Balloon catheters versus vaginal prostaglandins for labour induction (CPI Collaborative): an individual participant data meta-analysis of randomised controlled trials

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Summary

Background Induction of labour is one of the most common obstetric interventions globally. Balloon catheters and vaginal prostaglandins are widely used to ripen the cervix in labour induction. We aimed to compare the effectiveness and safety profiles of these two induction methods.

Methods We did an individual participant data meta-analysis comparing balloon catheters and vaginal prostaglandins for cervical ripening before labour induction. We systematically identified published and unpublished randomised controlled trials that completed data collection between March 19, 2019, and May 1, 2021, by searching the Cochrane Library, ClinicalTrials.gov, WHO International Clinical Trials Registry Platform, and PubMed. Further trials done before March 19, 2019, were identified through a recent Cochrane review. Data relating to the combined use of the two methods were not included, only data from women with a viable, singleton pregnancy were analysed, and no exclusion was made based on parity or membrane status. We contacted authors of individuals trials and participant-level data were harmonised and recoded according to predefined definitions of variables. Risk of bias was assessed with the ROB2 tool. The primary outcomes were caesarean delivery, indication for caesarean delivery, a composite adverse perinatal outcome, and a composite adverse maternal outcome. We followed the intention-to-treat principle for the main analysis. The primary meta-analysis used two-stage random-effects models and the sensitivity analysis used one-stage mixed models. All models were adjusted for maternal age and parity. This meta-analysis is registered with PROSPERO (CRD42020179924).

Findings Individual participant data were available from 12 studies with a total of 5460 participants. Balloon catheters, compared with vaginal prostaglandins, did not lead to a significantly different rate of caesarean delivery (12 trials, 5414 women; crude incidence 27·0%; adjusted OR [aOR] 1·09, 95% CI 0·95–1·24; I^2=0%), caesarean delivery for failure to progress (11 trials, 4601 women; aOR 1·20, 95% CI 0·91–1·58; I^2=39%), or caesarean delivery for fetal distress (10 trials, 4441 women; aOR 0·86, 95% CI 0·71–1·04; I^2=0%). The composite adverse perinatal outcome was lower in women who were allocated to balloon catheters than in those allocated to vaginal prostaglandins (ten trials, 4452 neonates, crude incidence 13·6%; aOR 0·80, 95% CI 0·70–0·92; I^2=0%). There was no significant difference in the composite adverse maternal outcome (ten trials, 4326 women, crude incidence 22·7%; aOR 1·02, 95% CI 0·89–1·18; I^2=0%).

Interpretation In induction of labour, balloon catheters and vaginal prostaglandins have comparable caesarean delivery rates and maternal safety profiles, but balloon catheters lead to fewer adverse perinatal events.

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Introduction

Induction of labour is one of the most common obstetric procedures, occurring in as many as one in four births in high-income countries, and one in ten births globally.[1] Induction is performed when the risks of continued pregnancy outweigh the benefits. Rates of labour induction have substantially increased since 2010, from 25% to 35% in Australia,[2] and from 20% to 32% in the UK.[3] This increase reflects the increased acceptability of the labour induction process to both women and health professionals.

In women with an unripe cervix, labour induction starts with cervical ripening and then uterine contractions can be initiated. Cervical ripening can be achieved with mechanical methods, commonly a single-balloon catheter or double-balloon catheter, or pharmacological methods, including exogenous prostaglandins such as misoprostol (PGE1) or dinoprostone (PGE2). One-fifth of labour

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Research in context

Evidence before this study

Induction of labour is one of the most common obstetric interventions that is applied to tens of millions of women each year globally. Balloon catheters and vaginal prostaglandins are widely used to ripen the cervix in labour induction. We searched PubMed on May 01, 2021, to identify systematic reviews and meta-analyses that compared balloon catheters and vaginal prostaglandins for labour induction, using the search terms "balloon", "Foley", "catheter", "prostaglandin", "dinoprostone", "misoprostol", "induction", and "ripening". Previous reviews have shown that balloon catheters are probably as effective as vaginal prostaglandins for vaginal birth, but the comparison between the two methods in terms of maternal and perinatal safety remains unclear because assessments of individual adverse outcomes using summary data of trials are underpowered.

Added value of this study

This is the first individual participant data meta-analysis that compared balloon catheters and vaginal prostaglandins for both effectiveness and safety. The robustness of the included trials, the collaborative process between the coordinating team and trial investigators, and the predefined analysis enabled the findings to be interpreted with confidence. The diverse settings of the included trials ensured good generalisability of the findings. We not only assessed the overall caesarean delivery but also specifically considered the two major indications for caesarean delivery: failure to progress and fetal compromise. Empowered by the participant-level data to construct composite outcomes for adverse events, new evidence regarding maternal and perinatal safety was obtained from analyses with sufficient power.

Implications of all the available evidence

Balloon catheters and vaginal prostaglandins are comparable regarding effectiveness, as measured by mode of birth and maternal safety profile. New evidence generated in this study indicates an improved neonatal safety profile with balloon catheters. Increasing the use of balloon catheters rather than vaginal prostaglandins in labour induction could potentially prevent a considerable number of adverse perinatal events given the large volume of labour inductions worldwide. Shared decision making with women that jointly considers effectiveness, safety, and practicalities is important for choosing the right method.

inductions in women with an unripe cervix do not result in a vaginal birth, and these women go on to require a caesarean section.[4] Induction of labour also carries the risks of rare adverse events, including maternal and neonatal morbidity and mortality. Hence, identifying the optimal method of labour induction is of enormous importance for women and babies worldwide.

Since the 2000s, advances have made it easier to identify which women would benefit from labour induction, through indications for maternal[5] or fetal concern,[6] and when in pregnancy labour should be induced. Studies have suggested that labour could even be induced at 39 weeks of gestation in uncomplicated pregnancies to reduce the caesarean delivery rate.[7,8] However, the use of a suboptimal method for induction could counteract the advances of these benefits for women and neonates, especially those related to a worse safety profile. Even if the difference in adverse events between induction methods is small on an individual basis, the global effect could be large given that induction of labour is applied to around 14 million women each year.

Several aggregate meta-analyses, including the latest Cochrane review, suggest that balloon catheters are equally effective as vaginal PGE2 for cervical ripening in achieving vaginal birth, although no firm conclusion can be drawn for the neonatal safety profile between the two methods.[9–17] Conventional meta-analyses using aggregate data will not answer this question given the low incidence of individual safety outcomes and the use of slightly different endpoints between studies. An individual patient data meta-analysis allows for the evaluation of interventions on the level of row-by-row data. The benefits of this approach include greater flexibility and scope of analyses, standardisation of definitions, improved statistical power, and improved quality and trustworthiness of data.[18] Importantly, an individual participant data meta-analysis allows composite outcomes to be assessed, potentially addressing the problem of underpowered analysis of individual safety measures in previous meta-analyses of labour induction, especially perinatal safety outcomes.

