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Adverse intrapartum outcome in pregnancies complicated by small for gestational age and late fetal growth restriction undergoing induction of labor with Dinoprostone, Misoprostol or mechanical methods: a systematic review and meta-analysis

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Short title: IOL in SGA and late FGR

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ABSTRACT

Objective: To investigate the outcome of pregnancies with small baby, including both small for gestational age (SGA) and late fetal growth restriction (FGR) fetuses, undergoing induction of labor (IOL) with Dinoprostone, Misoprostol or mechanical methods.

Study design: Medline, Embase and Cochrane databases were searched. Inclusion criteria were non-anomalous singleton pregnancies complicated by the presence of a small fetus, defined as a fetus with estimated fetal weight (EFW) or abdominal circumference (AC) <10th centile undergoing IOL from 34 weeks of gestation with vaginal Dinoprostone, vaginal misoprostol, or mechanical methods (including either Foley or Cook balloon catheters). The primary outcome was a composite measure of adverse intrapartum outcome. Secondary outcomes were the individual components of the primary outcome, perinatal mortality and morbidity. All the explored outcomes were reported in three different sub-groups of pregnancies complicated by a small fetus including: all small fetuses (defined as those with an EFW and/or AC <10th centile irrespective of fetal Doppler status), late FGR fetuses (defined as those with EFW and/or AC <3rd centile or AC/EFW <10th centile associated with abnormal cerebroplacental Dopplers) and SGA fetuses (defined as those with EFW and/or AC <10th but >3rd centile with normal cerebroplacental Dopplers). Quality assessment of each included study was performed using the Risk of Bias in Non-randomized Studies–of Interventions tool (ROBINS-I), while the GRADE methodology was used to assess the quality of the body of retrieved evidence. Meta-analyses of proportions and individual data random-effect logistic regression were used to analyze the data.

Results: 12 studies (1711 pregnancies) were included. In the overall population of small fetuses, composite adverse intra-partum outcome occurred in 21.2% (95% CI 10.0-34.9) of pregnancies induced with Dinoprostone, 18.0% (95% CI 6.9-32.5) of those with Misoprostol and 11.6% (95% CI 5.5-19.3) of those undergoing IOL with mechanical methods. Cesarean section (CS) for non-reassuring fetal status (NRFS) was required in 18.1% (95% CI 9.9-28.3) of pregnancies induced with Dinoprostone, 9.4% (95% CI 1.4-22.0) of those with Misoprostol and 8.1% (95% CI 5.0-11.6) of those undergoing mechanical induction. Likewise, uterine tachysystole, was recorded on CTG in 13.8% (95% CI 6.9-22.3) of cases induced with Dinoprostone, 7.5% (95% CI 2.1-15.4) of those with Misoprostol and 3.8% (95% CI 0-4.4) of those induced with mechanical methods. Composite adverse perinatal outcome following delivery complicated 2.9% (95% CI 0.5-6.7) newborns after IOL with Dinoprostone, 0.6% (95% CI 0-2.5) with Misoprostol and 0.7% (95% CI 0-7.1) with mechanical methods. In pregnancies complicated by late FGR, adverse intrapartum outcome occurred in 25.3% (95% CI 18.8-32.5) of women undergoing IOL with Dinoprostone, compared to 7.4% (95% CI 3.9-11.7) of those with mechanical methods, while CS for NRFS was performed in 23.8% (95% CI 17.3-30.9) and 6.2% (95% CI 2.8-10.5) of the cases, respectively. Finally, in SGA fetuses, composite adverse intrapartum outcome complicated 8.4% (95% CI 4.6-13.0) of pregnancies induced with Dinoprostone, 18.6% (95% CI 13.1-25.2) of those with Misoprostol and 8.7 (95% CI 2.5-17.5) of those undergoing mechanical IOL, while CS for NRF was performed in 8.4% (95% CI 4.6-13.0) of women induced with Dinoprostone, 18.6% (95% CI 13.1-25.2) of those with Misoprostol and 8.7% (95% CI 2.5-17.5) of those undergoing mechanical induction. Overall, the quality of the included studies was low and was downgraded due to considerable clinical and statistical heterogeneity.

Conclusions: There is limited evidence on the optimal type of IOL in pregnancies with small fetuses. Mechanical methods seem to be associated with a lower occurrence of adverse intrapartum outcomes, but a direct comparison between different techniques could not be performed.

Keywords: IOL, induction of labor, SGA, FGR, dinoprostone, misoprostol, Foley balloon catheter, Cook balloon catheter.

INTRODUCTION

Suboptimal fetal growth due to impaired placental function is among the major determinants of perinatal mortality and short- and long-term morbidities in singleton pregnancies. The most common phenotypic expression of abnormal in utero fetal growth is the presence of a small fetus, commonly defined on the basis of an estimated fetal weight (EFW) <10th centile. Although all small fetuses are considered to be generically at higher risk of adverse perinatal outcome, recent evidence suggests that there are at least two different subsets of small fetuses. Small for gestational age (SGA), defined as fetuses with an EFW<10th centile in the absence of Doppler abnormalities in either umbilical (UA), middle cerebral (MCA) or uterine artery Doppler, which commonly refers to constitutionally small fetuses and those affected by "true" fetal growth restriction (FGR), who show signs of Doppler anomalies reflecting an adaptive status to chronic hypoxemia and undernutrition.[1]

There are still no published randomized controlled trials (RCT) on the optimal type and time of monitoring in SGA and FGR fetuses occurring late in pregnancy, while an ongoing trial on the timing of delivery (TRUFFLE-2) is still ongoing.[2] National guidelines are mostly based on non-randomized series and suggest that late growth restricted fetuses should undergo induction of labor (IOL) at around 37-38 weeks of gestation, while SGA can benefit of a late induction at approximately 40 weeks of gestation.[3]

However, none of the national and international societies reports in their guidelines which method of IOL should be offered to pregnancies complicated by a small fetus.

A recent systematic review including RCTs comparing vaginal Misoprostol, Dinoprostone and Foley's catheter for cervical ripening during IOL did not demonstrate an overall superiority of one method above the others.[4] Despite including high quality RCTs, the findings from this systematic review cannot be entirely applied to small fetuses as the large majority of the included RCTs did not included pregnancies complicated by late FGR or SGA[4] and some of the outcomes explored in uncomplicated pregnancies are considered less relevant when considering small fetuses. Furthermore, a significant proportion of small fetuses close to or at term is affected by placental insufficiency, thus being at higher risk of decompensation during labor especially once exposed to uterine hyperstimulation.[5] In this scenario, the choice of the optimal method to induce labor in pregnancies complicated by a small fetus should be guided by the need to reduce the risk of adverse events related to hypoxemia, rather than that of achieving delivery in the shortest period of time.[6]

The aim of this systematic review was to investigate the outcome of pregnancies complicated by the presence of a SGA and late FGR fetus undergoing IOL with Dinoprostone, Misoprostol or mechanical methods.

MATERIAL AND METHODS

Protocol, information sources and literature search

This review was performed according to an a-priori designed protocol and recommended for systematic reviews and meta-analysis.[7-9] Medline and Embase databases were searched electronically on the 10th August 2019 utilizing combinations of the relevant medical subject heading (MeSH) terms, key words, and word variants for "induction of labor", "cervical ripening", "fetal growth restriction", "small for gestational age", "and "outcome". The search and selection criteria were restricted to English language. Reference lists of relevant articles and reviews were hand searched for additional reports. Prisma guidelines were followed.[10] The study was registered with the PROSPERO database.

