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ORIGINAL RESEARCH ARTICLE

Maternal and neonatal outcomes of pregnancies complicated by late fetal growth restriction undergoing induction of labor with dinoprostone compared with cervical balloon: A retrospective, international study

The induCtion of labOr in Late fetaL Growth rEstriction (COLLEGE) Study Group

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Abstract

Introduction: The aim of this study was to compare vaginal dinoprostone and mechanical methods for induction of labor (IOL) in pregnancies complicated by late fetal growth restriction.

Material and methods: Multicenter, retrospective, cohort study involving six referral centers in Italy and Spain. Inclusion criteria were pregnancies complicated by late fetal growth restriction as defined by Delphi consensus criteria. The primary outcome was the occurrence of uterine tachysystole; secondary outcomes were either cesarean delivery or operative vaginal delivery for non-reassuring fetal status, a composite score of adverse neonatal outcome and admission to neonatal intensive care unit (NICU). Univariate and multivariate logistic regression analysis was used to analyze the data.

Results: A total of 571 pregnancies complicated by late fetal growth restriction undergoing IOL (391 with dinoprostone and 180 with mechanical methods) were included in the analysis. The incidence of uterine tachysystole (19.2% vs. 5.6%; $p = 0.001$) was higher in women undergoing IOL with dinoprostone than in those undergoing IOL with mechanical methods. Similarly, the incidence of cesarean delivery or operative delivery for non-reassuring fetal status (25.6% vs. 17.2%; $p = 0.027$), composite adverse neonatal outcome (26.1% vs. 16.7%; $p = 0.013$) and NICU admission (16.9% vs. 5.6%; $p < 0.001$) was higher in women undergoing IOL with dinoprostone than in those undergoing IOL with mechanical methods. At logistic regression analysis, IOL with mechanical methods was associated with a significantly lower risk of uterine tachysystole (odds ratio 0.26, 95% confidence interval 0.13-0.54; $p < 0.001$).

Conclusions: In pregnancies complicated by late fetal growth restriction, IOL with mechanical methods is associated with a lower risk of uterine tachysystole, cesarean

Abbreviations: AC, abdominal circumference; CD, cesarean delivery; CI, confidence interval; CPR, cerebroplacental ratio; CTG, cardiotocography; EFW, estimated fetal weight; FGR, fetal growth restriction; IOL, induction of labor; NICU, neonatal intensive care unit; NRFS, non-reassuring fetal status; OR, odds ratio; UA-PI, uterine artery pulsatility index.

*Full list in Appendix 1.

delivery or operative delivery for non-reassuring fetal status, and adverse neonatal outcome compared with pharmacological methods.

KEYWORDS
Cook balloon catheter, dinoprostone, fetal growth restriction, Foley balloon catheter, induction of labor, late fetal growth restriction, mechanical induction, prostaglandins

1 | INTRODUCTION

Late fetal growth restriction (FGR) is associated with a high risk of short- and long-term adverse perinatal outcomes, including intrauterine fetal death, cesarean delivery (CD) for fetal distress, neonatal acidosis, admission to neonatal intensive care unit (NICU), poor school performance and occurrence of adult-onset metabolic disorders. [1–4]

Management of late FGR is challenging, particularly due to the lack of randomized controlled trials on the timing of delivery of these fetuses. Most guidelines are mainly 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. However, only few international societies report in their guidelines which method of IOL should be offered to pregnancies complicated by fetal FGR.[1,5]

In a recent systematic review, we have reported that, in pregnancies complicated by late-onset FGR, IOL with mechanical methods seem to be associated with a lower risk of adverse intrapartum outcomes compared to dinoprostone. However, the inclusion of non-randomized studies, small sample size and the heterogeneity in study design and outcome assessment did not provide robust evidence on which IOL method should be preferred.[6] Placental insufficiency and prolonged chronic hypoxemia characterizing late FGR pregnancies may lead to fetal decompensation during labor, especially once exposed to uterine hyperstimulation, thus highlighting the need for a careful choice of the optimal type of IOL in these women.[7]

The aim of this study was to compare vaginal dinoprostone and mechanical methods for IOL in pregnancies complicated by FGR.

> **Key message**
>
> Compared with prostaglandins, induction of labor with mechanical methods is associated with a lower risk of uterine tachysystole, cesarean delivery or operative delivery for non-reassuring fetal status, uterine tachysystole and adverse perinatal outcomes.