Here, we report an individual participant data meta-analysis that compares the effectivness and safety of use of balloon catheters and vaginal prostaglandins for labour induction. We hypothesised that induction of labour with balloon catheters would result in similar caesarean delivery rates to vaginal prostaglandins, with better perinatal and maternal outcomes.

Methods

Overview

This international collaborative individual participant data meta-analysis followed a prospectively registered protocol (PROSPERO [CRD42020179924]) and a statistical analysis plan produced in advance. Ethics approval was obtained from the Monash Health Human Research Ethics Committee on May 15, 2020 (RES-20–0000328Q-64577). Findings are reported following the PRISMA-IPD statement.[19]

Search strategy and selection criteria

We searched the Cochrane Library of registered trials, ClinicalTrials.gov, WHO International Clinical Trials Registry Platform, and PubMed on May 1, 2021, for all published and unpublished randomised controlled trials that had completed data collection after March 19, 2019. For example, we searched the Cochrane Library using the search terms ("balloon" OR "Foley" OR "catheter") AND ("induction" OR "ripening"). The full search strategy is outlined in the appendix (p 50). Further trials done before March 19, 2019, were identified through the recent Cochrane review by de Vaan and colleagues.[17] Eligible studies were randomised controlled trials that compared induction of labour with balloon catheters (single or double) versus vaginal prostaglandins (PGE1 or PGE2) for cervical ripening. Although some trials also included a study group that combined mechanical and hormonal cervical ripening methods, data from these participants were not sought for inclusion in the analysis. For PGE1, only low doses (≤50 µg and given every ≥4 h)[17] were included because convincing evidence suggests that low-dose PGE1 has a better safety profile than high-dose PGE1 and is equally effective.[20] Only data from women with a viable, singleton pregnancy were analysed. Trials that used other methods for induction of labour or alternative routes for administration of prostaglandins were excluded. No exclusion was made based on parity or membrane status. Titles and abstracts of identified literature were screened independently by two researchers (MNJ and WL), as were full publications of potentially relevant trials. MNJ and WL extracted the data. Discrepancies were resolved by discussion with a third researcher (BWM).

Data access

We approached investigators for all eligible trials with the request to share participant-level data. Trial investigators' contact details were identified through the published articles or the websites of their associated institutions, and invitations to participate were sent by email at least three times if there was no response. For cases in which the primary or corresponding authors' contact details were unavailable or no response was obtained, we attempted to contact other authors involved in the trials. Once trial investigators responded that they were interested in participation, emails were sent every 2–4 months to coordinate data sharing agreements and clarify details.

See Online for appendix

Trial investigators supplied participant-level data, which were harmonised and recoded according to the predefined definitions of variables. We requested data for

Panel: **Definition of outcomes and potential effect modifiers**

Primary outcomes

Caesarean section delivery and its indication: rate of caesarean section following randomisation per woman randomly assigned, including analysis of caesarean section delivery for fetal compromise or failure to progress (if both fetal compromise and failure to progress apply as indications, fetal compromise prevails).

Composite of adverse perinatal outcome: Apgar score <7 at 5 min, arterial umbilical cord pH <7·1, admission to neonatal intensive care unit, severe respiratory compromise, neonatal infection, neonatal death, or stillbirth.

Composite of adverse maternal outcome: admission to intensive care unit, maternal infection (temperature ≥38°C at any time during labour or delivery, antibiotics use, or clinically diagnosed infection, such as endometritis), severe postpartum haemorrhage (>1000 mL estimated blood loss), or maternal death.

Secondary outcomes

Delivery outcome:

- Mode of delivery (vaginal birth, unassisted vaginal birth, instrumental vaginal birth)
- Indication for instrumental vaginal birth
- Cumulative rate of vaginal birth (time-to-event analysis)

Labour progression outcomes:

- Uterine tachysystole
- Uterine hyperstimulation
- Oxytocin augmentation
- Meconium-stained amniotic fluid

Neonatal safety outcomes:

- Apgar score <7 at 5 minutes
- Arterial umbilical cord pH <7·1
- Neonatal intensive care unit admission

Maternal safety outcomes:

- Antibiotic administration
- Maternal fever ≥38°C
- Severe postpartum haemorrhage (>1000 mL estimated blood loss)
- Other complications requiring hospital assistance*

Potential effect modifiers

- Maternal parity
- Maternal age
- Maternal BMI
- Initial Bishop score
- Indication for induction of labour
  - Post-term gestation
  - Hypertensive disorders
  - Diabetes or gestational diabetes
  - Intrauterine or fetal growth restriction
  - Oligohydramnios
  - Obstetric cholestasis†
  - Advanced maternal age†
  - Elective or maternal request to be induced
  - Multiple indications

All intended outcomes are listed in the statistical analysis plan. *We intended to examine complications requiring maternal hospital assistance; however, this was not readily available from the trials included. †Insufficient data were available to perform the planned analysis.

all randomly assigned participants, even those who had been excluded from original trial analyses. The received data were examined for missing data, errors, internal consistency, consistency with the publication, and pattern of treatment allocation and data presentation, where possible. We communicated any identified data issues with trial investigators for a solution before accepting data into the dataset.

Outcomes and effect modifiers

The primary outcomes were caesarean delivery and its indication (fetal compromise or progress in labour), composite measures of adverse perinatal outcomes, and composite measures of adverse maternal outcome (panel).

Secondary outcomes further explored various aspects of effectiveness and safety, including delivery outcomes, labour progression outcomes, neonatal safety outcomes, and maternal safety outcomes.

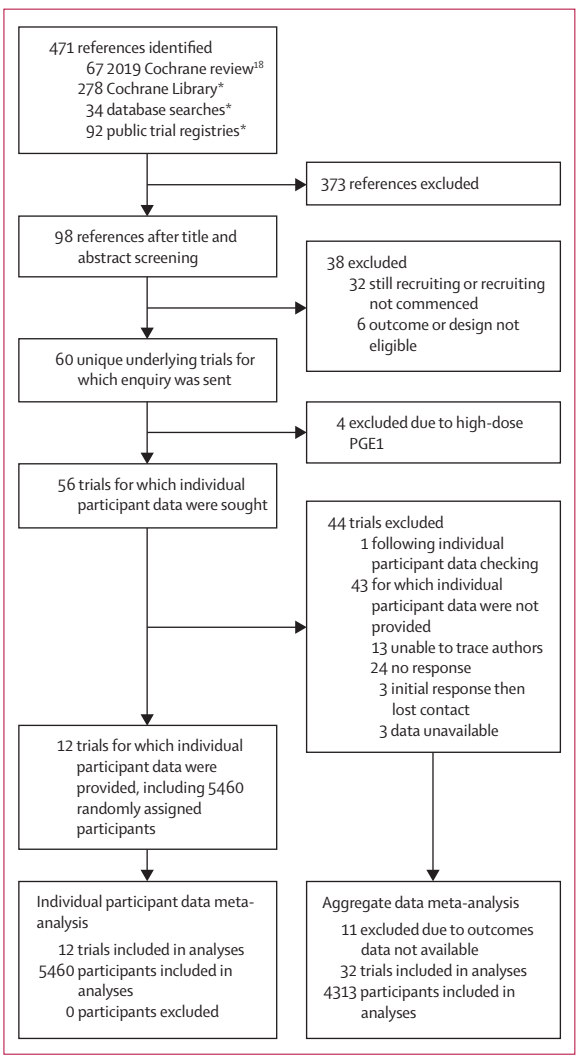


Figure 1: **Trial identification (PRISMA-IPD flow diagram)**
*Search from March 19, 2019, to May 1, 2021.

