CI = confidence interval; ctrl = control; NA = not applicable; trt = treatment.

Figure F-23. Uterine infection – prostaglandins vs. placebo, endometritis by post-term pregnancy



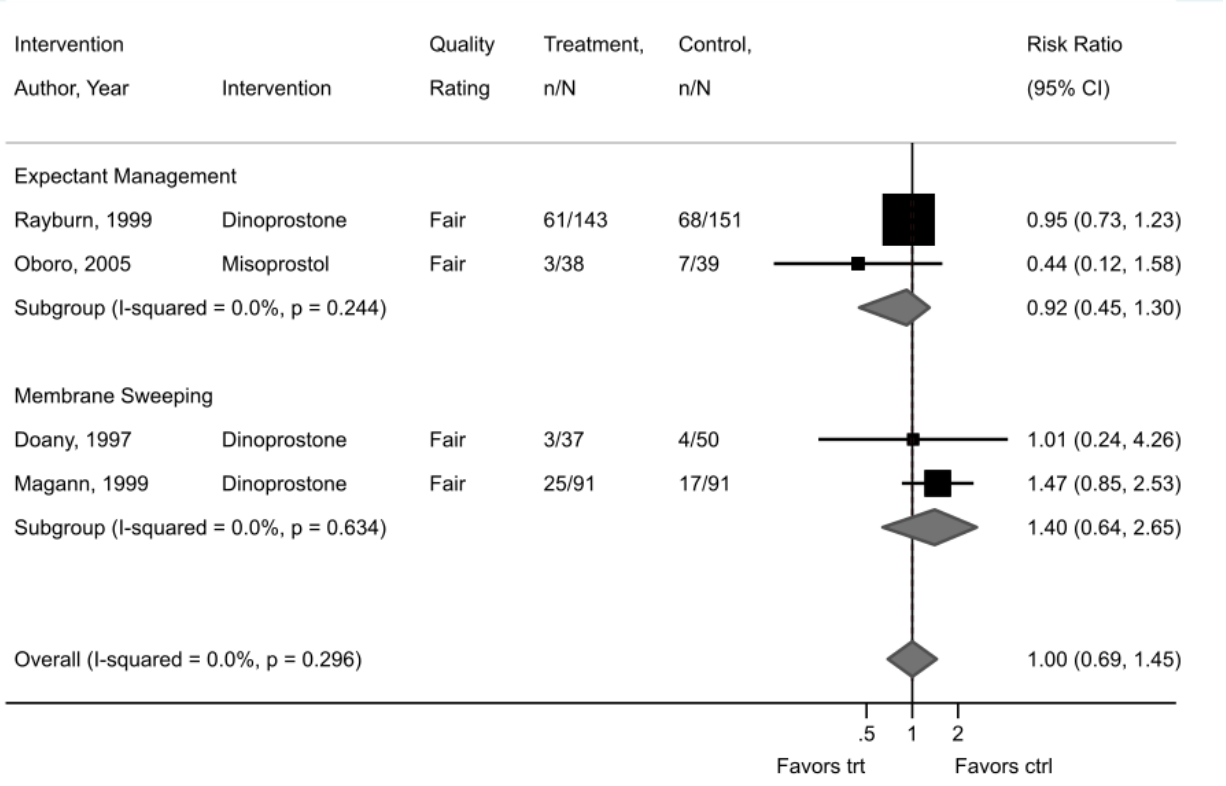
CI = confidence interval; ctrl = control; NA = not applicable; trt = treatment.

Figure F-24. Time from admission to delivery – dinoprostone vs. membrane sweeping



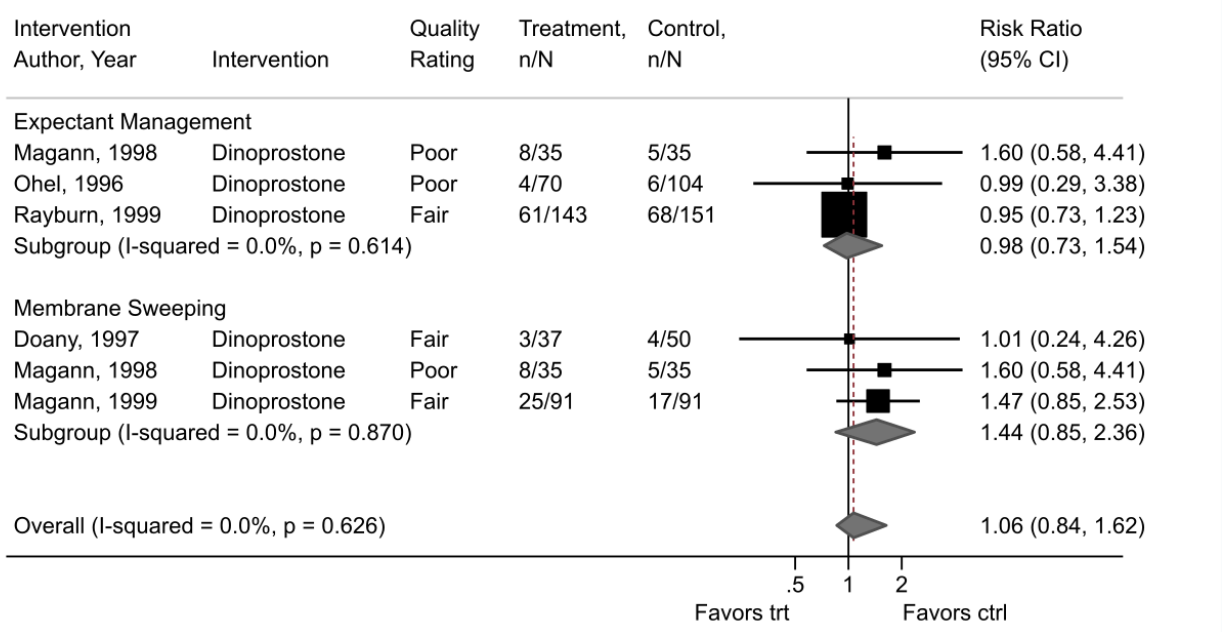
CI = confidence interval; ctrl = control; NA = not applicable; trt = treatment.

Figure F-25. Rate of cesarean delivery – prostaglandins vs. expectant management excluding poor-quality studies



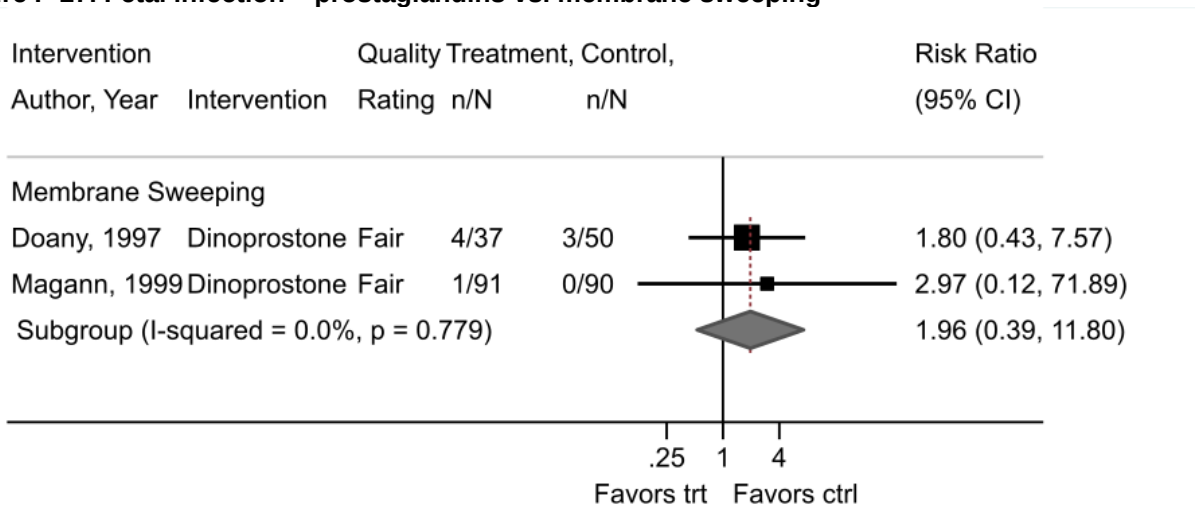
CI = confidence interval; ctrl = control; trt = treatment.