Inclusion criteria, outcome measures, study selection and data collection

Inclusion criteria were non-anomalous singleton pregnancies complicated by the presence of a small fetus, defined as a fetus with estimated fetal weight (EFW) or abdominal circumference (AC) <10th centile per locally used reference curve undergoing IOL from 34 weeks of gestation with the following methods:

- Vaginal Dinoprostone
- Vaginal Misoprostol
- Mechanical methods (including either Foley or Cook balloon catheters)

For the purpose of the analysis, we planned to stratify the study population in three different sub-group of pregnancies complicated by a small fetus:

- ***All small fetuses***, including fetuses with EFW and/or AC <10th centile irrespective of fetal Doppler status.
- ***Late FGR fetuses***, defined, according to the recently published Delphi consensus statement by Gordijn et al,[1] as a fetus with EFW or AC <3rd centile (solitary parameter) or, alternatively, those with EFW or AC <10th centile, AC or EFW crossing centiles more than 2 quartiles associated with Doppler abnormalities (UA-PI > 95th centile or abnormal CPR) (contributory parameters) >32 weeks of gestation.
- ***SGA fetuses***, defined as those with EFW and/or AC<10th but >3rd centile with normal cerebroplacental Doppler.

The primary outcome was a composite measure of adverse intrapartum outcome, including either CS or operative vaginal delivery for non-reassuring fetal status (NRFS), uterine tachysystole, NRFS on CTG, fever, chorioamnionitis or meconium stained amniotic fluid).

Secondary outcomes were:

- Vaginal delivery (overall and within 12 h, 24 h and 48 h)
- CS (overall, emergency, for NRFS, for other obstetric indications)
- Instrumental vaginal delivery (overall, for arrested labor or for non-reassuring fetal status)
- NRFS during labor, defined as the presence of a suspicious or pathological CTG tracings according to the FIGO consensus guideline on CTG interpretation
- Uterine tachysystole, defined as more than 5 contractions per 10 minutes in 2 consecutive intervals
- Need for oxytocin for augmentation of labor
- Units of oxytocin administered (expressed in international units, IU)
- Chorioamnionitis
- Intrapartum pyrexia
- Meconium stained amniotic fluid
- Global time for IOL (expressed in hours) required to reach an active phase of labor (including the time needed for cervical ripening)
- Time at cervical ripening, defined as the time (expressed in hours) necessary to achieve cervical ripening (Bishop ≥7) since the placement of either one of the labor induction methods
- Time until delivery, defined as the time interval (expressed in hours) from the beginning of IOL and delivery
- Length of stay (LOS) in the hospital (expressed in days)
- Postpartum hemorrhage (PPH)
- 1-minute Apgar score
- 5-minute Apgar score
- Neonatal pH
- Admission to neonatal intensive care unit (NICU)
- Composite adverse perinatal outcome, including either Apgar <7 at 5 minutes, pH<7.2, or admission to NICU

Only studies reporting the outcome of singleton pregnancies complicated by a small fetus >34 weeks of gestation undergoing IOL with Dinoprostone, Misoprostol or mechanical methods were considered suitable for the inclusion in the present systematic review. Studies not reporting the explored

outcomes for the three different induction techniques separately, those not including exclusively small fetuses and those for which the type of IOL was not specified were excluded. Studies published before 2000 were also excluded, as we considered that advances in prenatal imaging and improvements in the diagnosis of pregnancies complicated by late FGR or SGA were excluded. Case reports, conference abstracts and case series with fewer than 3 cases were also excluded in order to avoid publication bias.

Two authors (AF, FDA) reviewed all abstracts independently. Agreement regarding potential relevance was reached by consensus with a third author (DB). Because the differentiation between small fetuses complicated (FGR) compared to those not complicated (SGA) by placental insufficiency has been reported only recently, we included in the sub-analyses considering late FGR and SGA fetuses separately only cases from which the EFW centile cut-off and the cerebro-placental Doppler status could be clearly extrapolated. Conversely, for those studies not differentiating between pregnancies complicated by FGR/SGA or not reporting data on Dopplers for which a clear sub-category could be assigned, the data were allocated in the category "all small fetuses".

Full text copies of those papers were obtained, and the same two reviewers independently extracted relevant data regarding study characteristics and pregnancy outcomes. Inconsistencies were discussed by the reviewers and consensus reached or by discussion with a third author. If more than one study was published for the same cohort with identical endpoints, the report containing the most comprehensive information on the population was included to avoid overlapping populations. For those articles in which information was not reported but the methodology was such that this information would have been recorded initially, the authors were contacted.

Quality assessment and risk of bias

Quality assessment of each included study was performed using the Risk Of Bias In Non-randomized Studies–of Interventions tool (ROBINS-I). ROBINS-I provides a detailed framework for assessment and judgement of risk of bias that may arise due to confounding, selection of participants into the study, measurement of interventions, departures from intended interventions, missing data, measurement of outcomes, and selection of reported results.[11] The ROBINS-I tool is equally appropriate for cross-sectional and longitudinal non-randomized studies as quality assessments are independent of study design. Each domain is determined to exhibit low, moderate, serious, or critical risk of bias. Low risk indicates that the study is "comparable to a well-performed randomized trial" in the domain being evaluated. Moderate risk of bias indicates the study is "sound for a non-randomized study" but not comparable to a rigorous randomized trial. Serious risk of bias indicates the presence of "important problems," while critical risk of bias indicates the study is "too

problematic" to provide any useful evidence on the effects of intervention". If insufficient information is provided to determine the risk of bias of a certain domain, the domain is marked as having no information. All studies were analyzed using this tool regardless of whether the original study design included randomization to other exposures, thus ensuring that the risk of bias was assessed specifically for the comparisons of interest to this review. The GRADE methodology was used to assess the quality of the body of retrieved evidence (GRADEpro, Version 20. McMaster University, 2014).[12]

Statistical analysis

We examined a total of 22 maternal and perinatal outcomes, either categorical (n=14) or continuous (n=8), in a sample of women with small fetuses (either SGA or late FGR) undergoing labor induction with: (a) Dinoprostone, or (b) Misoprostol, or (c) Cook or Foley's balloon catheter (mechanical induction). The categorical outcomes were: (1) Composite adverse intrapartum outcome (including: caesarean section for non-reassuring fetal status-NRFS, tachysystole, operative delivery for NRFS, fever, chorioamnionitis, meconium-stained amniotic fluid); (2) vaginal delivery (either overall or instrumental); (3) caesarean section; (4) NRFS; (5) uterine tachysystole; (6) oxytocin administration; (7) maternal fever; (8) meconium-stained amniotic fluid; (9) postpartum hemorrhage (PPH); (10) chorioamnionitis; (11) 1 minute Apgar score; (12) 5 minute Apgar score; (13) neonatal pH; (14) admission to neonatal intensive care unit (NICU); (15) composite adverse perinatal outcome (including Apgar <7 at 5 minutes, pH<7.2 and admission to NICU). The continuous outcomes were: (1) time to induction; (2) time to active labor; (3) time to cervical ripening; (4) time to delivery; (5) length of in hospital stay; (6) units of oxytocin administered; (7) Apgar score (measured both after 1 and 5 minutes); (8) neonatal pH.

First, we performed meta-analyses of proportions to compute the pooled rates (and 95% Confidence Intervals - CIs) of each categorical outcome among women induced with: (a) Dinoprostone; (b) Misoprostol; (c) mechanical methods. Data from individual studies were also combined to estimate, for each induction method, the weighted mean (plus 95% CIs) of all continuous outcomes, using the metan package in Stata. Both proportion meta-analyses and single-group meta-analyses of continuous data were performed using a random-effect model to account for the inter-study heterogeneity. When only one study was available, no meta-analysis could be performed, thus raw proportions and means were reported for categorical and continuous outcomes, respectively. All of the above proportion and single-group meta-analyses were carried out three times: (a) including all small fetuses; (b) including only SGA fetuses; (c) including only late FGR fetuses. Thus, a total of 198 meta-analyses were performed.

Second, for all small fetuses considered together, and for 5 maternal and perinatal outcomes separately (those for which at least two studies could be included in the meta-analysis: composite adverse intrapartum outcome; composite adverse perinatal outcome; vaginal delivery; caesarean section; NRFS) we performed three direct comparisons: (1) Dinoprostone vs mechanical induction; (2) Misoprostol vs mechanical induction; (3) Misoprostol vs Dinoprostone, for a total of fifteen head-to-head meta-analyses.