2 | MATERIAL AND METHODS

2.1 | Study design and participants

This was a multicenter, retrospective, cohort study involving six referral centers in Italy and Spain (Chieti, Madrid, Valencia, Naples, Modena and Brescia) from 2017 to 2020. A part of the present cohort was reported previously in another study from one of the participating centers.[8] Inclusion criteria were pregnancies complicated by late FGR (gestational age ≥32 weeks of gestation at diagnosis), as defined by the recently proposed Delphi consensus criteria, including[9]:

- abdominal circumference (AC) and/or estimated fetal weight (EFW) ratio <3rd centile

or at least two of three of the following:

- AC/EFW <10th centile
- AC/EFW crossing centiles >2 quartiles on growth centiles
- Cerebroplacental ratio (CPR) <5th centile or uterine artery pulsatility index (UA-PI) >95th centile.

Exclusion criteria were multiple gestations, pregnancies affected by early FGR (gestational age <32 weeks of gestation at diagnosis), structural or chromosomal anomalies, maternal medical complications or drug intake.

According to the local protocol, gestational age was defined either by crown-rump length during the first trimester ultrasound or by last menstrual period, using crown-rump length only when it differed from last menstrual period for more than 7 days.

Pulsed Doppler parameters were performed automatically from three or more similar and consecutive waveforms using ultrasound machines equipped with a 3.5-MHz convex probe, during fetal quiescence, in the absence of fetal tachycardia, and keeping the insonation angle as close as possible to 0°. The middle cerebral artery was examined at the point at which it passes the sphenoid wing, close to the circle of Willis, and the UA was examined at a free loop of the umbilical cord.[10] Once the diagnosis of late FGR was established, weekly scans including these Doppler examinations were performed until delivery, but only the data of the last exam before delivery were used for the analysis.

In the absence of absolute criteria coming from a randomized controlled trial, timing and mode of delivery were managed according to each local institution protocol, all having in common that IOL was recommended once 37–38 weeks were reached.

2.2 | Outcome measures

The primary outcome was the occurrence of uterine tachysystole during IOL, defined as the occurrence of more than five contractions in 10 min, in two successive 10-min periods, or averaged over a 30-min period.

Secondary outcomes were:

- CD or operative vaginal delivery for non-reassuring fetal status (NRFS). NRFS was defined as the presence of a suspicious or pathological cardiotocography tracings according to the Federation International of Gynecology and Obstetrics (FIGO) consensus guideline on cardiotocography interpretation during labor.[11]
- A composite score of adverse neonatal outcome, including 5-min Apgar score <7, umbilical cord pH <7.15,[12] necrotizing enterocolitis, neonatal respiratory (including respiratory distress syndrome, transient tachypnea of the newborn, continuous positive airway pressure for at least 24 h, mechanical ventilation, need for supplemental oxygen, pulmonary hypertension or bronchopulmonary dysplasia), neurological (including seizures, intraventricular hemorrhage or periventricular leukomalacia of any grade detected on ultrasound scan), infectious (including pneumonia, meningitis, culture proven sepsis), morbidity.
- Admission to NICU.

For the purpose of the analysis the study population was divided into two groups:

- Pregnancies undergoing IOL with vaginal dinoprostone (10 mg)
- Pregnancies undergoing IOL with mechanical methods (either Cook's or Foley ripening balloons)

Furthermore, we aimed to perform a subgroup analysis for the primary outcome considering fetuses AC and/or EFW ratio <3rd centile and those with AC/EFW <10th centile, AC/EFW crossing centiles >2 quartiles on growth centiles and/or CPR <5th centile or UA-PI >95th centile separately.

The dinoprostone vaginal insert contains 10 mg of dinoprostone dispersed throughout the matrix of a thin fat polymeric hydrogel drug delivery device. Mechanical methods involved either a double-balloon catheter (CRB plus stylet; Cook Medical) or a Foley balloon. The double-balloon catheter IOL consisted in placing the catheter through the internal cervical os, as part of a vaginal examination; 80 ml of saline was then instilled into the cervical and vaginal balloons. Foley balloon IOL consisted in placing the balloon above the level of the internal cervical os and filling it with 30–80 ml of sterile water, applying traction every 3 h.

2.3 | Statistical analyses

We compared the demographic and gestational characteristics, and the predefined outcomes between women undergoing IOL using dinoprostone vs cervical ripening balloon.