Figure F-26. Rate of cesarean delivery – prostaglandins vs. expectant management excluding misoprostol studies



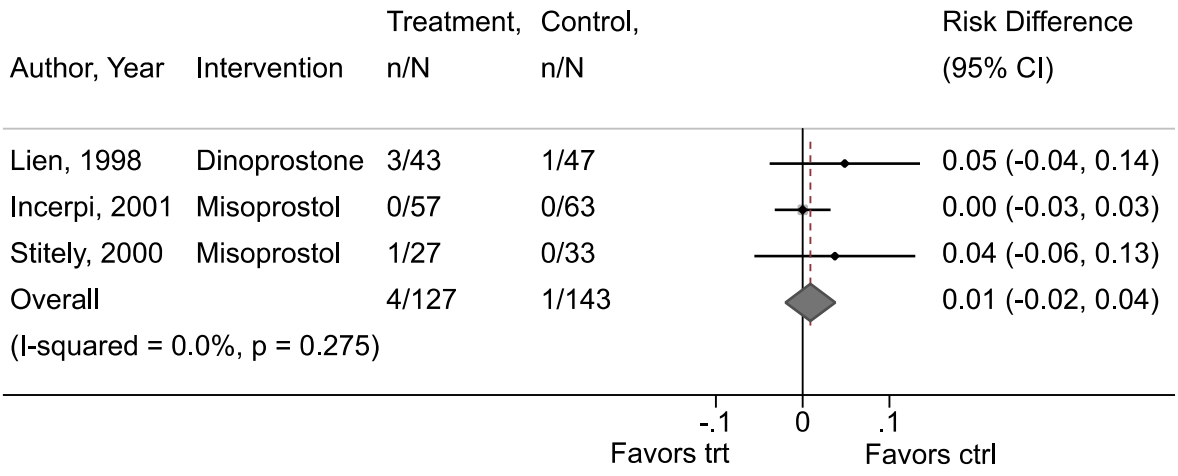
CI = confidence interval; ctrl = control; trt = treatment.

Figure F-27. Fetal infection – prostaglandins vs. membrane sweeping



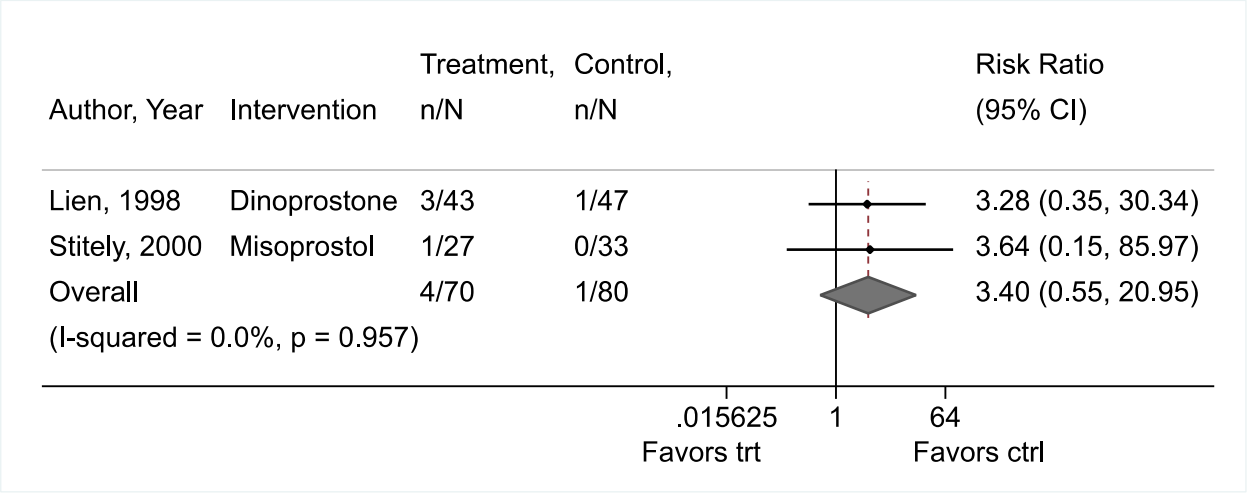
CI = confidence interval; ctrl = control; trt = treatment.

Figure F-28. Shoulder dystocia – prostaglandins vs. placebo



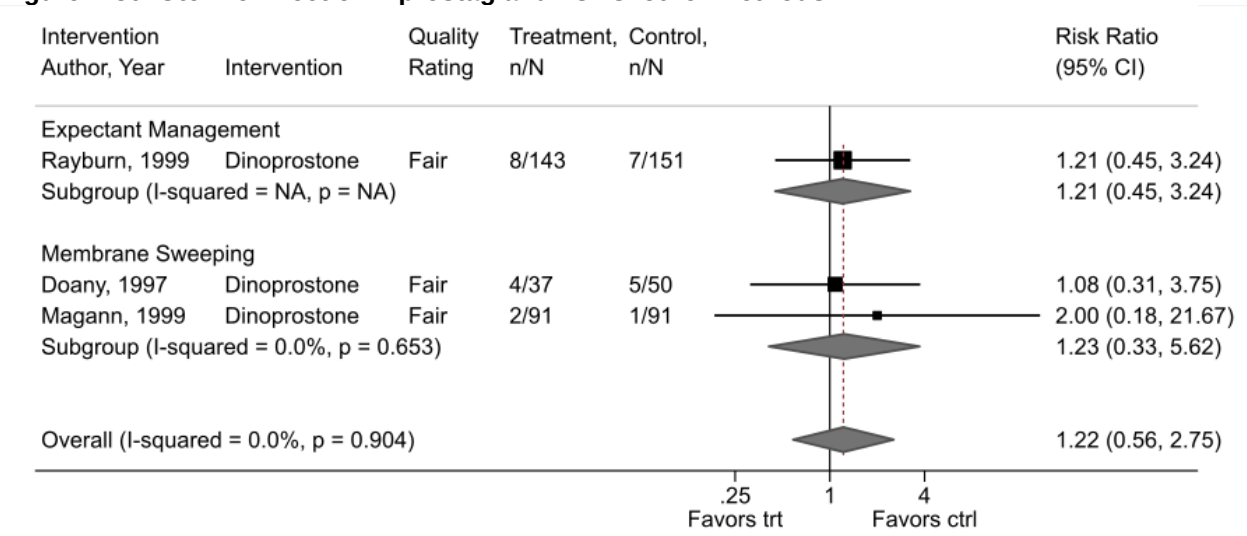
CI = confidence interval; ctrl = control; trt = treatment.