In the latter analyses, we included observational cohort studies in which exposed and unexposed group sizes were frequently severely unbalanced, and some studies reported zero events in one or both of the compared groups. When the events are rare, many of the most commonly used meta-analytical methods can produce biased estimates. When the studies are also substantially imbalanced, the best performing methods are the Mantel-Haenszel odds ratio without zero-cell continuity corrections, logistic regression and an exact method. Mantel-Haenszel odds ratios cannot be computed in studies reporting zero events in both groups, the exclusion of which may however cause a relevant loss of information and the potential inflation of the magnitude of the pooled exposure effect. Therefore, to keep all studies into the analyses, all fifteen meta-analyses were carried out using individual data random-effect logistic regression, with single study as the cluster unit. The pooled datasets with individual data were reconstructed using published 2X2 tables.[13-15]

For each outcome, the total number of publications included in the meta-analyses was <10, thus we were not able to assess publication bias, either graphically, through funnel plots, or formally, through Egger's regression asymmetry test (in such cases, the power is too low to distinguish chance from real asymmetry). All analyses were carried out using Stata, version 13.1 (Stata Corp., College Station, TX, 2013).

RESULTS

Study selection and characteristics

201 articles were identified, 129 were assessed with respect to their eligibility for inclusion (Supplementary Table 1) and 12 studies[16-27] were included in the systematic review (Table 1, Figure 1). These 12 studies included 1711 singleton pregnancies complicated by the presence of a small fetus, defined as EFW <10th centile. There was no RCT trial comparing the different methods of IOL in pregnancies complicated by a small fetus; therefore, the pooled data synthesis was carried out included only non-randomized series. Among the included studies, we could perform separate analysis only for seven studies on late FGR and six on SGA (Table 1).

Data were available for 571 pregnancies undergoing IOL with Dinoprostone, 693 with Misoprostol and 341 with mechanical methods (either Cook's or Foley's Balloon catheters). When considering the different sub-categories of small fetuses, information for the outcomes explored in the present systematic review was available for 432 late FGR and 984 SGA fetuses.

Baseline maternal and pregnancy characteristics are reported in Table 1, while the induction protocols from each individual study are reported in Supplementary Table 2. Weighted mean maternal age was 29.5 years (95% CI 27.9-31.1) in women undergoing IOL with Dinoprostone, 26.8 (95% CI 24.8-28.8) in those with Misoprostol and 29.5 (95% CI 26.9-32.1) in those with mechanical methods. Mean gestational age at IOL was 37.8 weeks (95% CI 37.0-38.6) in pregnancies induced with Dinoprostone, 38.8 (38.7-38.9) weeks in those with Misoprostol and 38.4 (95% CI 37.1-39.7) weeks in those with mechanical methods, while weighted mean Bishop score at IOL was 2.7 (95% CI 1.4-3.9), 3.6 (95% CI 0.8-6.3) and 4 (95% CI 1.8-4.6), respectively. 63.2% (95% CI 51.4-74.2) of women induced with Dinoprostone were nulliparous, compared to 67.3% (95% CI 60.8-73.6) and 69.9% (95% CI 56.2-82.2) of those with Misoprostol and mechanical methods, respectively (Table 3). Mean neonatal birthweight was 2.41 Kg (95% CI 2.3-2.5) in pregnancies induced with Dinoprostone, 2.42 kg (95% CI 2.4-2.5) of those with Misoprostol and 2.37 kg (95% CI 2.3-2.4). Unfortunately, we could not perform a meaningful data synthesis on the other major maternal and neonatal characteristics in view of the lack of information from the original studies; medical complications including pre-eclampsia and gestational diabetes mellitus were reported only by one[16] and two studies[16-17] respectively, while prior CS by two studies.[16-17]

Details of risk of bias assessment are reported in Table 2. Most of the included studies were at low or moderate risk of bias. The main weaknesses of these studies were their retrospective non-randomized design, relatively small sample size, heterogeneity of outcomes observed and different protocols for antenatal management of the pregnancies complicated by late FGR and SGA fetuses.

Synthesis of the results

1. All small fetuses

Maternal outcomes

When considering the overall population of pregnancies complicated by a small fetus, composite adverse intra-partum outcome occurred in 21.2% (95% CI 10.0-34.9) of pregnancies induced with Dinoprostone, 18.0% (95% CI 6.9-32.5) of those with Misoprostol and 11.6% (95% CI 5.5-19.3) of those undergoing IOL with mechanical methods (either Foley or Cooks catheter) (Table 4).

Vaginal delivery was accomplished in 73% (95% CI 59.8-85.1) of pregnancies induced with Dinoprostone, 78.6% (95% CI 71.5-85.0) with Misoprostol and 80% (95% CI 72.7-86.7) of cases undergoing mechanical IOL, while the corresponding figures for vaginal delivery within 24 hours from the induction were 49.15 (95% CI 38.4-59.8), 63% (95% CI 47.5-76.8) and 74.6% (95% CI 64.2-99.7), respectively. Instrumental vaginal delivery for arrested labor or NRFS was needed in 7.6% (95% CI 2.9-13.7) of pregnancies undergoing IOL with Dinoprostone, 12.5% (95% CI 2.7-32.4) of those with Misoprostol and 6.8% (955 CI 2.9-11.9) of those undergoing mechanical induction. Overall, IOL ended in a CS in 24.4% (95% CI 12.7-38.2) of pregnancies induced with Dinoprostone, 16.6% (95% CI 7.0-28.9) of those with Misoprostol and 17.3% (95% CI 11.5-23.8) of those undergoing induction with mechanical methods. However, when considering only cases undergoing CS for NRFS, CS was required in 18.1% (95% CI 9.9-28.3) of pregnancies induced with Dinoprostone, 9.4% (95% CI 1.4-22.0) of those with Misoprostol and 8.1% (95% CI 5.0-11.6) of those undergoing mechanical induction (Table 4).

NRFS on CTG complicated 17.5% (95% CI 8.8-28.0) pregnancies induced with Dinoprostone, 18.0% (955 CI 6.9-32.6) of those with Misoprostol and 11.8% (95% CI 12.5-22.5) of those undergoing mechanical IOL. Likewise, uterine tachysystole, was recorded on CTG in 13.8% (95% CI 6.9-22.3) of cases induced with Dinoprostone, 7.5% (95% CI 2.1-15.4) of those with Misoprostol and 3.8% (95% CI 0-4.4) of those induced with mechanical methods.

The pooled prevalence of all maternal outcomes occurring in pregnancies complicated by the presence of a small fetus according to the type of IOL are reported in Table 4.

The weighted mean time to induction (expressed in hours) was 16.4 (95% CI 14.2-18.5) in pregnancies induced with Dinoprostone, 17.9 (95% 17.0-18.7) in those with Misoprostol and 17.0 (95% CI 13.3-20.7) in those undergoing mechanical IOL, while the mean time to active labor was 4.2 (95% CI 2.0-6.4), 4.5 (95% CI 4.1-4.9) and 5.8 (95% CI 5.6-5.9) in the three different sub-group of methods (Table 5). The overall time interval from the IOL to delivery was 21.2 (95% CI 17.3-25.1) hours in women undergoing IOL with Dinoprostone compared to 18.4 (8.8-28.0) and 24.3 (95% CI 16.1-32.4) of those induced with Misoprostol and mechanical methods, respectively. Finally, the

weighted means of in hospital stay was 2.0 (95% CI 0.9-3.0) days in women induced with Dinoprostone, 2.7 (95% CI 2.4-3.0) days in those with Misoprostol and 3.0 (95% CI 2.8-3.2) days in those undergoing mechanical IOL.