Potential effect modifiers for caesarean birth were maternal parity, maternal age, maternal BMI, initial Bishop score, and indications for labour induction (post-term gestation, hypertensive disorder, diabetes or gestational diabetes, intrauterine or fetal growth restriction, oligohydramnios, obstetric cholestasis, advanced maternal age (>35 years), elective or maternal request to have labour induction, and multiple indications).

Quality and certainty of evidence

The risk of bias (RoB) was independently assessed by two researchers (MNJ and WL) using the Cochrane RoB 2 tool.[18] Differences were resolved by discussion; if the information was insufficient, clarification was sought from trialists. We used the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) approach to assess the overall certainty of the evidence.[21]

Data analysis

For each outcome, we did an intention-to-treat analysis using all available data comparing balloon catheters to vaginal prostaglandins (ie, reference group). Our primary analysis strategy was a two-stage meta-analysis method to synthesise the individual participant data. For outcomes that had zero events in any intervention group in any included trial, a one-stage method was used. For the two-stage method, as the first step, we compared balloon catheter and vaginal prostaglandin outcomes, adjusting for maternal age and parity for each included study. For binary outcomes, odds ratios (ORs) with 95% CIs were calculated using logistic regression. For the cumulative rate of vaginal delivery, we estimated subdistribution hazard ratios and 95% CIs using the subdistribution hazard competing risk models, which considered caesarean delivery as a competing risk. In the second step, generated relative estimates were combined using random-effects models (restricted maximum likelihood estimator with Hartung-Knapp-Sidik-Jonkman variance correction). For the one-stage method, we used multilevel mixed-effects logistic regression (a stratified intercept by study and a random treatment effect, covariates as fixed effects, maximum likelihood estimator) adjusting for maternal age and parity. We tested treatment-covariate interactions for caesarean delivery using interaction terms between treatment and potential effect modifiers. Only within-trial interaction was considered to avoid ecological bias. In the event of missing values for covariates or potential effect modifiers in any trial, we did multiple imputations using chained equations (ten imputed datasets) within the trial before the analysis.

We did subgroup analysis to compare single-balloon catheter to vaginal prostaglandin and double-balloon catheter to vaginal prostaglandin separately. We extracted summary data for caesarean delivery from publications for trials that did not contribute individual participant

	Year	Country	Balloon catheters	Prostaglandins	Inclusion criteria	Number of participants
Moraes Filho et al[22]	2002	Brazil	Single-balloon catheter, 14F filled 30 mL on traction	PGE1 (misoprostol) 25 µg every 6 h (max four doses)	Primip + multip, ≥37·0 weeks gestation, NS ROM, BS ≤5, no previous caesarean section	240
Prager et al[23]	2008	Sweden	Single-balloon catheter, filled 50 mL with traction hourly until expulsion	PGE1 (misoprostol) 25 µg tablet to posterior fornix every 4 h PGE2 2 mg gel to posterior fornix every 6–8 h	Primip + multip, full-term gestation, NS ROM, BS ≤6, no previous caesarean section	592
Pennell et al[24]	2009	Australia	Single-balloon catheter, 16F filled 30 mL, on traction, removed after 12 h; Double-balloon catheter, both filled, no tension, removed after 12 h	PGE2 (dinoprostone) 2 mg gel placed in posterior fornix every 6 h until able to ARM or regular painful contractions	Primip only, ≥36·0 weeks gestation, no ROM, BS ≤4, no previous caesarean section	330
Oliveira et al[25]	2010	Brazil	Single-balloon catheter, 14F or 16F filled 30 mL, for up to 48 h	PGE1 (misoprostol) 25 µg every 6 h to max dose 200 µg	Primip + multip, ≥37·0 weeks gestation, no ROM, BS ≤4, no previous caesarean section	160
Jozwiak et al[26]	2011	Netherlands	Single-balloon catheter, 16F or 18F filled 30 mL, no traction, until expelled or removed, up to 48 h	PGE2 (dinoprostone) gel initial PV dose of 2 mg for nulliparous, 1 mg for parous, repeat 1 mg in 6 h if needed	Primip + multip, ≥37·0 weeks gestation, no ROM, BS ≤5, no previous caesarean section	824
Henry et al[27]	2013	Australia	Single-balloon catheter, 16F filled 30 mL (outpatient) return next morning for ARM, if not able then PGE2	PGE2 (dinoprostone) gel initial PV dose of 2 mg for nulliparous, 1 mg for parous, repeat 1 mg in 6 h if needed	Primip + multip, ≥37·0 weeks gestation, no ROM, BS ≤6, no previous caesarean section	101
Jozwiak et al[28]	2013	Netherlands	Single-balloon catheter, 16F or 18F filled 30 mL, no traction, until expelled or removed, up to 48 h	PGE2 (dinoprostone) 10 mg insert, left for 12 h or until active labour, second insert placed if needed	Primip + multip, ≥37·0 weeks gestation, no ROM, BS ≤5, no previous caesarean section	232
Jozwiak et al[29]	2014	Netherlands	Single-balloon catheter, 16F or 18F filled 30 mL, no traction, until expelled or removed, up to 48 h	PGE1 (misoprostol) 25 µg vaginal tablets	Primip + multip, ≥37·0 weeks gestation, no ROM, BS ≤5, no previous caesarean section	120
Edwards et al[30]	2014	USA	Single-balloon catheter, 16F filled 30 mL, left for 12 h	PGE2 (dinoprostone) 10 mg insert, left for 12 h	Primip + multip, ≥36·0 weeks gestation, no ROM, BS NS, no previous caesarean section	376
Løkkegaard et al[31]	2015	Denmark	Double-balloon catheter both filled with 80 mL left in for 12 h, if unable to ARM, given rectal enema, then syntocinon infusion	PGE2 (dinoprostone) 3 mg tablet inserted in vagina; if ARM not possible 4–5 h later, repeat 3 mg tablet; if still not, procedure repeated next day	Primip + multip, NS gestation, no ROM, BS ≤4, allows previous caesarean section	822
Diguisto et al[32]	2021	France	Double-balloon catheter both filled with 80 mL	PGE2 (dinoprostone) modified release 10 mg	Primip + multip, 41·0–42·0 weeks gestation, no ROM, BS ≤5, no previous caesarean section	1216
Beckmann et al[33]	2020	Australia	Double-balloon catheter both filled with 80 mL left in for 12 h (outpatient), if unable to ARM, for 6 h PGE2 until favourable or CS	PGE2 (dinoprostone) 2 mg gel or 10 mg inserted and reviewed 12 h later, if unable to ARM, for 6 h PGE2 until favourable or CS	Primip + multip, ≥37·0 weeks gestation, NS ROM, BS ≤6, no previous caesarean section	448