Figure F-29. Shoulder dystocia – prostaglandins vs. placebo excluding trial with no events



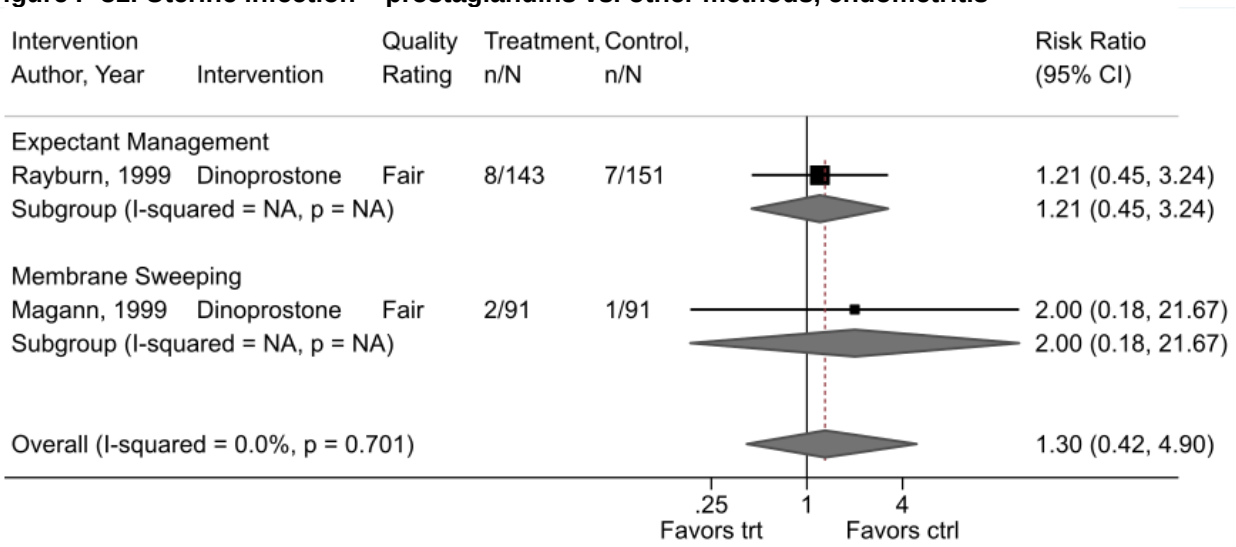
CI = confidence interval; ctrl = control; trt = treatment.

Figure F-30. Uterine infection – prostaglandins vs. other methods



CI = confidence interval; ctrl = control; NA = not applicable; trt = treatment.

Figure F-31. Uterine infection – prostaglandins vs. other methods, endometritis



CI = confidence interval; ctrl = control; NA = not applicable; trt = treatment.

Figure F-32. Prostaglandins vs. placebo rate of cesarean delivery – Egger's test for publication bias

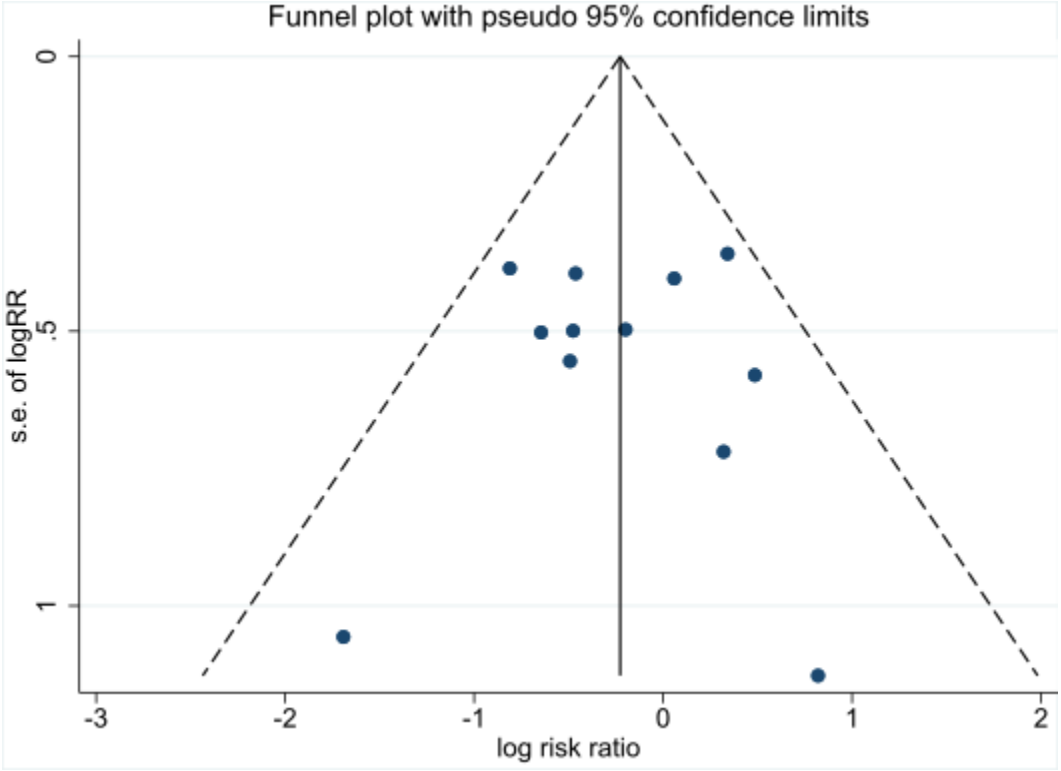


Figure F-33. Dinoprostone vs. placebo rate of cesarean delivery – Egger's test for publication bias