Perinatal outcomes

Composite adverse perinatal outcome following delivery complicated 2.9% (95% CI 0.5-6.7) of the newborns after IOL with Dinoprostone, 0.6% (95% CI 0-2.5) with Misoprostol and 0.7% (95% CI 0-7.1) with mechanical methods (Table 6). Weighted mean neonatal 5- minutes Apgar score was 9.5 (95% CI 9.0-10.10) after IOL with Dinoprostone, 9.5 (95% CI 8.6-10.0) with Misoprostol and 9.6 (95% CI 9.1-10.0) with mechanical methods, while an Apgar score <7 at 5 minutes was observed in 0.6% (95% CI 0-4.2) of newborns after IOL with Dinoprostone, 0.1% (95% CI 0-3.1) with Misoprostol and 0.9% (0-3.0) with mechanical methods (Table 5). Weighted mean pH was 7.26 (95% CI 7.2-7.3) after IOL with Dinoprostone, 7.27 (95% CI 7.26-7.3) with Misoprostol and 7.28 (95% CI 7.26-7.3) with mechanical methods, a pH<7.2 was observed in 3.9% (95% CI 0.9-8.1) in the group of pregnancies induced with Dinoprostone and in none of the cases in those induced with Misoprostol and mechanical methods (Table 6). 12.7% (95% CI 4.7-23.0) of newborns after IOL with Dinoprostone required admission to NICU, compared to 9.0% (95% CI 1.1-22.2) of those with Misoprostol and 14.6% (95% CI 6.8-24.4) of those with mechanical methods (Table 6).

2. Sub-group analysis: Pregnancies complicated by late FGR

Sub-analysis considering only pregnancies complicated by late FGR was affected by the very small number of included cases and even smaller number of events which might have affected the robustness of the results. More importantly, the large majority of the explored outcome in the Misoprostol group were reported only by one study, thus making inter-group comparison difficult.

When considering only pregnancies complicated by late FGR, adverse intrapartum outcome occurred in 25.3% (95% CI 18.8-32.5) of women undergoing IOL with Dinoprostone, compared to 7.4% (95% CI 3.9-11.7) of those with mechanical methods and 4.2% (95% CI 01.-21.1) of those with Misoprostol, although only one study reported the outcome for this type of IOL (Table 7). Vaginal delivery was accomplished in 66.6% (95% CI 59.0-73.8) of pregnancies induced with Dinoprostone, 83.3% (95% CI 61.8-95.3) with Misoprostol and 83.2% (95% CI 73.2-91.5) with mechanical methods, while the corresponding figures for the need of an operative vaginal delivery were 12.5% (95% CI 2.7-32.4), 11.3% (95% CI 3.0-23.0) and 6.9% (95% CI 3.4-11.3). CS for NRFS was performed in 23.8% (95% CI 17.3-30.9), 0% (95% CI 0-16.8) and 6.2% (95% CI 2.8-10.5) of the cases, respectively. Uterine tachysystole was observed on CTG in 16.1% (95% CI 9.8-23.4) of pregnancies undergoing IOL with Dinoprostone, 25.0% (95% CI 12.9-39.3) of those with

Misoprostol and 8.0% (95% CI 4.2-12.8) of those undergoing mechanical IOL, while NRFS in 24.4% (95% CI 12.3-38.5), 4.5% (95% CI 0-13.7) and 6.5% (95% CI 3.1-10.7) in the three different sub-group of pregnancies, respectively. Weighted mean time to induction was 15.3% (95% CI 13.2-17.3) in women induced with Dinoprostone, 17.9 (95 CI 17.0-18.7) in those with Misoprostol and 17.0 (95% CI 13.3-20.7) in those with mechanical methods, while the corresponding figures for the mean time to delivery were 19.0 (95% CI 17.5-20.5), 25.1 (95% CI 24.8-25.3) and 27.7 (95% CI 18.2-37.2).

Composite adverse perinatal outcome occurred in 4.8% (95% CI 1.1-10.4) of the newborns after IOL with Dinoprostone, 0% (95% CI 0-14.2) with Misoprostol and 1.1% (95% CI 0-5.2) with mechanical methods. Apgar score <7 at 5 minutes was observed in 6.5% (95% CI 2.1-14.5) of newborns after IOL with Dinoprostone compared to 1.6% (95% 0-5.3) of those with mechanical methods, while none of the studies included in the present systematic review reported this outcome in the subgroup of late FGR fetuses after IOL with misoprostol (Table 9). Similarly, a neonatal pH< 7.2 was observed in 3.6% (95% CI 0.9-7.6) after IOL with Dinoprostone compared to 0% (95% CI 0-0.5) with mechanical methods (Table 9).

3. Sub-group analysis: Pregnancies complicated by SGA fetus

Sub-analysis including only SGA fetuses was also affected by the smaller number of included cases. Furthermore, the large majority of the explored outcomes were not reported for pregnancies undergoing IOL with Misoprostol, and for the remaining ones, only one study was included. The composite adverse intrapartum outcome complicated 8.4% (95% CI 4.6-13.0) of pregnancies induced with Dinoprostone, 18.6% (95% CI 13.1-25.2) of those with Misoprostol and 8.7 (95% CI 2.5-17.5) of those undergoing mechanical IOL (Table 10). Vaginal delivery was achieved in 84.6% (95% CI 74.9-92.5) of women undergoing IOL with Dinoprostone, 74.4% (95% CI 67.2-80.8) of those with Misoprostol and 80.4% (95% CI 69.4-89.6) of those with mechanical methods. CS for NRF was performed in 8.4% (95% CI 4.6-13.0) of women induced with Dinoprostone, 18.6% (95% CI 13.1-25.2) of those with Misoprostol and 8.7% (95% CI 2.5-17.5) of those undergoing mechanical IOL. Uterine tachysystole was recorded in none of the pregnancies complicated by the presence of a SGA fetus, while NRFS on CTG was observed in 13.9% (95% CI 4.4-26.5) of cases undergoing IOL with Dinoprostone, 18.6% (95% CI 13.1-25.2) of those with Misoprostol and 8.7% (95% CI 2.5-17.5) of those with mechanical methods.

Composite adverse perinatal outcome occurred in 0.5% (95% CI 0-2.6) of the newborns after IOL with Dinoprostone, 1.7% (95% CI 0.4-5.0) of those with Misoprostol and in none of the cases after mechanical induction. The weighted mean neonatal Apgar score was 9.1 8955 CI 8.1-9.3) of cases after IOL with Dinoprostone, 9.0 (95% CI 8.9-9.0) with Misoprostol and 9.0 (95% CI 8.9-9.1) with mechanical methods, while an Apgar score <7 at 5 minutes was described in 0.3% (95% CI 0-2.9) of newborns after IOL with Dinoprostone, 1.7% (95% CI 0.4-5.0) after Misoprostol and in none of the cases after mechanical induction (Tables 11 and 12). Admission to NICU was required in 12.9% (955 CI 3.8-25.2) of newborns after IOL with Dinoprostone, 18.0% (95% CI 12.6-24.6) after Misoprostol and in 15.0% (95% CI 6.8-25.2) after mechanical induction (Table 11).

4. Sub-analysis on direct comparison in all small fetuses

Direct comparison between different techniques for IOL could be performed only for 4 maternal and perinatal outcomes separately (those for which at least two studies could be included in the meta-analysis: composite adverse intrapartum outcome; composite adverse perinatal outcome; vaginal delivery; CS; NRFS) using individual data random-effect logistic regression, with single study as the cluster unit. Dinoprostone was associated with a higher risk of composite adverse intrapartum outcome compared to mechanical IOL with a pooled OR of 3.27 (95% CI 1.7-6.3) and CS (OR: 2.05, 95% CI 1.2-3.5), while no significant differences were observed for the other comparisons. Unfortunately, these analyses could not be performed for the most potentially clinically relevant outcomes when inducing a pregnancy complicated by a small fetus (i.e., tachysystole or CS for NRFS).

5. GRADE assessment

Overall evidence was qualified using GRADE pro. Overall, low quality of evidence was found to support the use of a particular method of IOL above the others. The level of evidence for RCTs was downgraded due to considerable clinical and statistical heterogeneity (Supplementary Table 4).