NS=not stated. ROM=rupture of membranes. BS=Bishop score. F=French size of a catheter. ARM=artificial rupture of the membrane. CS=caesarean section. PV=per vaginam. Primip=primiparous women. Multip=multiparous women.

Table 1: **Characteristics of included trials**

data and did a summary data meta-analysis using the same random-effects model to assess the data availability bias of the individual participant data meta-analysis. This method was not possible for the two composite outcomes of maternal and neonatal safety. We also extracted summary data for secondary outcomes as a post-hoc analysis. Sensitivity analysis for primary outcomes was done as a one-stage meta-analysis to investigate the effect of the meta-analytical method on the pooled estimates, as well as an as-treated analysis to compare to the intention-to-treat analysis.

Statistical analysis was done using Stata 17.0 in-built commands and packages for meta-analysis (ipdmetan for two-stage individual participant data meta-analysis, meqrlogit for one-stage individual participant data meta-analysis, and admetan for summary data meta-analysis).

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

We identified 471 unique references through our search (figure 1). After screening titles and abstracts, 60 completed trials were potentially eligible for inclusion and enquiries were sent, of which four were further excluded for using high-dose PGE1 and 43 that did not provide individual participant data. Out of 43 trials that did not share data, we could extract summary data for primary and secondary outcomes from 32 trials (4313 women). Characteristics of trials excluded after enquiry or not contributing to the analysis are in the appendix (pp 25–36). Out of 13 studies

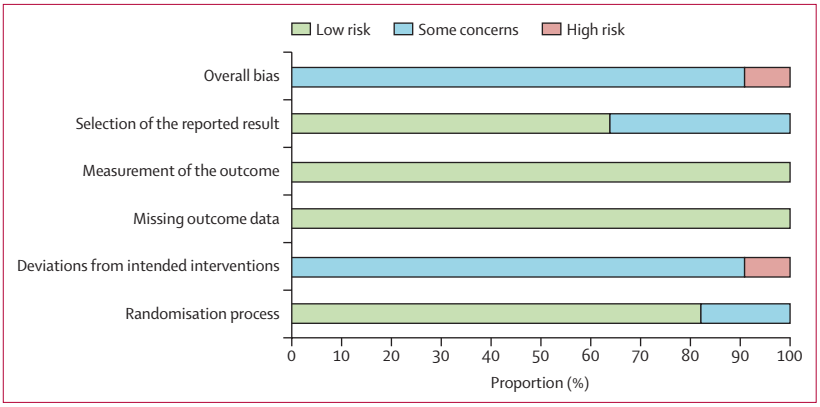


Figure 2: **Risk of bias assessment of included trials in the intention-to-treat population**

that shared individual participant data (5575 women), one was excluded because of inconsistencies between the individual participant data and the published trial that could not be resolved following discussion with the trial investigators.[34] Thus, the final analysis included 12 trials (5460 women).[22,23,24,25,26,27,28,29,30,31,32,33]

For the balloon groups, eight trials used single-balloon catheters, three used double-balloon catheters, and one trial had two groups with balloons, one for single-balloon and one for double-balloon catheters. For the prostaglandin groups, eight trials used PGE2, three trials used PGE1, and one trial had a group for both PGE1 and PGE2. Of 2663 women randomly assigned to balloon catheters, 1324 (49·7%) were allocated to a single-balloon catheter and 1339 (50·3%) to a double-balloon catheter. For the vaginal prostaglandins, 462 (16·5%) of 2797 women were allocated to PGE1 and 2335 (83·5%) of 2797 to PGE2. One participating trial only included nulliparous participants, and all others randomly assigned both nulliparous and multiparous women. Although most trials specified that women with ruptured membranes or previous uterine surgery were excluded, one trial did include women who previously had a caesarean section. Nine trials included women from 36–37 weeks' gestation. The maximum Bishop score at recruitment for all trials was between 4 and 6 (table 1). Baseline participant characteristics of each included trial study are available in the appendix (pp 37–43). On screening for risk of bias, trials were mostly identified as having some concerns, largely owing to the inability to mask participants to the method used (figure 2; appendix p 2).

The crude incidence of caesarean delivery was 27·0% (1462 of 5414), the composite adverse perinatal outcome was 13·6% (605 of 4452), and the composite maternal outcome was 22·7% (982 of 4326). The rate of caesarean delivery was comparable between both balloon catheter and vaginal prostaglandin groups, as shown by 12 trials and 5414 women (adjusted OR [aOR] 1·09, 95% CI 0·95–1·24), for which I^2 was 0%, representing a high certainty of evidence (figure 3A). A summary data meta-analysis including trials in which individual participant data were unavailable for the rate of caesarean delivery led to a similar finding (OR 1·05, 0·85–1·29; appendix p 24), suggesting the magnitude of data availability bias is small. We found no significant difference in caesarean delivery for failure to progress, as shown by 11 trials and 4601 women (aOR 1·20, 0·91–1·58), for which I^2 was 39%, representing moderate certainty of evidence as downgraded according to GRADE (figure 3B). We also found no significant difference for fetal distress, as shown by ten trials and 4441 women (aOR 0·86, 0·71–1·04), for which I^2 was 0%, representing moderate certainty of evidence as downgraded according to GRADE (figure 3C).