First, the differences in categorical and continuous variables by IOL mode were evaluated using the Chi-square test and Kruskal–Wallis test, respectively. The potential independent predictors of each outcome were then evaluated using multivariate logistic regression analysis.

In all models, induction mode, maternal age and ultrasound fetal parameters were included, whereas the other covariates were included only if significant at the 0.05 level (using a stepwise forward model fitting). A minimum events-to-variable ratio of 10 was always maintained to reduce overfitting. Among the recorded ultrasound fetal parameters, CPR and umbilicocerebral ratio (UCR) were highly collinear, as were gestational age at induction and gestational age at birth (Spearman ρ −0.99 and 0.95, respectively): we included the covariates with the higher R^2, namely CPR and gestational age at induction. Due to the slightly skewed distribution of the UCR (and CPR), the analyses were repeated including the variable after log-transformation, with no substantial changes. We thus included CPR in its original form.

Standard diagnostic procedures were adopted to check the validity of all models: influential observation analysis (Dbeta, change in Pearson chi-square), and Hosmer-Lemeshow test for the goodness of fit and C statistic (area under the receiving operator curve). Missing data were <5% in all primary analyses, thus no missing imputation technique was adopted. Statistical significance was defined as a two-sided $p < 0.05$, and all analyses were carried out using STATA, version 13.1 (Stata Corp.).

2.4 | Ethical approval

The study was approved by the Institutional Review Board of the Department of Medicine and Aging Sciences – University of Chieti "G. D'Annunzio," Italy (ref. 7/1a—July 2020) as a quality improvement study with anonymized data. The approval was sent to each participating center; however, according to their local academic institution and ethical committees, none of them required approval from an ethical committee.

3 | RESULTS

In all, 571 pregnancies complicated by late FGR undergoing IOL were included in the analysis, including 391 (68.5%) IOL with dinoprostone and 180 (31.5%) with mechanical methods. The general characteristics of the study population are shown in Table 1. Mean maternal age was 31.1 ± 6.1 years, and mean maternal body mass index (BMI) 23.8 ± 4.8 kg/m^2. The majority of the included women were white (84.4%) and nulliparous (79.7%). A prior CD was reported in 17.2% of women. Mean gestational age at last ultrasound was 37.0 ± 1.6 weeks and mean EFW was 2334 ± 323 g. Mean gestational age at IOL was 37.9 ± 1.4, and mean gestational age at delivery 38.1 ± 1.5 weeks.

When comparing maternal characteristics, there was a significant difference between women undergoing IOL with dinoprostone

TABLE 1 General characteristics of the study population

	Overall sample	Dinoprostone	Cervical ripening balloon	*p* value
Variables	(*n* = 571)	(*n* = 391)	(*n* = 180)	
Maternal characteristics				
Mean age, years (SD)	31.1 (6.1)	30.9 (5.9)	31.6 (6.5)	0.17
Mean BMI, kg/m^2 (SD)	23.8 (4.8)	23.4 (4.7)	24.5 (4.9)	0.011
Caucasian ethnicity, %	84.4	88.5	75.6	<0.001
Current smoking, %	11.4	7.7	19.4	<0.001
Pre-existing comorbidities[a], %	19.3	22.8	11.7	<0.001
Medical complications occurring in pregnancy[b], %	14.7	14.1	16.1	0.5
Parity status, %				
Nulliparous women	79.7	81.3	76.1	0.2
Primiparous women	15.4	14.8	16.7	0.8
Multiparous women	4.9	3.8	7.2	0.7
Previous CD, %[a]	17.2	17.8	16.3	0.8
IVF, %	4.9	4.9	5.0	0.9
PE, %	10.9	9.4	13.9	0.11
GDM, %	4.6	5.1	3.3	0.3
Mean GA at last US, weeks (SD)	37.0 (1.6)	37.3 (1.4)	36.5 (1.8)	<0.001
Mean EFW, MoM (SD)	1.00 (0.14)	0.96 (0.13)	1.02 (0.14)	<0.001
Labor induction, %				
Dinoprostone	68.5	—	—	—
Cervical ripening balloon	31.5	—	—	—
Ultrasound and perinatal parameters				
Mean fetal AC, MoM (SD)	1.00 (0.06)	0.98 (0.05)	1.08 (0.06)	<0.001
Mean UA-PI, MoM (SD)	1.01 (0.25)	1.05 (0.28)	1.00 (0.23)	0.037
Mean MCA-PI, MoM (SD)	1.00 (0.24)	1.02 (0.24)	0.99 (0.24)	0.166
Mean CPR, MoM (SD)	1.07 (0.41)	1.08 (0.48)	1.07 (0.38)	0.806
Oligohydramnios[c], %	8.1	9.9	3.9	0.013
Mean GA at induction (SD)	38.0 (1.4)	38.1 (1.44)	37.9 (1.4)	0.114
Median Bishop score (IQR)	2.0 (2.0)	2.0 (2.0)	3.0 (2.0)	0.561
Mean GA at birth (SD)	38.1 (1.5)	38.2 (1.5)	37.8 (1.4)	0.005
Male gender, %	46.2	47.3	43.9	0.4