DISCUSSION

Main findings

The findings from this systematic review show that there is still limited evidence on the optimal method of IOL in pregnancies with a small fetus. Inclusion of non-randomized studies, small sample size and heterogeneity in the outcomes explored and in the prenatal management of these pregnancies do not allow extrapolation of an objective evidence on which IOL method should be preferred when facing with a pregnancy complicated by a small fetus. When considering the overall population of small fetuses, mechanical IOL seems to be associated with a lower occurrence of composite adverse intra-partum outcome, operative vaginal delivery CS for NRFS, uterine tachysystole and NRFS on CTG, although a direct comparison between the different techniques could not be performed. Sub-analysis considering only late FGR or SGA fetuses was hampered by the smaller number of studies and by the fact that the large majority of the explored outcomes in the Misoprostol group were reported only by one study, thus making inter-group comparison difficult. In late FGR fetuses, mechanical methods seem to be associated with a low occurrence of adverse events compared to Dinoprostone, while the magnitude of this effect was lower when considering only pregnancies with an SGA fetus.

Strengths and limitations

This is the first systematic review and meta-analysis exploring the outcome of pregnancies complicated by a small fetus undergoing IOL with Dinoprostone, Misoprostol or mechanical induction. Rigorous design, multitude of outcomes explored and stratification of the analyses according to late FGR or SGA status represent the major strengths of the present review. Furthermore, the major maternal and pregnancy clinical characteristics potentially affecting the success of IOL and the occurrence of adverse events (i.e. birthweight, gestational age at IOL and Bishop score) were similar among the study groups (Table 3).

Inclusion of non-randomized studies, their retrospective design, small sample size and heterogeneity in prenatal management of pregnancies complicated by a small fetus represent the major limitation of the present review. Furthermore, despite the fact that we could perform sub-group analysis according to late FGR and SGA status, the small number of cases included, and the even smaller number of events may have affected the robustness of the results. The definition of pregnancies complicated by late FGR has been proposed only recently and it may be entirely possible that some of the cases labelled as SGA in the original studies were actually affected by SGA and vice versa. In order to partially overcome this limitation, we decided to report all the explored outcomes also in the overall population of small fetuses. Although such approach has preserved the power of the statistical

analysis (at least for the main outcomes' measures), it may have affected the magnitude of some of the reported proportions. Furthermore, although the more relevant pregnancy characteristics were similar among the different study groups, it may be entirely possible that other pregnancy and fetal characteristics, such as pre-eclampsia or severity of Doppler findings, may have unbalanced the results, thus potentially affecting our study findings. Finally, the small proportion of studies (with very few numbers of cases and even fewer events) reporting perinatal outcomes of each IOL method according to the final way of delivery made it impossible to draw any convincing evidence for such analysis.

Despite these limitations, the present systematic review represents the most comprehensive up-to-date evidence on IOL in pregnancies with a small fetus.

Comparison with other systematic reviews

Several systematic reviews on IOL have been published in the recent past. Chen *et al.* compared vaginal Misoprostol, Dinoprostone and Foley's catheter for cervical ripening during IOL in a network systematic review.[4] Vaginal misoprostol was associated with a higher rate of vaginal delivery within 24 hours from the induction, although it carried a higher risk of uterine hyperstimulation with fetal heart rate (FHR) changes. Conversely, Foley's catheter was associated with the lowest rate of uterine hyperstimulation accompanied by FHR changes. Finally, the caesarean section rate was lowest when using oral misoprostol.[4] Alfirevic et al. have explored the effectiveness and safety of prostaglandins used for IOL in another network meta-analysis and found that low dose titrated oral misoprostol solution had the lowest probability of caesarean section, whereas vaginal misoprostol had the highest probability of achieving a vaginal delivery within 24 hours.[28] More recently, de Vann et al., in a Cochrane systematic review, have explored the effectiveness and safety of mechanical methods for third trimester IOL in comparison with prostaglandin E2 (vaginal and intracervical), low-dose misoprostol (oral and vaginal), amniotomy or oxytocin. The authors reported that mechanical induction with a balloon is probably as effective as IOL with vaginal PGE2. However, a balloon seems to have a more favorable safety profile.[29]

However, all these reviews did not include small fetuses or not stratify their analysis considering only pregnancies complicated by impaired fetal growth, thus making their findings not applicable to a population of fetuses with suspected growth abnormalities.

Clinical and research implications

Management of pregnancies with suspected late FGR is challenging. FGR is commonly defined as the inability to reach the growth potential in utero. Although the most classical clinical phenotype of

FGR is the presence of a small fetus, not all small fetuses are growth restricted, thus making identification of "true" growth restriction difficult. The main clinical question when managing a pregnancy suspected to be complicated by late FGR is the optimal type of monitoring and the most appropriate time of delivery in order to reduce the risk of adverse perinatal outcome. Fetuses with late FGR commonly exhibits a reduced impedance to blood flow in the brain, expressed as a low MCA PI or CPR.[30] Although initially considered a protective mechanism, the persistence of cerebral blood flow redistribution has been linked with a higher risk of adverse neurological outcome compared to fetuses showing normal brain hemodynamic parameters.[31-34] Elective IOL in these pregnancies has been suggested, although it is not entirely certain whether delivery may improve perinatal outcome.[35-36]

National and international guidelines on FGR generally recommend that pregnancies with late FGR should be induced at around 37-38 weeks of gestation.[3] However, these guidelines do not mention which method of IOL should be undertaken in order to achieve a safe vaginal delivery. The choice of an optimal methods to induce labor is fundamental as these pregnancies are already suffering from chronic hypoxemia and undernutrition, and for this reason, few authors speculated that elective cesarean delivery could be a reasonable option to avoid superimposed sudden hypoxemia, as that induced by uterine tachysystole, but there is currently no evidence to support this policy.

The findings form this systematic review showed that the occurrence of some adverse maternal outcomes is lower in pregnancies induced with mechanical methods. The findings are not surprising, as mechanical IOL is likely to have a minor impact on placental perfusion and fetal hemodynamic changes compared to prostaglandins. However, it is not possible to extrapolate a clear recommendation on the method of IOL form this systematic review in view of the non-randomized and mostly retrospective design of the included studies.

SGA fetuses with normal umbilical and cerebral Doppler are commonly considered to be at lower risk of adverse perinatal outcome compared to late FGR and have perinatal outcomes similar to appropriately grown fetuses.[37-39]

Although a significant proportion of these fetuses are constitutionally small, but healthy, they may still be at a higher risk of some adverse events, mainly CS for NRFS.[40-42] In the present systematic review, the impact of mechanical methods of IOL when applied to "simple" SGA fetuses, was more difficult to ascertain in view of the small number of included cases, with the large majority of outcomes in the Misoprostol group reported only by a single study. However, even in this subset of fetuses, mechanical IOL was associated with a lower incidence of some adverse intrapartum outcome, especially when compared to Dinoprostone. However, these findings should be interpreted with

caution as it may be entirely possible that some of the cases included in this review and labelled as simple SGA, may be "true" growth restriction.

Given all the above-mentioned limitations of the present systematic review, only a properly designed RCT comparing the impact of different methods of IOL in pregnancies complicated by late FGR or SGA can answer the question. Ideally, this RCT should investigate perinatal outcomes, such as the occurrence of fetal distress on CTG, uterine tachysystole and neonatal acid base status, rather than those related to a "fast" vaginal delivery. Furthermore, this RCT should also ideally examine whether fetal Dopplers, especially MCA and CPR, may represent an additional risk factor in pregnancies undergoing IOL, in order to plan the most appropriate and safe IOL.

CONCLUSIONS

There is limited evidence on the optimal method of IOL in pregnancies with a small fetus. Mechanical methods seem to be associated with a lower incidence of some intrapartum outcomes, including operative vaginal delivery, CS for NRFS and uterine tachysystole, when compared to Dinoprostone or Misoprostol and should be ideally preferred when inducing labor in pregnancies suspected to be at risk of growth restriction. However, the non-randomized design and lack of direct comparison in the original studies imposes caution when interpreting the findings from this study. A multicenter RCT is urgently needed in order to establish the optimal method for inducing labor in pregnancies complicated by late FGR or SGA fetus.

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Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Table 1. General characteristics of the studies included in the systematic review.