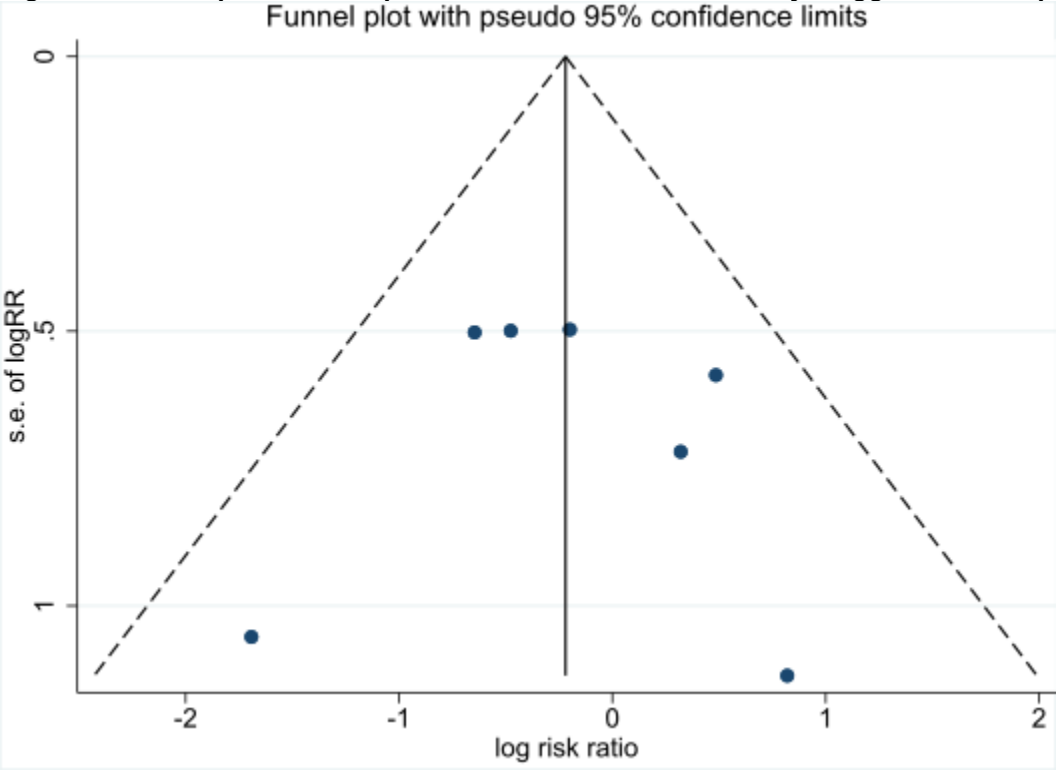
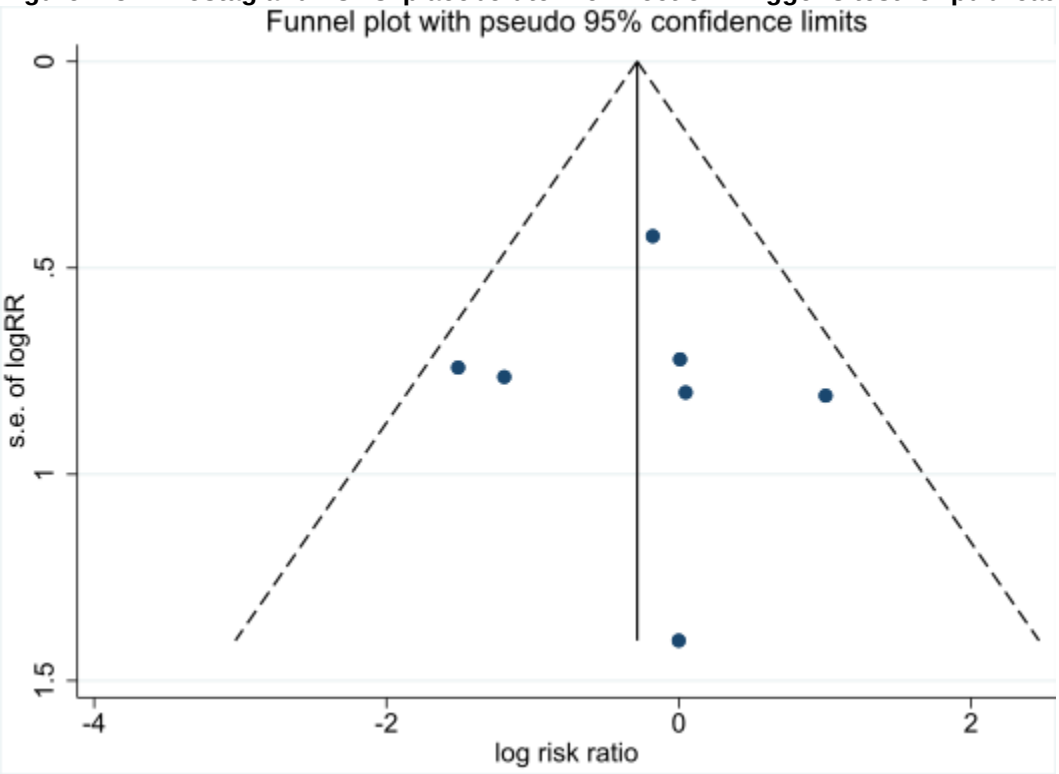


Figure F-34. Prostaglandins vs. placebo uterine infection – Egger's test for publication bias



Appendix G. Risk of Bias Assessments

Shown in associated Excel file.

Appendix H. Strength of Evidence

Table H-1. KQ1: Prostaglandins in outpatient versus inpatient setting

Comparison	Outcome	Number of Studies (N) and Total Participants	Study Limitations	Directness	Consistency (1 study= Unknown)	Precision	Publication Bias	Main Findings Effect Size (95% CI)	Strength of Evidence Grade
Dinoprostone, outpatient vs. inpatient: Birth Outcomes	Cesarean delivery	2 RCTs (N=1,120)[44,60] 4 Cohort studies (N=2,511)[25,26,56,63]	Moderate Moderate	Direct Direct	Consistent Consistent	Imprecise Precise	Unknown	RCTs: 23% vs. 23%; RR 0.97 (0.75 to 1.25), I^2=0% Cohort studies: 33% vs. 33%; RR 0.79 (95% CI 0.67 to 0.98), I^2=0%	Low
Dinoprostone, outpatient vs. inpatient: Fetal Harm Outcomes	Perinatal mortality[a]	1 Cohort study (N=992)[25]	Moderate	Direct	Unknown	Imprecise	Unknown	0.11% (1/907) vs. 0% (0/85); RR 0.28 (0.01 to 6.92) at 3 months (resulted in death)[a]	Insufficient
	Infection	2 RCTs (N=1,120)[44,60]	Moderate	Indirect (NICU admissions, infection not confirmed)	Consistent	Imprecise	Unknown	4% vs. 3%; RR 1.39 (0.67 to 3.03), I^2=0%	Low
	Hypoxic-ischemic encephalopathy	1 RCT (N=821)[60] 1 Cohort study (N=992)[25]	Moderate Moderate	Direct Indirect (outcome not specific)	Consistent	Imprecise Imprecise	Unknown	RCT: 0.74% (3/407) vs. 0.72% (3/414); RR 1.02 (0.21 to 5.01) Cohort study ("neonatal encephalopathy"): 0.11% (1/907) vs. 0% (0/85); RR 0.28 (0.01 to 6.92)	Insufficient

Comparison	Outcome	Number of Studies (N) and Total Participants	Study Limitations	Directness	Consistency (1 study= Unknown)	Precision	Publication Bias	Main Findings Effect Size (95% CI)	Strength of Evidence Grade
Dinoprostone, outpatient vs. inpatient: Fetal Harm Outcomes (continued)	Meconium Aspiration Syndrome	1 RCT (N=299)[44] 1 Cohort study (N=992)[25]	Moderate Moderate	Indirect (neither reports the syndrome specifically)	Consistent	Imprecise Imprecise	Unknown	RCT: 0% (0/149) vs. 0.67% (1/150); RR 0.34 (0.01 to 8.17) (NICU admission) Cohort study: 0.11% (1/907) vs. 0% (0/85); RR 0.28 (0.01 to 6.92) (lead to death at 3 months)[a]	Insufficient
Dinoprostone, outpatient vs. inpatient: Maternal Harm Outcomes	Hemorrhage requiring transfusion	1 RCT (N=299)[44]	Moderate	Direct	Unknown	Imprecise	Unknown	0.67% (1/149) vs. 0% (0/150); RR 3.02 (0.12 to 73.55)	Insufficient
Misoprostol, outpatient vs. inpatient: Birth Outcomes	Time from admission to vaginal birth	1 Cohort study (N=273)[61]	Moderate	Direct	Unknown	Imprecise	Unknown	Nulliparous: MD –3.1 hours (–4.74 to –1.46) Multiparas: MD –5.30 hours (–6.84 to –3.76)	Insufficient
	Cesarean delivery	1 Cohort study (N=273)[61]	Moderate	Direct	Unknown	Imprecise	Unknown	14% vs. 19%; RR 0.75 (0.43 to 1.31)	Insufficient
Misoprostol, outpatient vs. inpatient: : Fetal Harm Outcomes	Meconium aspiration syndrome	1 Cohort study (N=273)[61]	Moderate	Direct	Unknown	Imprecise	Unknown	meconium "uncommon and not more frequent in outpatient"	Insufficient

CI = confidence interval; MD = mean difference; NICU = neonatal intensive care unit; NOS = not otherwise specified; NR = not reported; RCT = randomized controlled trial; RR = risk ratio.