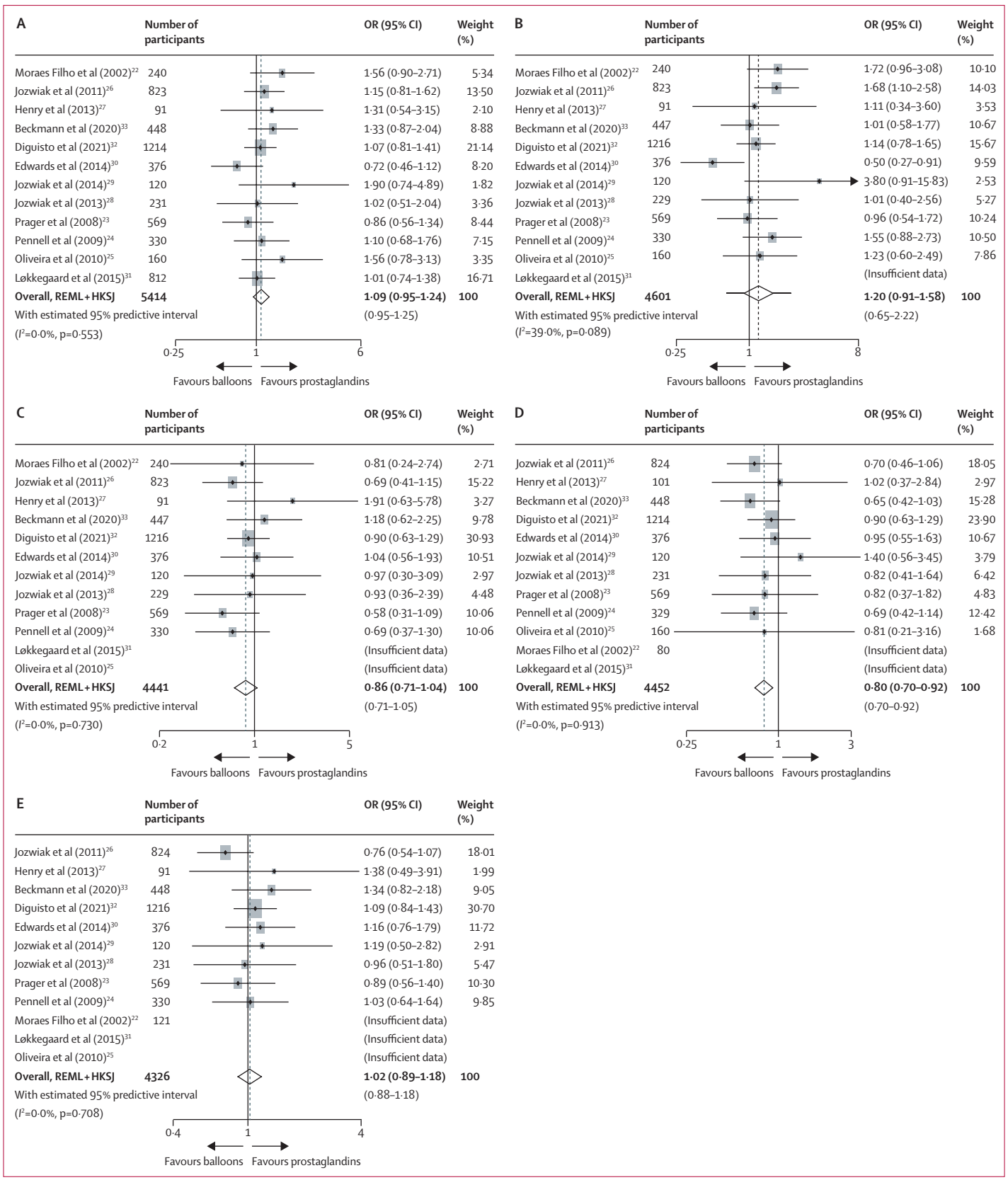
The composite adverse perinatal outcome was reduced by the use of balloon catheters, as shown by ten trials and 4452 neonates (aOR 0·80, 0·70–0·92), for which I^2 was 0%, representing a high certainty of evidence (figure 3D). For an illustrative baseline risk of 10%, the OR of 0·80 equates to an absolute risk reduction of 1·8% (number needed to treat 56) whereas for a baseline of 15%, the same OR gives an absolute risk reduction of 2·6% (number needed to treat 39). A post-hoc analysis of the individual components of the composite outcome is provided in the appendix (p 44). The composite adverse maternal outcome was comparable between both groups, across ten trials and 4326 women (aOR 1·02, 0·89–1·18), for which I^2 was 0%, representing moderate certainty evidence as downgraded according to GRADE due to concerns on data completeness (figure 3E).

There was no significant difference in the rate of total vaginal births or unassisted vaginal births between the two methods (table 2; appendix pp 3–18). Time-to-event analysis for the cumulative rate of vaginal birth did not show a significant difference between the two methods and showed substantial heterogeneity (table 2). In post-hoc analyses, rates of vaginal birth within 24 h and time to delivery were not significantly different between balloon catheters and vaginal prostaglandins (data not shown). Balloon catheters were associated with fewer instrumental vaginal births than were vaginal prostaglandins (table 2). There were fewer instrumental births indicated for fetal distress when the balloon catheter was used (number needed to treat 39 with an illustrative baseline risk of 8% birth), but not for instrumental birth indicated for failure to progress in the second stage (table 2).

We found a significant reduction in both uterine tachysystole (number needed to treat 35 with an illustrative baseline risk of 3%) and uterine hyperstimulation (number needed to treat 78 with an illustrative

Figure 3: **Two-stage meta-analyses comparing balloon catheters versus vaginal prostaglandins for labour induction, by rate of caesarean delivery (A); rate of caesarean delivery when indicated for failure to progress (B); rate of caesarean section delivery when indicated for fetal distress (C); composite adverse perinatal outcome (D); composite adverse maternal outcome (E)**

Weights are from random-effects model. OR=odds ratio. REML=restricted maximum likelihood. HKSJ=Hartung-Knapp-Sidik-Jonkman variance correction.