Abbreviations: AC, abdominal circumference; BMI, body mass index; CD, cesarean delivery; CPR, cerebroplacental ratio; CPR, cerebroplacental ratio; EFW, estimated fetal weight; GA, gestational age; GDM, gestational diabetes mellitus; IQR, interquartile range; IVF, in vitro fertilization; MCA, middle cerebral artery; MoM, multiple of the median; PE, preeclampsia; PI, pulsatility index; SD, standard deviation; UA, umbilical artery; US, ultrasound.

[a]Defined as the presence of chronic hypertension, type I or II diabetes, autoimmune, inflammatory, cardiac, pulmonary or renal diseases.

[b]Defined as the presence of gestational hypertension, preeclampsia, gestational diabetes mellitus or intrahepatic cholestasis of pregnancy.

[c]Defined as maximum vertical pocket of amniotic fluid <2 cm on ultrasound.

and mechanical methods in terms of mean BMI (23.4 ± 4.7 vs. 24.5 ± 4.9; $p = 0.011$), white ethnicity (88.5% vs. 75.6%; $p < 0.001$), smoking during pregnancy (7.7% vs. 19.4%; $p < 0.001$), pre-existing comorbidities (14.1% vs. 16.1%; $p < 0.001$) and mean gestational age at last ultrasound (37.3 ± 1.4 vs. 36.5 ± 1.8; $p < 0.001$) (Table 1).

Furthermore, there was a significant difference between women undergoing IOL with dinoprostone and mechanical methods in terms of mean fetal AC multiple of the median (MoM) (0.98 ± 0.05 vs. 1.08 ± 0.06; $p < 0.001$), EFW MoM (0.96 ± 0.13 vs. 1.02 ± 0.14; $p < 0.001$), UA-PI MoM (1.05 ± 0.28 vs. 1.00 ± 0.23; $p = 0.037$ and the occurrence of oligohydramnios, defined as maximum vertical pocket of amniotic fluid <2 cm on ultrasound (9.9% vs. 3.9%; $p = 0.013$) (Table 1). Conversely, there was no difference in the mean Bishop score (2.0, vs. 3.0; $p = 0.560$) or gestational age at IOL (38.1 ± 1.4 vs. 37.9 ± 1.4; $p = 0.114$) (Table 1). There were no cases of uterine rupture or intrapartum fetal deaths.

The incidence of uterine tachysystole (19.2% vs. 5.6%; $p = 0.001$) was higher in women undergoing IOL with dinoprostone than in those undergoing IOL with mechanical methods.

Likewise, the incidence of CD or operative delivery for NRFS (25.6% vs. 17.2%; $p = 0.027$), composite adverse neonatal outcome (26.1% vs. 16.7%; $p = 0.013$) and NICU admission (16.9% vs. 5.6%; $p < 0.001$) was significantly higher in women undergoing IOL with dinoprostone than in those undergoing IOL with mechanical methods, whereas no difference was found when comparing Apgar score, neonatal pH at birth and respiratory distress syndrome (Table 2).

At logistic regression analysis, IOL with mechanical methods was associated with a significantly lower risk of uterine tachysystole (odds ratio (OR) 0.26, 95% confidence interval (CI) 0.13–0.54; $p < 0.001$), composite intrapartum outcome (OR 0.72, 95% CI 0.46–0.83; $p = 0.002$), CD/operative delivery for NRFS (OR 0.60, 95% CI 0.18–0.69; $p = 0.003$), and adverse neonatal outcome (OR: 0.60, 95% CI 0.36–0.99, $p = 0.046$) compared with IOL with dinoprostone (Table 3).