[a] Same neonate who was counted under perinatal mortality is counted under meconium aspiration syndrome for the cohort only; this neonate died at 3 months due to complications from meconium aspiration.

Table H-2. KQ2: Mechanical devices in outpatient versus inpatient setting

Comparison	Outcome	Number of Studies (N) and Total Participants	Study Limitations	Directness	Consistency (1 study= Unknown)	Precision	Publication Bias	Main Findings Effect Size (95% CI)	Strength of Evidence Grade
Single-balloon catheter, outpatient vs. inpatient: Birth Outcomes	Cesarean delivery	3 RCTs (n=370)[35,39,50] 2 Cohort studies (n=1,057)[64,67]	Moderate Moderate	Direct Direct	Consistent	Imprecise Precise	Unknown	RCTs: 12% vs. 20%; RR 0.59 (0.21 to 1.03), I^2=0% Cohort studies: 33% vs. 30%; RR 0.95 (0.72 to 1.22), I^2=0%	Low
Single-balloon catheter, outpatient vs. inpatient: Fetal Harm Outcomes	Neonatal sepsis confirmed by culture	1 Cohort study (n=615)[67]	Moderate	Direct	Unknown	Precise	Unknown	2% vs. 2%; RR 0.75 (0.24 to 2.34)	Insufficient
	Birth trauma[a]	1 RCT (n=129)[50]	Moderate	Direct	Unknown	Imprecise	Unknown	2% vs. 3%; RR 0.49 (0.05 to 5.30)	Low
	Shoulder dystocia	1 RCT (n=129)[50]	Moderate	Direct	Unknown	Imprecise	Unknown	3% vs. 11%; RR 0.28 (0.06 to 1.30)	Low
Single-balloon catheter, outpatient vs. inpatient: Maternal Harm Outcomes	Postpartum hemorrhage (any mode; blood loss >1,000 ml)	1 RCT (n=129)[50]	Moderate	Direct	Unknown	Imprecise	Unknown	0% (0/65) vs. 1.6% (1/64); RR 0.33 (0.01 to 7.91)	Insufficient
	Uterine infection (endometritis requiring readmission)	1 RCT (n=129)[50] 2 Cohort studies (n=1,057)[64,67]	Moderate Moderate	Direct Direct	Consistent	Imprecise Precise	Unknown	RCT: 2% vs. 2%; RR 0.98 (0.06 to 15.41) Cohort studies: 7% vs. 4%; RR 1.70 (0.90 to 3.69), I^2=0%)	Low

Comparison	Outcome	Number of Studies (N) and Total Participants	Study Limitations	Directness	Consistency (1 study= Unknown)	Precision	Publication Bias	Main Findings Effect Size (95% CI)	Strength of Evidence Grade
Single-balloon catheter, outpatient vs. inpatient: Maternal Harm Outcomes (continued)	Uterine infection (chorioamnionitis)	2 RCTs (n=259)[35,50]	Moderate	Direct	Consistent	Imprecise	Unknown	5% vs. 5%; RR 0.99 (0.28 to 3.51), I^2=0%	Low
	Any uterine infection (chorioamnionitis and/or endometritis)	2 RCTs (n=259)[35,50]	Moderate	Direct	Consistent	Imprecise	Unknown	5% vs. 5%; RR 0.99 (0.31 to 3.19), I^2=0%	Low
Double-balloon catheter, outpatient vs. inpatient: Birth Outcomes	Time from admission to vaginal birth	1 RCT (n=48)[42]	Moderate	Direct	Unknown	Imprecise	Unknown	14.25 vs. 21.45 hours; MD –7.2 hours (–11.45 to –2.95)	Insufficient
	Cesarean delivery	1 RCT (n=48)[42]	Moderate	Direct	Unknown	Imprecise	Unknown	18% vs. 33%; RR 0.55 (0.20 to 1.51)	Insufficient
Double-balloon catheter, outpatient vs. inpatient: Fetal Harm Outcomes	Perinatal mortality; Infection	1 RCT (n=48)[42]	Moderate	Direct	Unknown	Imprecise	Unknown	No case reported in either group	Insufficient
	Meconium aspiration syndrome	1 RCT (n=48)[42]	Moderate	Direct	Unknown	Imprecise	Unknown	3.0% (1/33) vs. 0% (0/15); RR 1.41 (0.06 to 32.78) (required NICU admit)	Insufficient
Double-balloon catheter, outpatient vs. inpatient: Maternal Harm Outcomes	Postpartum hemorrhage (blood loss >500 ml for vaginal birth or >1 L for cesarean delivery)	1 RCT (n=48)[42]	Moderate	Direct	Unknown	Imprecise	Unknown	18% vs. 13%; RR 1.36 (0.31 to 5.99)	Insufficient

Comparison	Outcome	Number of Studies (N) and Total Participants	Study Limitations	Directness	Consistency (1 study= Unknown)	Precision	Publication Bias	Main Findings Effect Size (95% CI)	Strength of Evidence Grade
Dilapan, outpatient vs. inpatient: Maternal Harm Outcomes	Uterine infection (endometritis)	1 Cohort study (n=42)[59]	Moderate	Direct	Unknown	Imprecise	Unknown	Narrative report of similar rates in both groups; no data reported	Insufficient
Catheter (outpatient) vs. dinoprostone (inpatient): Birth Outcomes	Cesarean delivery	2 RCTs (N=549)[28,65]	Moderate	Direct	Consistent	Imprecise	Unknown	33% vs. 26%; RR 1.24 (0.88 to 1.70), I^2=0%	Low
Catheter (outpatient) vs. dinoprostone (inpatient): Fetal Harm Outcomes	Perinatal mortality; hypoxic-ischemic encephalopathy; seizure	1 RCT (n=448)[65]	Moderate	Direct	Unknown	Imprecise	Unknown	No case reported in either group.	Insufficient
	Infection (confirmed)	1 RCT (n=448)[65]	Moderate	Direct	Unknown	Imprecise	Unknown	0.93% (2/215) vs. 0% (0/233); RR 5.42 (0.26 to 112.20)	Insufficient
Catheter (outpatient) vs. dinoprostone (inpatient): Maternal Harm Outcomes	Postpartum hemorrhage (any mode)	2 RCTs (N=549)[28,65]	Moderate	Direct	Inconsistent	Imprecise	Unknown	28% vs. 25%; RR 1.10 (0.62 to 1.56), I^2=0%	Low
	Uterine infection (NOS)	1 RCT (n=448)[65]	Moderate	Direct	Unknown	Imprecise	Unknown	0% (0/215) vs. 0.43% (1/233); RR 0.36 (0.01 to 8.82)	Insufficient