A
Number of participants
OR (95% CI)
Weight (%)
Moraes Filho et al (2002)[22] 240 1·56 (0·90–2·71) 5·34
Jozwiak et al (2011)[26] 823 1·15 (0·81–1·62) 13·50
Henry et al (2013)[27] 91 1·31 (0·54–3·15) 2·10
Beckmann et al (2020)[33] 448 1·33 (0·87–2·04) 8·88
Diguisto et al (2021)[32] 1214 1·07 (0·81–1·41) 21·14
Edwards et al (2014)[30] 376 0·72 (0·46–1·12) 8·20
Jozwiak et al (2014)[29] 120 1·90 (0·74–4·89) 1·82
Jozwiak et al (2013)[28] 231 1·02 (0·51–2·04) 3·36
Prager et al (2008)[23] 569 0·86 (0·56–1·34) 8·44
Pennell et al (2009)[24] 330 1·10 (0·68–1·76) 7·15
Oliveira et al (2010)[25] 160 1·56 (0·78–3·13) 3·35
Løkkegaard et al (2015)[31] 812 1·01 (0·74–1·38) 16·71
Overall, REML+HKSJ 5414 1·09 (0·95–1·24) 100
With estimated 95% predictive interval (0·95–1·25)
(I²=0·0%, p=0·553)
0·25
1
6
Favours balloons
Favours prostaglandins
B
Number of participants
OR (95% CI)
Weight (%)
Moraes Filho et al (2002)[22] 240 1·72 (0·96–3·08) 10·10
Jozwiak et al (2011)[26] 823 1·68 (1·10–2·58) 14·03
Henry et al (2013)[27] 91 1·11 (0·34–3·60) 3·53
Beckmann et al (2020)[33] 447 1·01 (0·58–1·77) 10·67
Diguisto et al (2021)[32] 1216 1·14 (0·78–1·65) 15·67
Edwards et al (2014)[30] 376 0·50 (0·27–0·91) 9·59
Jozwiak et al (2014)[29] 120 3·80 (0·91–15·83) 2·53
Jozwiak et al (2013)[28] 229 1·01 (0·40–2·56) 5·27
Prager et al (2008)[23] 569 0·96 (0·54–1·72) 10·24
Pennell et al (2009)[24] 330 1·55 (0·88–2·73) 10·50
Oliveira et al (2010)[25] 160 1·23 (0·60–2·49) 7·86
Løkkegaard et al (2015)[31] (Insufficient data)
Overall, REML+HKSJ 4601 1·20 (0·91–1·58) 100
With estimated 95% predictive interval (0·65–2·22)
(I²=39·0%, p=0·089)
0·25
1
8
Favours balloons
Favours prostaglandins
C
Number of participants
OR (95% CI)
Weight (%)
Moraes Filho et al (2002)[22] 240 0·81 (0·24–2·74) 2·71
Jozwiak et al (2011)[26] 823 0·69 (0·41–1·15) 15·22
Henry et al (2013)[27] 91 1·91 (0·63–5·78) 3·27
Beckmann et al (2020)[33] 447 1·18 (0·62–2·25) 9·78
Diguisto et al (2021)[32] 1216 0·90 (0·63–1·29) 30·93
Edwards et al (2014)[30] 376 1·04 (0·56–1·93) 10·51
Jozwiak et al (2014)[29] 120 0·97 (0·30–3·09) 2·97
Jozwiak et al (2013)[28] 229 0·93 (0·36–2·39) 4·48
Prager et al (2008)[23] 569 0·58 (0·31–1·09) 10·06
Pennell et al (2009)[24] 330 0·69 (0·37–1·30) 10·06
Løkkegaard et al (2015)[31] (Insufficient data)
Oliveira et al (2010)[25] (Insufficient data)
Overall, REML+HKSJ 4441 0·86 (0·71–1·04) 100
With estimated 95% predictive interval (0·71–1·05)
(I²=0·0%, p=0·730)
0·2
1
5
Favours balloons
Favours prostaglandins
D
Number of participants
OR (95% CI)
Weight (%)
Jozwiak et al (2011)[26] 824 0·70 (0·46–1·06) 18·05
Henry et al (2013)[27] 101 1·02 (0·37–2·84) 2·97
Beckmann et al (2020)[33] 448 0·65 (0·42–1·03) 15·28
Diguisto et al (2021)[32] 1214 0·90 (0·63–1·29) 23·90
Edwards et al (2014)[30] 376 0·95 (0·55–1·63) 10·67
Jozwiak et al (2014)[29] 120 1·40 (0·56–3·45) 3·79
Jozwiak et al (2013)[28] 231 0·82 (0·41–1·64) 6·42
Prager et al (2008)[23] 569 0·82 (0·37–1·82) 4·83
Pennell et al (2009)[24] 329 0·69 (0·42–1·14) 12·42
Oliveira et al (2010)[25] 160 0·81 (0·21–3·16) 1·68
Moraes Filho et al (2002)[22] 80 (Insufficient data)
Løkkegaard et al (2015)[31] (Insufficient data)
Overall, REML+HKSJ 4452 0·80 (0·70–0·92) 100
With estimated 95% predictive interval (0·70–0·92)
(I²=0·0%, p=0·913)
0·25
1
3
Favours balloons
Favours prostaglandins
E
Number of participants
OR (95% CI)
Weight (%)
Jozwiak et al (2011)[26] 824 0·76 (0·54–1·07) 18·01
Henry et al (2013)[27] 91 1·38 (0·49–3·91) 1·99
Beckmann et al (2020)[33] 448 1·34 (0·82–2·18) 9·05
Diguisto et al (2021)[32] 1216 1·09 (0·84–1·43) 30·70
Edwards et al (2014)[30] 376 1·16 (0·76–1·79) 11·72
Jozwiak et al (2014)[29] 120 1·19 (0·50–2·82) 2·91
Jozwiak et al (2013)[28] 231 0·96 (0·51–1·80) 5·47
Prager et al (2008)[23] 569 0·89 (0·56–1·40) 10·30
Pennell et al (2009)[24] 330 1·03 (0·64–1·64) 9·85
Moraes Filho et al (2002)[22] 121 (Insufficient data)
Løkkegaard et al (2015)[31] (Insufficient data)
Oliveira et al (2010)[25] (Insufficient data)
Overall, REML+HKSJ 4326 1·02 (0·89–1·18) 100
With estimated 95% predictive interval (0·88–1·18)
(I²=0·0%, p=0·708)
0·4
1
4
Favours balloons
Favours prostaglandins

	Number of trials	Number of women	Crude incidence (%)	aOR (95% CI)	I^2 (95% CI)	Analysis method*	Certainty of the evidence (GRADE)
Delivery outcomes							
Vaginal birth	12	5414	73·0	0·92 (0·80–1·05)	0·0 (0·0–43·5)	Two-stage	++++ High
Unassisted vaginal birth	10	4888	58·9	1·02 (0·85–1·22)	30·3 (0·0–67·4)	Two-stage	++++ High
Instrumental vaginal birth	10	4888	15·3	0·82 (0·68–1·00)	0·5 (0·0–52·9)	Two-stage	++++ High
Indicated for not progressing in second stage	7	3362	6·4	0·99 (0·73–1·33)	0·0 (0·0–47·4)	Two-stage	++–– Low†‡
Indicated for fetal distress	8	3838	8·9	0·66 (0·49–0·88)	5·7 (0·0–58·8)	Two-stage	+++– Moderate†
Time to vaginal birth	12	5192	..	sHR 0·88 (0·74–1·04)	76·8 (17·8–89·3)	Two-stage	+++– Moderate§
Labour progression outcomes							
Uterine tachysystole	4	2132	2·3	0·05 (0·02–0·17)	..	One-stage	++–– Low†‡
Uterine hyperstimulation	8	3611	2·2	0·35 (0·19–0·64)	..	One-stage	+++– Moderate†
Oxytocin augmentation	10	4312	73·9	4·43 (2·82–6·97)	70·2 (0·0–87·2)	Two-stage	+++– Moderate§
Meconium-stained amniotic fluid	9	4095	14·0	0·91 (0·77–1·07)	0·0 (0·0–27·4)	Two-stage	++++ High
Maternal safety outcomes							
Antibiotic use during labour	7	3521	18·6	1·04 (0·91–1·19)	0·0 (0·0–18·6)	Two-stage	+++– Moderate‡
Maternal fever	7	1921	11·8	1·03 (0·74–1·44)	0·0 (0·0–49·2)	Two-stage	++–– Low†‡
Severe postpartum haemorrhage	9	4020	8·1	0·95 (0·72–1·25)	..	One-stage	++++ High
Neonatal safety outcomes							
Apgar score <7 at 5 min	11	4531	1·5	0·86 (0·53–1·39)	..	One-stage	++++ High
Arterial umbilical cord pH <7·1	8	3043	6·0	0·72 (0·53–0·98)	..	One-stage	+++– Moderate†
Admission to neonatal intensive care unit	10	4353	8·4	0·91 (0·72–1·14)	..	One-stage	++++ High