Finally, the incidence of uterine tachysystole was lower in pregnancies undergoing IOL with mechanical methods compared with dinoprostone both in fetuses with AC and/or EFW ratio <3rd centile (5.7% vs. 16.7%, $p = 0.01$) and in those with AC/EFW <10th centile, AC/EFW crossing centiles >2 quartiles on growth centiles and/or CPR <5th centile or UA-PI >95th centile separately (5.9% vs. 21.1%, $p < 0.001$).

4 | DISCUSSION

The findings from this study showed that in pregnancies affected by late FGR, IOL with mechanical methods was associated with a lower risk of uterine tachysystole, CD and operative delivery for NRFS compared with those undergoing induction with dinoprostone. Of note, IOL with mechanical methods was also associated with a lower incidence of composite adverse neonatal outcome and admission to NICU, regardless of perinatal fetal Doppler parameters, thus suggesting that, in pregnancies complicated by impaired placental function and chronic hypoxemia, the use of prostaglandins may lead to a higher risk of fetal decompensation.

To the best of our knowledge, this is the largest study comparing different types of IOL in pregnancies complicated by late FGR. Several systematic reviews on IOL were published recently. A 2016 network meta-analysis compared vaginal misoprostol, dinoprostone and Foley's catheter for cervical ripening during IOL and found that Foley's catheter was associated with the lowest rate of uterine hyperstimulation accompanied by FHR changes, although the lowest rate of CD was achieved when using oral misoprostol.[14] Another previous meta-analysis explored the effectiveness and safety of

TABLE 2 Primary and secondary outcomes

	Overall sample ($n = 571$)	Dinoprostone ($n = 391$)	Cervical ripening balloon ($n = 180$)	p value[b]
Uterine tachysystole, %	14.9	19.2	5.6	0.001
Cesarean delivery/ operative delivery for NRFS, %	22.9	25.6	17.2	0.027
Composite adverse neonatal outcome, %[a]	23.1	26.1	16.7	0.013
Mean neonatal birthweight in g (SD)	2410 (342)	2442 (342)	2340 (332)	0.001
Median 1-min Apgar score (IQR)	9.0 (1.0)	9.0 (1.0)	9.0 (1.0)	0.09
Median 5-min Apgar score (IQR)	10.0 (1.0)	10.0 (1.0)	10.0 (1.0)	0.08
Apgar score <7, %	2.1	2.1	2.2	0.9
Mean neonatal pH at birth (SD)	7.3 (0.08)	7.3 (0.08)	7.3 (0.09)	0.9
Abnormal neonatal pH, %	10.9	10.0	12.8	0.3
Respiratory distress, %	4.2	4.9	2.8	0.2
NICU admission, %	13.3	16.9	5.6	<0.001

Abbreviations: BMI, body mass index; IQR, interquartile range; NICU, neonatal intensive care unit; NRFS, non-reassuring fetal status; SD, standard deviation.

[a]Including 5 min Apgar score <7, umbilical cord pH <7.15, neonatal respiratory or neurological morbidity.

[b]Chi-square test and Kruskal–Wallis test for categorical and continuous variables, respectively.

TABLE 3 Logistic regression predicting composite adverse intrapartum outcome[a], uterine tachysystole or cesarean section/operative delivery for non-reassuring fetal status (NRFS)