CI = confidence interval; MD = mean difference; NICU = neonatal intensive care unit; NOS = not otherwise specified; RCT = randomized controlled trial; RR = risk ratio.
[a] There were 3 cases total (1 in the outpatient and 2 in the inpatient group) which included 1 case each of brachial plexus injury, cephalohematoma, and scalp laceration plus cephalohematoma; authors did not report which specific injuries occurred in which group)

Table H-3. KQ3: Prostaglandins in outpatient setting

Comparison	Outcome	Number of Studies (N) and Total Participants	Study Limitations	Directness	Consistency (1 study= Unknown)	Precision	Publication Bias	Main Findings Effect Size (95% CI)	Strength of Evidence Grade
Misoprostol 25 mcg intravaginal vs. dinoprostone gel 0.5 mg intracervical: Birth Outcomes	Cesarean delivery	1 RCT (n=82)[52]	Moderate	Direct	Unknown	Imprecise	Unknown	21% vs. 19%; RR 1.13 (0.48 to 2.63)	Insufficient
Misoprostol 25 mcg oral vs. 50 mcg oral: Birth Outcomes	Cesarean delivery	1 RCT (n=49)[29]	Moderate	Direct	Unknown	Imprecise	Unknown	22% vs. 21%; RR 1.05 (0.37 to 3.01)	Insufficient
Dinoprostone gel intracervical 2.5 mg vs. 5.0 mg: Birth Outcomes	Cesarean delivery	1 RCT (n=116)[58]	Low	Direct	Unknown	Imprecise	Unknown	20% vs. 19%; RR 1.07 (0.51 to 2.22)	Low
Dinoprostone gel 3 mg intracervical vs. oral 3 mg: Birth Outcomes	Cesarean delivery	1 RCT (n=50)[66]	High	Direct	Unknown	Imprecise	Unknown	20% vs. 32%; RR 0.63 (0.24 to 1.65)	Insufficient
Dinoprostone vs. Placebo: Birth Outcomes	Cesarean delivery	7 RCT (n=473)[27,30,31,33,38,45,57]	Moderate	Direct	Consistent	Imprecise	Unknown	13% vs. 16%; RR 0.80 (0.50 to 1.31), I^2=0%	Low
Misoprostol vs. Placebo: Birth Outcomes	Cesarean delivery	5 RCTs (n=461)[34,36,40,46,49]	Moderate	Direct	Consistent	Imprecise	Unknown	19% vs. 25%; RR 0.79 (0.48 to 1.26), I^2=21.5%	Low

Comparison	Outcome	Number of Studies (N) and Total Participants	Study Limitations	Directness	Consistency (1 study= Unknown)	Precision	Publication Bias	Main Findings Effect Size (95% CI)	Strength of Evidence Grade
Any prostaglandin vs. Placebo: Birth Outcomes	Cesarean delivery	12 RCT s (n=934)[27,30,31,33,34,36,38,40,45,46,49,57]	Moderate	Direct	Consistent	Imprecise	Undetected Egger test P=0.969	16% vs. 21%; RR 0.80 (0.58 to 1.09), I^2=4.3%	Low
Any prostaglandin vs. Placebo: Fetal Harms Outcomes	Hypoxic-ischemic encephalopathy	1 RCT (n=126)[36]	Low	Direct	Unknown	Imprecise	Unknown	0 cases	Insufficient
	Infection: confirmed sepsis (GBS)	1 RCT (n=74)[57]	Moderate	Direct	Unknown	Imprecise	Unknown	3.1% (1/32) vs. 0% (0/42); RR 3.91 (0.16 to 92.91)	Insufficient
	Meconium aspiration syndrome	2 RCTs (n=134)[30,38]	Moderate	Direct	Inconsistent	Imprecise	Unknown	2% vs. 4%; RR 0.76 (0.03 to 22.33), I^2=0%	Insufficient
	Shoulder dystocia	3 RCTs (n=270)[31,40,49] 2 RCTs (n=150)[31,40]	Moderate	Direct	Consistent	Imprecise	Unknown	3.1% (4/127) vs. 0.70% (1/143); RD 0.01 (–0.02 to 0.04), I^2=0%; 5.7% (4/70) vs. 1.3% (1/80); RR 3.40 (0.55 to 20.95)[a], I^2=0%	Low
Any prostaglandin vs. Placebo: Maternal Harm Outcomes	Uterine infection (chorioamnionitis or endometritis)	7 RCTs (n=771)[27,30,31,34,36,46,57]	Moderate	Direct	Consistent	Imprecise	Undetected Egger test p=0.981	7% vs. 10%; RR 0.75 (0.40 to 1.39), I^2=0%	Low
	Postpartum hemorrhage (any mode)	3 RCTs (n=339)[27,33,46]	Moderate	Direct	Consistent	Imprecise	Unknown	2.7% (3/110) vs. 0.97% (1/103); RR 1.66 (0.18 to 14.63), I^2=0%	Insufficient

Comparison	Outcome	Number of Studies (N) and Total Participants	Study Limitations	Directness	Consistency (1 study= Unknown)	Precision	Publication Bias	Main Findings Effect Size (95% CI)	Strength of Evidence Grade
Any Prostaglandin vs. Expectant Management: Birth Outcomes	Cesarean delivery	4 RCTs (n=615)[32,37,54,55]	Moderate	Direct	Consistent	Imprecise	Unknown	27% vs. 26%; RR 0.95 (0.68 to 1.33), I^2=0%	Low
Any Prostaglandin vs. Expectant Management: Fetal Harm Outcomes	Perinatal mortality	1 RCT (n=77)[54]	Moderate	Direct	Unknown	Imprecise	Unknown	0% (0/38) vs. 2.6% (1/39); RR 0.34 (0.01 to 8.14)	Insufficient
Any Prostaglandin vs. Expectant Management: Maternal Harm Outcomes	Postpartum hemorrhage (undefined; any mode)	1 RCT (n=77)[54]	Moderate	Direct	Unknown	Imprecise	Unknown	3% vs. 3%; RR 1.03 (0.07 to 15.82)	Insufficient
	Uterine infection (Endometritis)	1 RCT (n=294)[37]	Moderate	Direct	Unknown	Imprecise	Unknown	6% vs. 5%; RR 1.21 (0.45 to 3.24)	Low
	"Infectious morbidity" (not further defined)	1 RCT (n=77)[54]	Moderate	Direct	Unknown	Imprecise	Unknown	5% vs. 8%; RR 0.68 (0.12 to 3.87)	Insufficient
Dinoprostone vs. Membrane sweeping: Birth Outcomes	Cesarean delivery	3 RCTs (n=339)[27,32,51]	Moderate	Direct	Consistent	Imprecise	Unknown	22% vs. 15%; RR 1.44 (0.85 to 2.36), I^2=0% Excluding poor-quality trial [32]: 2 RCTs, 22% vs. 15%; RR 1.40 (0.64 to 2.65), I^2=0%	Low
Dinoprostone vs. Membrane sweeping: Fetal Harm Outcomes	Meconium ("syndrome" not specified) requiring NICU admission	1 RCT (n=182)[51]	Moderate	Direct	Unknown	Imprecise	Unknown	1% vs. 1%; RR 1.0 (0.06 to 15.75)	Insufficient