Author	Year	Country	Study design	Period analyzed	Intervention	Sub-analysis according to SGA/late FGR status	Pregnancies (n)
Villalain[16]	2018	Spain	Retrospective Case-control study	2014-2015	Dinoprostone (10 mg), or Foley catheter	Yes (FGR)	148
Rossi[17]	2018	United States	Retrospective Cohort study	2008-2012	Dinoprostone (10 mg), misoprostol (25 mcg) or Foley catheter with oxytocin (Pitocin)	Yes (SGA)	260
Hidaka[18]	2017	Japan	Retrospective Cohort study	2008-2016	Foley catheter with oxytocin (Pitocin)	Yes (SGA and FGR)	73
Simeone[19]	2017	Italy	Retrospective Cohort study	2009-2015	Misoprostol (25 mcg) or Foley catheter	Yes (FGR)	8
Duro-Gomez[a 20]	2017	Spain	Retrospective case-control study	2014-2015	Dinoprostone (10 mg), misoprostol (25 mcg) or Cook catheter	Yes (FGR)	99
Duro-Gomez[a 21]	2017	Spain	Retrospective case-control study	2014-2016	Dinoprostone (10 mg), misoprostol (25 mcg) or Cook catheter	Yes (FGR)	150
Chavacula[22]	2015	India	Unmasked randomized controlled trial	2011-2012	Misoprostol (25 mcg) or Foley catheter	No	100
Foeller[23]	2015	United States	Retrospective case-control study	2002-2008	Misoprostol (25mcg)	Yes (SGA)	451
Visentin[24]	2014	Italy	Retrospective Cohort study	2009-2012	Dinoprostone (10 mg)	Yes (SGA)	96
Savchev[b 25]	2012	Spain	Prospective Cohort study	2008-2010	Dinoprostone (10mg)	Yes (SGA and FGR)	132
Cruz Martinez[b 26]	2011	Spain	Prospective Cohort study	2008-2010	Dinoprostone (10mg)	Yes (SGA and FGR)	327
Ben Harousch[27]	2004	Israel	Retrospective Cohort study	1998-2000	Dinoprostone (3mg)	No	90

a: These two studies share the same population but were both included as information as some of the outcomes explored in the present systematic review could not be extrapolated just by one study
b: These two studies are likely to share the same population but looked at different outcomes in two different sub-set of pregnancies.

Table 2. ROBINS-I risk of bias assessment

Author	Year	Confounding	Selection	Measurements of Intervention	Missing data	Measurements of outcomes	Reported results	Overall
Villalain[16]	2018	**Low**	**Low**	**Low**	**Low**	**Low**	**Low**	**Low**
Rossi[17]	2018	**Critical**	**Low**	**Low**	**Low**	**Moderate**	**Low**	**Moderate**
Hidaka[18]	2017	**Low**	**Low**	**Low**	**Low**	**Moderate**	**Low**	**Moderate**
Simeone[19]	2017	**Critical**	**Low**	**Moderate**	**Moderate**	**Moderate**	**Moderate**	**Moderate**
Duro-Gomez[20]	2017	**Low**	**Low**	**Moderate**	**Moderate**	**Low**	**Low**	**Low**
Duro-Gomez[21]	2017	**Low**	**Low**	**Low**	**Low**	**Low**	**Low**	**Low**
Chavacula[22]	2015	**Low**	**Low**	**Low**	**Low**	**Moderate**	**Low**	**Moderate**
Foeller[23]	2015	**Low**	**Moderate**	**Low**	**Low**	**Moderate**	**Low**	**Moderate**
Visentin[24]	2014	**Critical**	**Low**	**Critical**	**Moderate**	**Low**	**Moderate**	**Moderate**
Savchev[25]	2012	**Critical**	**Low**	**Low**	**Low**	**Low**	**Low**	**Low**
Cruz Martinez[26]	2011	**Critical**	**Low**	**Low**	**Low**	**Low**	**Low**	**Low**
Ben Harousch[27]	2004	**Critical**	**Moderate**	**Moderate**	**Moderate**	**Moderate**	**Moderate**	**Moderate**

Low risk of bias: The study is comparable to a well performed randomized trial with regard to this domain[13]
Moderate risk of bias: The study is sound for a non-randomized study with regard to this domain but cannot be considered comparable to a well performed randomized trial[13]
Serious risk of bias: The study has some important problems in this domain[13]
Critical risk of bias: The study is too problematic in this domain to provide any useful evidence on the effects of intervention[13]
No information (?): No information on which to base a judgement about risk of bias for this domain[13]

Table 3. Results of single-group meta-analyses of continuous data, and of proportion meta-analyses estimating baseline maternal and gestational characteristics among women undergoing IOL with (a) Dinoprostone, (b) Misoprostol or (c) mechanical induction (Foley's or Cook balloon catheter).

	Dinoprostone	Misoprostol	Mechanical induction
Maternal age at birth in years			
N. studies (N. pregnancies)	6 (447)	4 (693)	6 (333)
Weighted mean (95% CI)	29.5 (27.9-31.1)	26.8 (24.8-28.7)	29.5 (26.9-32.1)
Gestational age at delivery in weeks			
N. studies (N. pregnancies)	4 (213)	3 (669)	5 (256)
Weighted mean (95% CI)	37.9 (37.6-38.1)	37.8 (37.6-38.0)	38.5 (37.5-39.4)
Gestational age at induction in weeks			
N. studies (N. pregnancies)	4 (319)	1 (24)	4 (229)
Weighted mean (95% CI)	37.8 (37.0-38.6)	38.8 (38.7-38.9) [§]	38.4 (37.1-39.7)
Bishop score			
N. studies (N. patients)	3 (109)	2 (70)	4 (210)
Weighted mean (95% CI)	2.7 (1.4-3.9)	3.6 (0.8-6.3)	3.2 (1.8-4.6)
Proportion of nulliparous women			
N. studies (n/N)*	5 (252 / 423)	3 (456 / 669)	4 (121 / 183)
Pooled % (95% CI)	63.2 (51.4-74.2)	67.3 (60.8-73.6)	69.9 (56.2-82.2)

CI = Confidence Interval. [§] Raw mean and 95% CI. [*] Number of nulliparous women / Total number of women.

Table 4. Pooled rates of each maternal outcome by induction method - All small fetuses. Data from single studies have been combined using proportion meta-analysis (random-effect model; see also online figures S1-S44).

	Dinoprostone		Misoprostol		Mechanical [§]	
Outcomes	**n/N[a]**	**Pooled % (95% CI)**	**n/N[a]**	**Pooled % (95% CI)**	**n/N[a]**	**Pooled % (95% CI)**
- Composite adverse intra-partum outcome [1]	119/447	21.2 (10.0-34.9)	48/242	18.0 (6.9-32.5)	41/333	11.6 (5.5-19.3)
Vaginal delivery						
- Overall	312/447	73.3 (59.8-85.1)	187/242	78.6 (71.5-85.0)	264/333	80.1 (72.7-86.7)
- Within 24 hours	84/447	49.1 (38.4-59.8)	29/242	63.0 (47.5-76.8)*	152/333	74.6 (64.2-99.7)
- Instrumental vaginal delivery [2]	11/122	7.6 (2.9-13.7)	3/24	12.5 (2.7-32.4)*	13/158	6.8 (2.9-11.9)
Caesarean section						
- Overall	131/444	24.4 (12.7-38.2)	52/238	16.6 (7.0-28.9)	56/314	17.3 (11.5-23.8)
- For NRFS	98/444	18.1 (9.9-28.3)	37/238	9.4 (1.4-22.0)	28/314	8.1 (5.0-11.6)
- For other obstetrical indications	33/444	5.0 (1.2-10.5)	15/238	5.7 (2.9-9.3)	28/314	7.9 (4.7-11.7)
- For failed induction of labor	4/157	0.8 (0.0-8.3)	10/192	4.5 (2.4-8.2)	8/189	2.4 (0.0-9.6)
- NRFS	13/70	17.5 (8.8-28.0)	48/242	18.0 (6.9-32.5)	33/262	11.8 (12.5-22.5)
- Uterine tachysystole	17/109	13.8 (6.9-22.3)	7/70	7.5 (2.1-15.4)	11/202	3.8 (0.0-11.9)
- Need for oxytocin	14/32	43.6 (26.0-61.9)	46/70	65.9 (54.2-76.8)	63/131	47.9 (39.3-56.6)
- Fever	9/106	3.2 (0.0-14.7)	0/66	0.0 (0.0-2.6)	3/183	0.8 (0.0-4.4)
- Meconium stained amniotic fluid	3/32	7.4 (0.1-20.7)	0/24	0.0 (0.0-14.2)*	3/77	3.9 (0.8-11.0)*
- Post-partum hemorrhage	0/29	0.0 (0.0-5.9)	0/20	0.0 (0.0-16.8)*	2/58	3.4 (0.4-11.9)*
- Chorioamnionitis	0/0	--	0/46	0.0 (0.0-7.7)*	0/54	0.0 (0.0-6.6)*

All small fetuses = including either Small for gestational age - SGA - and Late fetal growth restricted - FGR - fetuses. CI = Confidence Interval. NRFS = Non-reassuring fetal status.