aOR=adjusted odds ratio. GRADE=Grading of Recommendations, Assessment, Development and Evaluations. sHR=sub-distribution hazard ratio. *Two-stage as primary strategy, one-stage used when zero events are encountered in any group of any included study. All analyses adjusted for maternal age and parity. †Downgraded one level for imprecision. ‡Downgraded one level for concerns on data completeness. §Downgraded one level for inconsistency.

Table 2: **Balloon catheters compared with vaginal prostaglandins for secondary outcomes**

baseline risk of 2%) with use of balloon catheters (table 2). Use of oxytocin augmentation was increased with balloon catheters (number needed to harm 5 with an illustrative baseline risk of 70%), with substantial heterogeneity (I^2=70·2%; table 2). There was no difference in the rate of meconium-stained amniotic fluid (table 2).

Balloon catheters significantly reduced rates of arterial umbilical cord pH levels less than 7·1 (number needed to treat 62 with an illustrative baseline risk of 6%; table 2). There was no significant difference between the methods for either Apgar score less than 7 at 5 min or admission to a neonatal intensive care unit (table 2). Neither method was superior in terms of rates of antibiotic use during labour or maternal fever (table 2). Rates of severe postpartum haemorrhage were also comparable between both groups (table 2). Results of aggregate data meta-analyses of trials not providing individual participant data were similar to those from the individual participant data meta-analysis for secondary outcomes (appendix p 45).

We identified no differential effect of treatment on the rate of caesarean delivery for maternal parity (parous *vs* nulliparous), across ten trials and 4272 women (interaction OR 1·05, 95% CI 0·68–1·61); age, across 12 trials and 4572 women (interaction OR 1·00, 0·98–1·02); BMI, across eight trials and 3543 women (interaction OR 1·01, 0·97–1·05); or initial Bishop score, across 11 trials and 4682 women (interaction OR 1·03, 0·96–1·12). There was no significant interaction with intervention for any of the indications of labour induction (appendix p 46).

Comparing single-balloon catheter to vaginal prostaglandins, there were no significant differences in caesarean delivery rate, regardless of indication, or composite adverse maternal outcome. However, there was a reduced chance of the composite adverse perinatal outcome (nine trials, 2683 women; aOR 0·84, 0·71–0·99) with use of the single-balloon catheter. There were no significant differences when comparing double-balloon catheters with vaginal prostaglandins for any of the primary outcomes, although the number of trials was small (appendix p 47).

Sensitivity analysis for primary outcomes using a one-stage method produced similar findings (appendix p 48). An as-treated analysis of the primary outcomes (appendix pp 19–23, 49) for seven of the included trials led to similar conclusions to the main analysis.

Discussion

This individual participant data meta-analysis of 12 randomised controlled trials reporting on 5460 women undergoing induction of labour showed that balloon catheter and vaginal prostaglandins led to similar caesarean delivery rates. The adverse composite maternal outcome was also comparable with both methods, but induction with a balloon catheter improved composite perinatal outcomes.

Strengths of this study include the continued, collaborative process between the coordinating team and the trial investigators to ensure the quality and accuracy of the dataset and detailed, predefined analysis including investigation of hypothesised effect modifiers. We designed the use of composite outcomes for safety measurement to obtain sufficient power for meaningful analysis. Included trials were, in general, at low risk of bias except for the fact that blinding was not possible. Other strengths include standardisation of definitions wherever possible and rigorous data checking before the analysis.

Our study has several limitations. First, individual participant data were unavailable for 43 trials that potentially met the criteria for inclusion. However, most of these were small trials and 21 trials that did not provide individual participant data were published more than 10 years ago. Also, a meta-analysis for the rate of caesarean delivery incorporating published summary data showed that data availability bias in our analysis is probably small. Additionally, evidence suggests that trials not sharing data for individual participant data meta-analysis have more methodological issues and poorer trustworthiness than those that shared data.[35] Second, some of the centres participating in trials did not have a neonatal intensive care unit (NICU) within their facilities, so neonates who had intensive care in these centres could not meet the criteria for the secondary outcome of NICU admission. Third, although we noted no difference in adverse maternal outcomes for the composite measure we defined, some of these secondary outcomes were only available from about half of the trials. Fourth, we acknowledge that composite outcomes are more difficult to interpret than individual outcomes. However, we believe this is the best approach so far to shed light on the safety of labour induction methods, which is important and difficult to study with traditional approaches. As adverse perinatal outcomes are rare, an adequately powered study to investigate any of the individual components is likely to require a sample size in the tens of thousands, which is not feasible. Lastly, some secondary outcomes analyses only included small numbers of trials and participants, and their results should be interpreted with caution.

We found that balloon catheters and vaginal prostaglandins are comparable in terms of effectiveness, as measured by mode of birth. Our findings are in line with most meta-analyses based on summary data in this area, in that no significant difference was identified for rates of caesarean delivery.[9–13] The exception to this is a meta-analysis that found a reduction in caesarean delivery rate with PGE1;[14] however, the authors noted the quality of evidence was very low. Using vaginal delivery rate within 24 h as a measure of efficacy, some meta-analyses concluded that prostaglandins might result in reduced time to vaginal birth compared with balloon catheters.[9,15] This outcome is determined by the time allowed for balloon catheters to function and the threshold to trigger caesarean delivery, which could vary between different settings. In a world with maternity services being overwhelmed by a shortage in staff and delivery suite space, shorter time to delivery is becoming a more important issue, as long as it does not affect safety outcomes. In our time-to-event analysis of cumulative vaginal birth, we did not find clear evidence that prostaglandins lead to quicker vaginal birth given the wide CIs and high heterogeneity, reflecting varied protocols across trials.