Comparison	Outcome	Number of Studies (N) and Total Participants	Study Limitations	Directness	Consistency (1 study= Unknown)	Precision	Publication Bias	Main Findings Effect Size (95% CI)	Strength of Evidence Grade
Dinoprostone vs. Membrane sweeping: Maternal Harm Outcomes	Postpartum hemorrhage (undefined)	1 RCT (n=87)[27]	Moderate	Direct	Unknown	Imprecise	Unknown	No cases in either group	Insufficient
	Uterine infection (chorioamnionitis or endometritis)	2 RCTs (n=269)[27,51]	Moderate	Direct	Consistent	Imprecise	Unknown	7% vs. 4%; RR 1.22 (0.56, 2.75), I^2=0%	Low
Dinoprostone vs. Estradiol cream: Birth Outcomes	Cesarean delivery	1 RCT (n=85)[30]	Moderate	Direct	Unknown	Imprecise	Unknown	12% vs. 31%; RR 0.41 (0.16 to 1.06)	Insufficient
Dinoprostone vs. Estradiol cream: Maternal Harm Outcomes	Uterine infection	1 RCT (n=85)[30]	Moderate	Direct	Unknown	Imprecise	Unknown	Chorioamnionitis: 2% vs. 9%; RR 0.27 (0.03 to 2.30) Endomyometritis: 5% vs. 7%; RR 0.72 (0.13 to 4.07)	Insufficient
Dinoprostone vs. Single-balloon catheter: Birth Outcomes	Cesarean delivery	1 Cohort study (n=153)[72]	Moderate	Direct	Unknown	Imprecise	Unknown	32% vs. 22%; RR 1.48 (0.87 to 2.50)	Insufficient
Dinoprostone vs. Single-balloon catheter: Fetal Harm Outcomes	Shoulder dystocia	1 Cohort study (n=153)[72]	Moderate	Direct	Unknown	Imprecise	Unknown	2.82% vs. 6.10%; RR 0.46 (0.09 to 2.31)	Insufficient

Comparison	Outcome	Number of Studies (N) and Total Participants	Study Limitations	Directness	Consistency (1 study= Unknown)	Precision	Publication Bias	Main Findings Effect Size (95% CI)	Strength of Evidence Grade
Dinoprostone vs. Single-balloon catheter: Maternal Harm Outcomes	Postpartum hemorrhage (undefined)	1 Cohort study (n=153)[72]	Moderate	Direct	Unknown	Imprecise	Unknown	1.41% vs. 6.10%; RR 0.23 (0.03 to 1.93)	Insufficient
Single-balloon catheter: silicone vs. latex: Birth Outcomes	Cesarean delivery	1 RCT (n=534)[23]	Moderate	Direct	Unknown	Imprecise	Unknown	39% vs. 40%; RR 0.98 (0.80 to 1.22)	Low
Single-balloon catheter: silicone vs. latex: Fetal Harm Outcomes	NICU admission due to infection risk	1 RCT (n=534)[23]	Moderate	Direct	Unknown	Imprecise	Unknown	2% vs. 1%; RR 1.27 (0.35 to 4.69)	Insufficient
Single-balloon catheter: silicone vs. latex: Maternal Outcomes	Intrapartum antibiotics for suspected chorioamnionitis	1 RCT (n=534)[23]	Moderate	Indirect	Unknown	Imprecise	Unknown	14% vs. 10%; RR 1.35 (0.85 to 2.16)	Insufficient
	Post-partum hemorrhage >1500 ml (any mode)	1 RCT (n=534)[23]	Moderate	Direct	Unknown	Imprecise	Unknown	2% vs. 1%; RR 1.69 (0.41 to 7.01)	Insufficient

CI = confidence interval; L&D = Labor and Delivery; MD = mean difference; NICU = neonatal intensive care unit; NOS = not otherwise specified; RCT = randomized controlled trial; RR = risk ratio.

[a] One RCT (Incerpi 2001)[49] reported no events and is not included in the RR analysis; therefore, an analysis using RD was also performed. Of note, one of the other two trials (Lien 1998) reported a higher proportion of neonates with shoulder dystocia in the dinoprostone group (7.0% vs. 2.1%), but there was also a difference in the proportion of neonates with birth weight >4000 gm in the dinoprostone group (33% vs. 15%).

Appendix I. Excluded Studies List

Table I-1. Key to exclusion codes

Exclusion Code	Exclusion Reason
1	Ineligible population
2	Ineligible intervention (include ineligible comparator)
3	Ineligible outcome
4	Ineligible setting
5	Ineligible study design
6	Ineligible publication type
7	Foreign language
8	Study not obtainable
9	Outdated or ineligible systematic review

1. Abaza R, Prall D. Drain placement can be safely omitted after the majority of robotic partial nephrectomies. J Urol. 2013 Mar;189(3):823-7. doi: 10.1016/j.juro.2012.08.236. PMID: 23009869. Exclusion: 1.

2. Abdelaziz A, Mahmoud AA, Ellaithy MI, et al. Pre-induction cervical ripening using two different dinoprostone vaginal preparations: a randomized clinical trial of tablets and slow release retrievable insert. Taiwan J Obstet Gynecol. 2018 Aug;57(4):560-6. doi: 10.1016/j.tjog.2018.06.016. PMID: 30122579. Exclusion: 4.

3. Abdellah MS, Hussien M, Aboalhassan A. Intravaginal administration of isosorbide mononitrate and misoprostol for cervical ripening and induction of labour: a randomized controlled trial. Arch Gynecol Obstet. 2011 Jul;284(1):25-30. doi: 10.1007/s00404-010-1572-4. PMID: 20582425. Exclusion: 2.

4. Abdul MA, Ibrahim UN, Yusuf MD, et al. Efficacy and safety of misoprostol in induction of labour in a Nigerian tertiary hospital. West Afr J Med. 2007 Jul-Sep;26(3):213-6. doi: 10.4314/wajm.v26i3.28312. PMID: 18399337. Exclusion: 4.

5. Acharya N, Gadge A, Agrawal M, et al. Mechanical cervical ripening with foley catheter balloon: rekindling a forgotten art. Journal of SAFOG. 2018;10(1):1-4. doi: 10.5005/jp-journals-10006-1548. Exclusion: 4.

6. Adair CD, Weeks JW, Barrilleaux S, et al. Oral or vaginal misoprostol administration for induction of labor: a randomized, double-blind trial. Obstet Gynecol. 1998 Nov;92(5):810-3. doi: 10.1016/s0029-7844(98)00278-6. PMID: 9794674. Exclusion: 2.

7. Adelson PL, Wedlock GR, Wilkinson CS, et al. A cost analysis of inpatient compared with outpatient prostaglandin E2 cervical priming for induction of labour: results from the OPRA trial. Aust Health Rev. 2013 Sep;37(4):467-73. doi: 10.1071/AH13081. PMID: 24018055. Exclusion: 3.

8. Adeniji AO, Akinola SE. A comparison of orally administered misoprostol and membrane sweeping for labour induction in uncomplicated singleton post-term pregnancies. S Afr J Obstet Gynaecol. 2013;19(1):4-7. doi: 10.7196/SAJOG.584. PMID: 00912287. Exclusion: 2.