[a] Number of women with the outcome / Total number of women.

* Only one study in the meta-analysis.

[§] Cook or Foley balloon catheter.

[1] Including Caesarean section for NRFS, tachysystole, operative delivery for NRFS, NRFS fever, chorioamnionitis, meconium stained amniotic fluid.

[2] For arrested labor or for NRFS.

Table 5. Maternal and perinatal continuous outcomes by birth induction method - All small fetuses. Weighted means were obtained combining data from individual studies to perform meta-analyses of single-group continuous data. For the sake of completeness, raw means were reported when only one study was available. (See also online figures S140-S156).

	Dinoprostone		**Misoprostol**		**Mechanical induction***	
	N studies (sample)	Weighted mean (95% CI)	N studies (sample)	Weighted mean (95% CI)	N studies (sample)	Weighted mean (95% CI)
A. Maternal outcomes						
Time to induction (hours)	3 (106)	16.4 (14.2-18.5)	1 (20)	17.9 (17.0-18.7)§	2 (129)	17.0 (13.3-20.7)
Time to active labor (hours)	2 (29)	4.2 (2.0-6.4)	1 (20)	4.5 (4.1-4.9)§	1 (58)	5.8 (5.6-5.9)§
Time to cervical ripening (hours)	1 (77)	15.0 (13.5-16.5)§	0	--	1 (71)	12.0 (10.8-13.2)§
Time to delivery (hours)	3 (106)	21.2 (17.3-25.1)	2 (70)	18.4 (8.8-28.0)	4 (210)	24.3 (16.1-32.4)
Length of in-hospital stay (days)	2 (156)	2.0 (0.9-3.0)	1 (24)	2.7 (2.4-3.0)§	1 (77)	3.0 (2.8-3.2)§
B. Perinatal outcomes						
1-minute Apgar score	2 (29)	8.8 (8.4-9.1)	1 (20)	8.9 (8.7-9.1)	3 (139)	8.6 (7.9-9.3)
5-minutes Apgar score	4 (147)	9.5 (9.0-10.0)	2 (196)	9.5 (8.6-10.0)	4 (206)	9.6 (9.1-10.0)
pH	3 (109)	7.26 (7.24-7.29)	1 (24)	7.27 (7.26-7.28)§	4 (229)	7.28 (7.26-7.30)

All small fetuses = including either Small for gestational age - SGA - and Late fetal growth restricted - FGR - fetuses. CI = Confidence Interval.
* Including either Cook or Fooley balloon catheter.
§ Raw mean and 95% CI.

Table 6. Pooled rates of each perinatal outcome by induction method - All small fetuses. Data from single studies have been combined using proportion meta-analysis (random-effect model; see also online figures S45-S56).

		Dinoprostone		**Misoprostol**		**Mechanical** [§]
Outcomes	**n/N[a]**	**Pooled % (95% CI)**	**n/N[a]**	**Pooled % (95% CI)**	**n/N[a]**	**Pooled % (95% CI)**
- Composite adverse perinatal outcome [1]	23/447	2.9 (0.5-6.7)	3/242	0.6 (0.0-2.5)	6/333	0.7 (0.0-7.1)
- Apgar <7 at five minutes	7/423	0.6 (0.0-4.2)	3/218	0.1 (0.0-3.1)	5/256	0.9 (0.0-3.0)
- pH <7.2	18/295	3.9 (0.9-8.1)	0/46	0.0 (0.0-7.7)*	0/206	0.0 (0.0-0.3)
- Admission to NICU	20/147	12.7 (4.7-23.0)	34/242	9.0 (1.1-22.2)	60/333	14.6 (6.8-24.4)

All small fetuses = including either Small for gestational age - SGA - and Late fetal growth restricted - FGR - fetuses. CI = Confidence Interval.
[a] Number of neonates with the outcome / Total number of neonates.
* Only one study in the meta-analysis.
[§] Cook or Foley balloon catheter.
[1] Including either Apgar <7 or pH <7.2.

Table 7. Pooled rates of each maternal outcome by induction method - Late FGR fetuses only. Data from single studies have been combined using proportion meta-analysis (random-effect model; see also online figures S57-S92).

	Dinoprostone		Misoprostol		Mechanical [§]	
Outcomes	**n/N[a]**	**Pooled % (95% CI)**	**n/N[a]**	**Pooled % (95% CI)**	**n/N[a]**	**Pooled % (95% CI)**
- Composite adverse intra-partum outcome [1]	41/161	25.3 (18.8-32.5)	1/24	4.2 (0.1-21.1)*	18/214	7.4 (3.9-11.7)
- Vaginal delivery, overall	107/161	66.6 (59.0-73.8)	20/24	83.3 (61.8-95.3)*	174/214	83.2 (73.2-91.5)
- Instrumental vaginal delivery [2]	3/24	12.5 (2.7-32.4)*	5/44	11.3 (3.0-23.0)	16/201	6.9 (3.4-11.3)
Caesarean section						
- Overall	50/158	29.3 (18.6-41.3)	1/20	5.0 (0.1-24.9)*	28/195	13.5 (8.7-19.0)
- For NRFS	38/158	23.8 (17.3-30.9)	0/20	0.0 (0.0-16.8)*	14/195	6.2 (2.8-10.5)
- For other obstetrical indications	12/158	5.4 (0.7-12.3)	1/20	5.0 (0.1-24.9)*	14/195	6.1 (2.7-10.4)
- NRFS	11/45	24.4 (12.3-38.5)	2/44	4.5 (0.0-13.7)	15/201	6.5 (3.1-10.7)
- Uterine tachysystole	20/122	16.1 (9.8-23.4)	11/44	25.0 (12.9-39.3)	17/206	8.0 (4.2-12.8)
- Need for oxytocin	12/24	50.0 (29.1-70.9)*	18/24	75.0 (53.3-90.2)*	47/77	61.0 (49.2-72.0)*
- Fever	9/98	7.7 (2.8-14.2)	0/20	0.0 (0.0-16.8)*	3/129	1.6 (0.0-4.9)
- Meconium stained amniotic fluid	3/24	12.5 (2.7-32.4)*	0/24	0.0 (0.0-14.2)*	3/77	3.9 (0.8-11.0)*
- Post-partum hemorrhage	0/21	0.0 (0.0-16.1)*	0/20	0.0 (0.0-16.8)*	2/58	3.4 (0.4-11.9)*
- Chorioamnionitis	0/0	--	0/0	--	0/0	--

Late FGR = Late fetal growth restricted fetuses. CI = Confidence Interval. NRFS = Non-reassuring fetal status.
[a] Number of women with the outcome / Total number of women.
* Only one study in the meta-analysis.
[§] Cook or Foley balloon catheter.
[1] Including Caesarean section for NRFS, tachysystole, operative delivery for NRFS, NRFS fever, chorioamnionitis, meconium stained amniotic fluid.
[2] For arrested labor or for NRFS.