	Composite intrapartum outcome (n = 152)		Uterine tachysystole (n = 85)		Cesarean section/operative delivery for NRFS (n = 131)	
Variables	OR (95% CI)	*p* value	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Maternal age[a]						
1-year increase	1.04 (1.01–1.08)	0.020	1.06 (1.01–1.10)	0.008	1.03 (0.99–1.07)	0.07
Maternal BMI, 1-unit increase	0.99 (0.96–1.04)	0.9	0.96 (0.91–1.02)	0.17	1.01 (0.97–1.06)	0.6
Smoke						
No	1 (ref. cat.)	—	1 (ref. cat.)	—	1 (ref. cat.)	—
Yes	0.71 (0.35–1.41)	0.3	0.19 (0.17–1.46)	0.2	0.65 (0.30–1.41)	0.3
Pre-existing comorbidities						
No	1 (ref. cat.)	—	—	—	1 (ref. cat.)	—
Yes	0.99 (0.61–1.63)	0.9	—	—	0.91 (0.54–1.54)	0.7
Pregnancy comorbidities						
No	1 (ref. cat.)	—	—	—	1 (ref. cat.)	—
Yes	2.02 (1.03–3.95)	0.039	—	—	2.94 (1.44–6.02)	0.003
Parity status						
Nulliparous	1 (ref. cat.)	—	1 (ref. cat.)	—	1 (ref. cat.)	—
Primiparous/multiparous	0.56 (0.32–0.97)	0.041	0.80 (0.40–1.58)	0.5	0.35 (0.18–0.69)	0.003
Labor induction						
Dinoprostone	1 (ref. cat.)	—	1 (ref. cat.)	—	1 (ref. cat.)	—
Cervical ripening balloon	0.72 (0.46–0.83)	0.002	0.26 (0.0.13–0.54)	<0.001	0.60 (0.36–0.99)	0.046
Oligohydramnios[b]						
No	1 (ref. cat.)	—	—	—	1 (ref. cat.)	—
Yes	1.39 (0.71–2.74)	0.3	—	—	1.14 (0.55–2.36)	0.7
Preeclampsia						
No	1 (ref. cat.)	—	—	—	1 (ref. cat.)	—
Yes	0.45 (0.20–1.01)	0.054	—	—	0.29 (0.12–.0.71)	0.007
Gestational diabetes						
No	1 (ref. cat.)	—	—	—	1 (ref. cat.)	—
Yes	1.16 (0.47–2.90)	0.8	—	—	0.83 (0.30–2.27)	0.7
Fetal abdominal circumference, 1-mm increase	0.99 (0.97–1.00)	0.068	0.99 (0.98–1.01)	0.5	0.98 (0.97–0.99)	0.014
CPR, 1-unit decrease	2.51 (1.31–4.82)	0.006	2.61 (1.17–5.82)	0.019	2.51 (1.26–5.00)	0.009
Gestational age at induction, 1-week increase	1.12 (0.95–1.33)	0.18	1.17 (0.94–1.45)	0.16	1.12 (0.93–1.34)	0.2
Birthweight, 10-g increase	0.99 (0.98–1.00)	0.18	—	—	0.99 (0.98–1.00)	0.2
Bishop score[a]						
1-unit increase	0.89 (0.79–1.02)	0.09	0.84 (0.71–0.99)	0.038	0.82 (0.71–0.95)	0.008

Note: In all models, maternal age and induction mode were included a priori.

Abbreviations: AC, abdominal circumference; BMI, body mass index; CI, confidence interval; CPR, cerebroplacental ratio; GA, gestational age; OR, odds ratio; Ref. cat., reference category.

[a]All models were repeated including age and Bishop score as continuous or dichotomic variables.

[b]Defined as maximum vertical pocket of amniotic fluid <2 cm on ultrasound.

prostaglandins used for IOL and found that low dose of titrated oral misoprostol solution had the lowest probability of CD, whereas vaginal misoprostol had the highest probability of achieving a vaginal delivery within 24 h.[15] However, neither of these reviews included or stratified their analysis, considering only pregnancies complicated by impaired fetal growth, thus making their findings not entirely applicable to pregnancies complicated by late-onset FGR.

The large sample size and the data coming from all referral centers for the surveillance and management of FGR, inclusion of true cases of late FGR as defined by the Delphi consensus criteria[8] and multitude of outcomes explored represent the main strengths of this study. The retrospective, non-randomized design represents the main weakness of the present study, mostly because two interventions are compared. Furthermore, the population analyzed was not completely homogeneous as regards the main maternal and pregnancy characteristics and it is entirely possible that certain maternal and pregnancy characteristics not assessed in this series might have affected the results. More importantly, the choice of the primary type IOL (dinoprostone or mechanical methods) was not conducted in a randomized manner. Moreover, the inclusion of data from previously published results might introduce a bias, although representing a small part of the total sample size. Finally, despite the relatively large sample size, the low incidence of some of the outcomes explored may have made the study underpowered for their analysis.