Regarding perinatal safety, results showed a consistently favourable effect for balloon catheters, including the composite adverse perinatal outcome and arterial umbilical cord pH level of less than 7·1, an objective measure of neonatal acidosis. Low arterial cord pH has been found to have temporal associations with neonatal mortality and morbidity. In a meta-analysis that included 51 studies, neonatal acidosis defined with a pH threshold of 7·1 showed strong associations with neonatal death and a composite measure of neonatal morbidity including hypoxic ischaemic encephalopathy, seizures, intraventricular haemorrhage, or periventricular leukomalacia.[36] Having arterial cord pH even lower than 7·1 could lead to increased risks of neonatal mortality and morbidity.

Importantly, although the analysis for Apgar score less than 7 at 5 min and NICU admission (two subjective assessments of neonatal wellbeing) did not reach significance, there was a numerically positive association with a protective effect with balloon catheters. Moreover, there were fewer instrumental vaginal deliveries for fetal distress after balloon catheters. These benefits of balloon catheters could be partly explained by their reduced chance of uterine hyperstimulation and uterine tachysystole, in which excessive uterine contractions increase the risk of fetal compromise. Some of the meta-analyses based on summary data analysed individual perinatal safety outcomes, with inconclusive findings for most outcomes due to underpowered studies and sparse data.[9–11,16] The safety outcomes that showed increased risk with vaginal prostaglandins were excessive uterine activity[9–11,12] and NICU admission.[10,11] Similar to our findings, one meta-analysis also found increased rates of umbilical cord arterial pH levels less than 7·1 with vaginal PGE2,[12] indicating an improved safety profile with balloon catheters.

Induction of labour is no longer used solely for conditions in which concern about fetal or maternal wellbeing indicated delivery. With the ARRIVE trial

suggesting that induction of labour from 39 weeks' gestation in uncomplicated pregnancies is safe and reduces caesarean delivery rate,[7] the acceptability of labour induction for both women and clinicians has increased, which is echoed in increasing rates of labour induction worldwide. However, the risks associated with induction of labour, even though relatively rare for individuals, will naturally become more common in the event of greater numbers of labour induction occurring. It is essential not to lose the possible benefits of induction of labour by choosing an induction method that leads to an increased risk.

The findings of our analysis are integral to improving the safety of obstetric practice, in which vaginal prostaglandins are still widely used as standard care for induction of labour and are the preferred agent in some countries. Balloon catheters have been repeatedly proven to be effective in labour induction,[17,26] are inexpensive, and do not require any specialised preparation or conditions for storage. Learning to insert balloon catheters is possible for a range of clinician skill levels. Balloon catheters have long been used for cervical ripening, and the significant reduction in adverse perinatal outcomes provides the rationale to recommend balloon catheters as the preferred choice. Health-care providers and policy makers should consider this information when developing policies and guidelines around induction of labour. Long-term outcomes of infants after induction should be an important consideration in decision making, but information on this issue is currently not available. Information on safety, effectiveness, and practicalities should be discussed with women during shared decision making. It is also worth noting that many theoretical or anecdotal adverse events of balloon catheters, such as infection, intraprocedure and post-procedure pain, bleeding, and rupture of membranes, are not supported by high-quality evidence.

The combined use of balloon catheters and prostaglandins has attracted attention given that this strategy potentially reduces time to delivery.[37] However, meta-analyses on this topic showed similar rates of vaginal birth and time to delivery when comparing Foley catheter and prostaglandins with Foley alone.[38] More importantly, existing data could not address concerns on safety issues due to the small sample size, inadequate reporting of safety outcomes, and varied definitions used. In light of the finding of this individual participant data meta-analysis that prostaglandins lead to worse perinatal safety outcomes than balloon catheters, the combined use of balloon catheters and prostaglandins could lead to a similar or even higher risk of adverse perinatal outcomes than using prostaglandins. To date, no major guidelines have recommended the use of this combination for cervical ripening, but it is still a topic of research in labour induction.

Another concurrent use of two methods (ie, Foley catheters and oxytocin for cervical ripening) seems to be gaining popularity. Meta-analyses on this topic suggested that the use of Foley and oxytocin reduced the time to vaginal delivery,[38] but it did not reduce caesarean rates nor improve maternal or neonatal outcomes.[39] Similarly, existing evidence does not have enough power to address concerns on safety. An individual participant data meta-analysis that compares balloon-oxytocin versus balloon alone would be helpful to elucidate these questions.

Further study into the efficacy of balloon catheters compared with vaginal prostaglandins is not warranted, as this has been extensively investigated. Although there was no evidence of increased composite adverse maternal outcomes for either method, data were only available from half of the trials included in our analysis, and this remains an area for possible further investigation. Also, long-term outcomes for the neonates and infants, as well as information on maternal experience and satisfaction, are not routinely collected in labour induction randomised controlled trials, representing a gap in the research.

With the balloon catheter shown to be a better option for perinatal safety, it would be beneficial to next consider ways in which their use can be optimised. A recent Cochrane review suggested that cervical priming with a balloon catheter in the outpatient setting might reduce the rates of caesarean delivery, with increased rates of maternal satisfaction, as compared with cervical ripening with a balloon catheter in the hospital.[40] Two of the randomised controlled trials included in our analysis used the outpatient setting for their balloon catheter group,[27,33] and several ongoing trials also aim to investigate this aspect.[41]

Contributors

BWM and WL designed the meta-analysis and were responsible for overseeing all aspects of conduct. MNJ, KRP, MMP, and WL contributed to various stages of the project including aspects of design, eligibility screening, data extraction, risk of bias assessment, individual participant data checking, and trial analysis. MNJ managed the project and collaborative process. WL did the data synthesis. KRP, DLR, and BWM provided clinical oversight and MNJ designed and did the literature searches. MNJ wrote the manuscript supervised by WL with input from all authors. All authors were involved in the decision to submit the manuscript. All contributing trial investigators had opportunities to comment on the initial scope, draft protocol, and draft statistical analysis plan, and participated in teleconference meetings as the project progressed. Trial investigators also prepared and supplied data and answered questions about their trials.

Declaration of interests

BWM has received grants from the Australian National Health and Medical Research Council (NHMRC), personal fees from ObsEva, personal fees from Merck, personal fees from Guerbet, and grants from Merck, outside the submitted work. BWM was also an investigator for one of the trials included in the individual participant data meta-analysis. DLR has received fees to participate in advisory boards from Alexion and travel support and lecture fees from the International Society of Ultrasound in Obstetrics and Gynecology, unrelated to this work. KRP has received research grant funds from GlaxoSmithKline and consultancy fees from Janssen Pharmaceuticals unrelated to this work. WL has received research grant funds from the Norman Beischer Medical Research Foundation, unrelated to this work.

Data sharing

The protocol, statistical analysis plan, and codebook are available on request. The trial investigators who shared individual participant data for the purposes of the meta-analysis retain ownership of their trial data and any requests for access to individual participant data should be made directly to them (they can be accessed via email and the email addresses can be found in their original publications which are cited in this manuscript).

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