Table 8. Selected maternal and perinatal continuous outcomes by birth induction method - Late FGR fetuses only. Weighted means were obtained combining data from individual studies to perform meta-analyses of single-group continuous data. For the sake of completeness, raw means were reported when only one study was available. (See also online figures S157-S170).

	Dinoprostone		**Misoprostol**		**Mechanical induction***	
	N studies (sample)	Weighted mean (95% CI)	N studies (sample)	Weighted mean (95% CI)	N studies (sample)	Weighted mean (95% CI)
A. Maternal outcomes						
Time to induction (hours)	2 (98)	15.3 (13.2-17.3)	1 (20)	17.9 (17.0-18.7)§	2 (129)	17.0 (13.3-20.7)
Time to delivery (hours)	2 (101)	19.0 (17.5-20.5)	1 (77)	25.1 (24.8-25.3)§	3 (156)	27.7 (18.2-37.2)
Length of stay (days)	2 (84)	2.3 (1.8-2.8)	1 (24)	2.7 (2.4-3.0)§	1 (77)	3.0 (2.8-3.2)§
B. Perinatal outcomes						
1-minute Apgar score	1 (21)	8.7 (8.3-9.1)§	1 (20)	8.9 (8.7-9.1)§	3 (124)	8.6 (7.9-9.3)
5-minutes Apgar score	2 (101)	9.9 (9.8-10.0)	2 (44)	9.9 (9.9-9.9)	4 (214)	9.9 (9.8-10.0)
pH	2 (101)	7.25 (7.22-7.28)	2 (44)	7.27 (7.26-7.28)	2 (214)	7.28 (7.26-7.30)

Late FGR = Late fetal growth restricted fetuses. CI = Confidence Interval.
* Including either Cook or Fooley balloon catheter
§ Raw mean and 95% CI.

Table 9. Pooled rates of each perinatal outcome by induction method among - Late FGR fetuses only. Data from single studies have been combined using proportion meta-analysis (random-effect model; see also online figures S93-S102).

	Dinoprostone		Misoprostol		Mechanical [§]	
Outcomes	**n/N[a]**	**Pooled % (95% CI)**	**n/N[a]**	**Pooled % (95% CI)**	**n/N[a]**	**Pooled % (95% CI)**
- Composite adverse perinatal outcome [1]	8/161	4.8 (1.1-10.4)	0/24	0.0 (0.0-14.2)*	5/214	1.1 (0.0-5.2)
- Apgar <7 at five minutes	5/77	6.5 (2.1-14.5)*	0/0	--	4/137	1.6 (0.0-5.3)
- pH <7.2	5/137	3.6 (0.9-7.6)	0/0	--	0/137	0.0 (0.0-0.5)
- Admission to NICU	13/101	12.0 (6.0-19.3)	2/24	8.3 (1.0-27.0)*	46/214	16.7 (5.1-32.5)

Late FGR = Late fetal growth restricted fetuses. CI = Confidence Interval.
[a] Number of neonates with the outcome / Total number of neonates.
* Only one study in the meta-analysis.
[§] Cook or Foley balloon catheter.
[1] Including either Apgar <7 or pH <7.2.

Table 10. Pooled rates of each maternal outcome by induction method - SGA fetuses only. Data from single studies have been combined using proportion meta-analysis (random-effect model; see also online figures S103-S128).

	Dinoprostone		Misoprostol		Mechanical [§]	
Outcomes	**n/N[a]**	**Pooled % (95% CI)**	**n/N[a]**	**Pooled % (95% CI)**	**n/N[a]**	**Pooled % (95% CI)**
- Composite adverse intra-partum outcome [1]	20/208	8.4 (4.6-13.0)	32/172	18.6 (13.1-25.2)*	6/65	8.7 (2.5-17.5)
- Vaginal delivery, overall	177/208	84.6 (74.9-92.5)	128/172	74.4 (67.2-80.8)*	52/65	80.4 (69.4-89.6)
- Instrumental vaginal delivery [2]	8/98	6.3 (1.6-13.0)	0/0	--	1/15	6.7 (0.2-31.9)*
Caesarean section						
- Overall	31/208	15.4 (7.5-25.1)	44/172	25.6 (19.2-32.8)*	12/65	17.7 (8.9-28.4)
- For NRFS	20/208	8.4 (4.6-13.0)	32/172	18.6 (13.1-25.2)*	6/65	8.7 (2.5-17.5)
- For other obstetrical indications	11/208	4.1 (0.1-11.4)	12/172	7.0 (3.7-11.9)*	6/65	7.6 (1.8-16.0)
- NRFS	7/46	13.9 (4.4-26.5)	32/172	18.6 (13.1-25.2)*	6/65	8.7 (2.5-17.5)
- Uterine tachysystole	0/8	0.0 (0.0-36.9)*	0/0	--	0/54	0.0 (0.0-6.6)*
- Need for oxytocin	2/8	25.0 (3.2-65.1)*	0/0	--	0/0	--
- Fever	0/8	0.0 (0.0-36.9)*	0/0	--	0/0	--
- Meconium stained amniotic fluid	0/8	0.0 (0.0-36.9)*	0/0	--	0/0	--
- Post-partum hemorrhage	0/8	0.0 (0.0-36.9)*	0/0	--	0/0	--
- Chorioamnionitis	0/0	--	0/0	--	0/0	--

SGA = Small for gestational age. CI = Confidence Interval. NRFS = Non-reassuring fetal status.
[a] Number of women with the outcome / Total number of women.
* Only one study in the meta-analysis.
[§] Cook or Foley balloon catheter.
[1] Including Caesarean section for NRFS, tachysystole, operative delivery for NRFS, NRFS fever, chorioamnionitis, meconium stained amniotic fluid.
[2] For arrested labor or for NRFS.

Table 11. Pooled rates of each perinatal outcome by induction method - SGA fetuses only. Data from single studies have been combined using proportion meta-analysis (random-effect model; see also online figures S129-S139).

	Dinoprostone		Misoprostol		Mechanical [§]	
Outcomes	**n/N[a]**	**Pooled % (95% CI)**	**n/N[a]**	**Pooled % (95% CI)**	**n/N[a]**	**Pooled % (95% CI)**
- Composite adverse perinatal outcome [1]	3/208	0.5 (0.0-2.6)	3/172	1.7 (0.4-5.0)*	0/65	0.0 (0.0-2.4)
- Apgar <7 at five minutes	2/136	0.3 (0.0-2.9)	3/172	1.7 (0.4-5.0)*	0/65	0.0 (0.0-2.4)
- pH <7.2	1/80	0.1 (0.0-3.7)	0/0	--	0/15	0.0 (0.0-21.8)*
- Admission to NICU	7/46	12.9 (3.8-25.2)	31/172	18.0 (12.6-24.6)*	10/65	15.0 (6.8-25.2)

SGA = Small for gestational age. CI = Confidence Interval.
[a] Number of neonates with the outcome / Total number of neonates.
* Only one study in the meta-analysis.
[§] Cook or Foley balloon catheter.
[1] Including either Apgar <7 or pH <7.2.

Table 12. Selected maternal and perinatal continuous outcomes by birth induction method - SGA fetuses only. Weighted means were obtained combining data from individual studies to perform meta-analyses of single-group continuous data. For the sake of completeness, raw means were reported when only one study was available. (See also online figures S171-S174).

	Dinoprostone		**Misoprostol**		**Mechanical induction***	
	N studies (sample)	Weighted mean (95% CI)	N studies (sample)	Weighted mean (95% CI)	N studies (sample)	Weighted mean (95% CI)
Perinatal outcomes						
5-minutes Apgar score	2 (101)	9.1 (8.9-9.3)	1 (172)	9.0 (8.9-9.0)[§]	1 (50)	9.0 (8.9-9.1)[§]

SGA = Small for gestational age. CI = Confidence Interval.* Including either Cook or Fooley balloon catheter. [§] Raw mean and 95% CI

Figure legend

Figure 1. Systematic review flowchart.