There is currently no randomized controlled trial comparing the different types of IOL in pregnancies complicated by late FGR and only a few observational studies focused on FGR have been published recently.[13,15] The DIGITAT trial is the main randomized controlled trial regarding late FGR, mainly focused on timing of delivery, and reported no differences in adverse outcomes between induction of labor and expectant monitoring in women with suspected intrauterine growth restriction at term. However, that study did not report Doppler data and the diagnosis of FGR was based on clinical suspicion, making the results of that trial not applicable to pregnancies complicated by late FGR as defined by the recent consensus criteria.[16]

Although evidence from observational studies and non-randomized series would recommend that pregnancies complicated by late FGR should undergo IOL at 37–38 weeks of gestation, there is still uncertainty as to how to induce these women, and none of the national and international societies reports in their guidelines which method of IOL should be offered to pregnancies complicated by late onset FGR.[1,5,17]

Villalain et al. reported a lower risk for uterine tachysystole (4.2% vs. 16.9%) and CD (15.5% vs. 37.7%) in IOL with Foley balloon than with IOL with dinoprostone in late FGR fetuses;[8] the authors reported in their logistic regression model that the use of a Foley balloon was the only modifiable risk factor which led to a higher chance of vaginal delivery. Conversely, Duro-Gomez et al did not find any difference between prostaglandins and mechanical methods concerning the risk of CD, uterine tachysystole, NRFS or neonatal adverse events, although the authors did not include fetuses with abnormal Dopplers.[13] However, such studies largely differ in regard to the definition of late FGR, thus making a direct comparison between populations 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.[18,19] Compared with appropriate-for-gestational-age fetuses, late FGR fetuses have a lower pre-labor pO_2 and pH with a greater fall in pH and higher lactate levels when FHR decelerations are present.[20–23] Thus, the choice of an optimal method to induce labor is fundamental, as these pregnancies are already complicated by chronic hypoxemia and undernutrition, which increases the risk of NRFS and fetal distress.[24]

In the present study, IOL with mechanical methods was associated with a lower risk of CD and operative delivery for NRFS and uterine tachysystole.

Of note, IOL with mechanical methods was also associated with a lower incidence of composite adverse neonatal outcome and admission to NICU, although the mean UA-PI was significantly higher in fetuses undergoing IOL with mechanical methods, suggesting that mechanical methods may lead to better perinatal outcomes, regardless of fetal perinatal Doppler status. Furthermore, the association between mechanical methods and better perinatal outcomes was strengthened when considering that some important maternal and fetal parameters such as mean BMI, mean EWF, mean AC and mean neonatal birthweight, were significantly worse in women undergoing IOL with mechanical methods, providing further evidence of the efficacy and safety of mechanical cervical ripening in fetuses affected by late FGR.

These findings are not surprising, as mechanical IOL is likely to have a minor impact on placental perfusion and fetal hemodynamics compared with dinoprostone, likely due to the more gradual stretching of the cervix and the slower release of prostaglandins.[23] Conversely, prostaglandins may determine an excessive uterine stimulation, potentially leading to sudden decompensation in an already compromised fetus.[17,25]

5 | CONCLUSION

In pregnancies complicated by late FGR, IOL with mechanical methods was associated with a lower risk of uterine tachysystole, CD and operative delivery for NRFS, composite adverse neonatal outcome and admission to NICU, suggesting that non-pharmacological IOL might be judiciously considered the first choice when inducing pregnancies complicated by impaired fetal growth. However, a properly designed randomized controlled trial comparing the impact of different methods of IOL in pregnancies complicated by late FGR is urgently required.

CONFLICT OF INTEREST

None.

REFERENCES

1. Lees CC, Stampalija T, Baschat AA, et al. ISUOG practice guidelines: diagnosis and management of small-for-gestational-age fetus and fetal growth restriction. *Ultrasound Obstet Gynecol*. 2020;56:298–312.
2. Cruz-Martinez R, Savchev S, Cruz-Lemini M, Mendez A, Gratacos E, Figueras F. Clinical utility of third-trimester uterine artery Doppler in the prediction of brain hemodynamic deterioration and adverse perinatal outcome in small-for-gestational-age fetuses. *Ultrasound Obstet Gynecol*. 2015;45:273–278.
3. Figueras F, Savchev S, Triunfo S, Crovetto F, Gratacos E. An integrated model with classification criteria to predict small-for-gestational-age fetuses at risk of adverse perinatal outcome. *Ultrasound Obstet Gynecol*. 2015;45:279–285.