9. Adeniji OA, Oladokun A, Olayemi O, et al. Pre-induction cervical ripening: transcervical foley catheter versus intravaginal misoprostol. J Obstet Gynaecol. 2005 Feb;25(2):134-9. doi: 10.1080/01443610500040737. PMID: 15814391. Exclusion: 4.

10. Afolabi BB, Oyeneyin OL, Ogedengbe OK. Intravaginal misoprostol versus foley catheter for cervical ripening and induction of labor. Int J Gynaecol Obstet. 2005 Jun;89(3):263-7. doi: 10.1016/j.ijgo.2005.02.010. PMID: 15919393. Exclusion: 4.

11. Aftab S, Noorani KJ. Comparison of efficacy of vaginal misoprostol and prostaglandin E2 for induction of labour in primigravidae title page. Medical Channel. 2011;17(1):39-43. Exclusion: 4.

12. Agarwal K, Batra A, Batra A, et al. Randomized comparison of isosorbide mononitrate and PGE2 gel for cervical ripening at term including high risk pregnancy. International Journal of Reproductive Medicine Print. 2014;2014:147274. doi: 10.1155/2014/147274. PMID: 25763391. Exclusion: 2.

13. Agarwal N, Gupta A, Kriplani A, et al. Six hourly vaginal misoprostol versus intracervical dinoprostone for cervical ripening and labor induction. J Obstet Gynaecol Res. 2003 Jun;29(3):147-51. doi: 10.1046/j.1341-8076.2003.00091.x. PMID: 12841697. Exclusion: 4.

14. Aghideh FK, Mullin PM, Ingles S, et al. A comparison of obstetrical outcomes with labor induction agents used at term. J Matern Fetal Neonatal Med. 2014 Apr;27(6):592-6. doi: 10.3109/14767058.2013.831066. PMID: 23919802. Exclusion: 4.

15. Akhtar A, Talib W, Shami N, et al. Induction of labour - a comparison between misoprostol and dinoprostone. Pakistan Journal of Medical and Health Sciences. 2011 Oct;5(4):617-9. PMID: 00902431. Exclusion: 4.

16. Al-Assadi AF, Al-Waeely FA, Ahmed H, et al. Extraamniotic versus vaginal misoprostol for ripening the unfavorable cervix. J Bahrain Med Soc. 2009;21(1):207-11. Exclusion: 4.

17. Al-Assadi AF, Al-Waeely FA, Kadhim SS. The use of extraamniotic dexamethasone for ripening the unfavourable cervix. J Bahrain Med Soc. 2007 Oct;19(4):148-53. doi: 10.1093/ajcn/31.10.S125. PMID: 00707362. Exclusion: 4.

18. Al-Ibraheemi Z, Brustman L, Bimson BE, et al. Misoprostol with foley bulb compared with misoprostol alone for cervical ripening: a randomized controlled trial. Obstet Gynecol. 2018 Jan;131(1):23-9. doi: 10.1097/AOG.0000000000002403. PMID: 29215514. Exclusion: 4.

19. Al-Taani MI. Intravaginal prostaglandin-E2 for cervical priming and induction of labour. East Mediterr Health J. 2007 Jul-Aug;13(4):855-61. PMID: 17955768. Exclusion: 4.

20. Allameh Z, Rouholamin S, Hekmat R. Comparison of vaginal misoprostol tablet with oxytocin infusion for induction of labor in term pregnancy. J Res Med Sci. 2012;17(1 SPL.1):S134-S9. Exclusion: 2.

21. Amon E, Fossick K, Sibai B. Serial changes in the biophysical profile in patients undergoing cervical ripening with a controlled release PGE2 vaginal pessary. J Matern Fetal Med. 1999 Jan-Feb;8(1):8-11. doi: 10.1002/(SICI)1520-6661(199901/02)8:1<8::AID-MFM2>3.0.CO;2-0. PMID: 10052838. Exclusion: 4.

22. Anabusi S, Mei-Dan E, Hallak M, et al. Mechanical labor induction in the obese population: a secondary analysis of a prospective randomized trial. Arch Gynecol Obstet. 2016 Jan;293(1):75-80. doi: 10.1007/s00404-015-3765-3. PMID: 26054823. Exclusion: 5.

23. Anand AK, Mir S. A randomized comparison between intravaginal misoprostol and intracervical dinoprostone for cervical ripening and labour induction in participants with unfavourable cervices. JK Science. 2012;14(3):115-9. Exclusion: 4.

24. Ande AB, Ezeanochie CM, Olagbuji NB. Induction of labor in prolonged pregnancy with unfavorable cervix: comparison of sequential intracervical Foley catheter-intravaginal misoprostol and intravaginal misoprostol alone. Arch Gynecol Obstet. 2012 Apr;285(4):967-71. doi: 10.1007/s00404-011-2094-4. PMID: 22012248. Exclusion: 4.

25. Andreasson B, Bock JE, Larsen J. Induction of labor. A double-blind randomized controlled study of prostaglandin E2 vaginal suppositories compared with intranasal oxytocin and with sequential treatment. Acta Obstet Gynecol Scand. 1985;64(2):157-61. doi: 10.3109/00016348509154710. PMID: 3885670. Exclusion: 2.

26. Anjum S, Sharma R. Oral misoprostol vs intravenous oxytocin infusion for induction of labor in prelabor rupture of membranes. Journal of SAFOG. 2016;8(1):4-7. doi: 10.5005/jp-journals-10006-1375. Exclusion: 4.

27. Anonymous. A clinical trial of induction of labor versus expectant management in postterm pregnancy. The National Institute of Child Health and Human Development Network of Maternal-Fetal Medicine Units. Am J Obstet Gynecol. 1994 Mar;170(3):716-23. PMID: 7710467. Exclusion: 4.

28. Arif A, Khan NR, Zeb L. Mode of delivery and fetal outcome in patients with prolonged pregnancy undergoing elective induction at 41 & 41+ weeks. Journal of Postgraduate Medical Institute. 2015;29(4):227-30. Exclusion: 4.

29. Arulkumaran S, Adaikan PG, Anandakumar C, et al. Comparative study of a two dose schedule of PGE2 3 mg pessary and 1700 micrograms film for induction of labour in nulliparae with poor cervical score. Prostaglandins Leukot Essent Fatty Acids. 1989 Oct;38(1):37-41. doi: 10.1016/0952-3278(89)90145-2. PMID: 2608700. Exclusion: 4.

30. Arulkumaran S, Gibb DM, Heng SH, et al. Perinatal outcome of induced labour. Asia Oceania J Obstet Gynaecol. 1985 Mar;11(1):33-7. doi: 10.1111/j.1447-0756.1985.tb00044.x. PMID: 4040358. Exclusion: 2.

31. Asher GN, Coeytaux RR, Chen W, et al. Acupuncture to initiate labor (Acumoms 2): a randomized, sham-controlled clinical trial. J Matern Fetal Neonatal Med. 2009 Oct;22(10):843-8. doi: 10.1080/14767050902906386. PMID: 19526433. Exclusion: 2.

32. Ashrafunnessa, Khatun SS, Chowdhury SA, et al. Induction of labor by intracervical prostaglandin gel and oxytocin infusion in primigravid women with unfavorable cervix. Bangladesh Med Res Counc Bull. 1997 Dec;23(3):66-71. PMID: 9621474. Exclusion: 8.

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