4. Cruz-Martínez R, Figueras F, Hernandez-Andrade E, Oros D, Gratacos E. Fetal brain Doppler to predict cesarean delivery for nonreassuring fetal status in term small-for-gestational-age fetuses. *Obstet Gynecol*. 2011;117:618–626.
5. The American College of Obstetricians and Gynecologists. Medically indicated late-preterm and early-term deliveries. ACOG Committee Opinion No. 764. *Obstet Gynecol*. 2019;133:151–155.
6. Familiari A, Khalil A, Rizzo G, et al. 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. *Eur J Obstet Gynecol Reprod Biol*. 2020;252:455–467.
7. Garcia-Simon R, Figueras F, Savchev S, Fabre E, Gratacos E, Oros D. Cervical condition and fetal cerebral Doppler as determinants of adverse perinatal outcome after labor induction for late-onset small-for-gestational-age fetuses. *Ultrasound Obstet Gynecol*. 2015;46:713–717.
8. Villalain C, Herraiz I, Quezada M, et al. Labor induction in late-onset fetal growth restriction: Foley balloon versus vaginal dinoprostone. *Fetal Diagn Ther*. 2019;46:67–74.
9. Gordijn SJ, Beune IM, Thilaganathan B, et al. Consensus definition of fetal growth restriction: a Delphi procedure. *Ultrasound Obstet Gynecol*. 2016;48:333–339.
10. Bhide A, Acharya G, Bilardo CM, et al. ISUOG practice guidelines: use of Doppler ultrasonography in obstetrics. *Ultrasound Obstet Gynecol*. 2013;41:233–239.
11. Ayres-de-Campos D, Spong CY, Chandraharan E, FIGO Intrapartum Fetal Monitoring Expert Consensus Panel. FIGO consensus guidelines on intrapartum fetal monitoring: Cardiotocography. *Int J Gynaecol Obstet*. 2015;131:13–24.
12. Nordstrom L, Arulkumaran S. In: Asphyxia P, Arulkumaran S, Jenkins HML, eds. *Biochemical Monitoring of Intra-partum Asphyxia*. Hyderabad: Orient Longman; 2000;156–171.
13. Duro-Gómez J, Garrido-Oyarzún MF, Rodríguez-Marín AB, de la Torre González AJ, Arjona-Berral JE, Castelo-Branco C. Efficacy and safety of misoprostol, dinoprostone and Cook's balloon for labour induction in women with foetal growth restriction at term. *Arch Gynecol Obstet*. 2017;296:777–781.
14. Chen W, Xue J, Peprah MK, et al. A systematic review and network meta-analysis comparing the use of Foley catheters, misoprostol, and dinoprostone for cervical ripening in the induction of labor. *BJOG*. 2016;123:346–354.
15. Alfirevic Z, Keeney E, Dowswell T, et al. Labour induction with prostaglandins: a systematic review and network meta-analysis. *BMJ*. 2015;350:h217.
16. Boers KE, Vijgen SMC, Bijlenga D, et al. Induction versus expectant monitoring for intrauterine growth restriction at term: randomised equivalence trial (DIGITAT). *BMJ (Clin Res ed.)*. 2010;341:c7087.
17. Royal College of Obstetricians and Gynaecologists (RCOG). *The Investigation and Management of the Small-for-Gestational-Age Fetus. Green-top Guideline No.31*. London, UK: RCOG Press; 2013. https://www.rcog.org.uk/en/guidelines-research-services/guidelines/gtg31/. Accessed October 1, 2020.
18. Rhoades JS, Rampersad RM, Tuuli MG, Macones GA, Cahill AG, Stout MJ. Delivery outcomes after term induction of labor in small-for-gestational age fetuses. *Am J Perinatol*. 2017;34:544–549.
19. Savchev S, Figueras F, Cruz-Martinez R, Illa M, Botet F, Gratacos E. Estimated weight centile as a predictor of perinatal outcome in small-for-gestational-age pregnancies with normal fetal and maternal Doppler indices. *Ultrasound Obstet Gynecol*. 2012;39:299–303.
20. D'Antonio F, Rizzo G, Gustapane S, et al. Diagnostic accuracy of Doppler ultrasound in predicting perinatal outcome in pregnancies at term: a prospective longitudinal study. *Acta Obstet Gynecol Scand*. 2020;99:42–47.
21. Buca D, Rizzo G, Gustapane S, et al. Diagnostic accuracy of Doppler ultrasound in predicting perinatal outcome in appropriate for gestational age fetuses: a prospective study. *Ultraschall Med*. 2020. https://doi.org/10.1055/a-1072-5161
22. Buca D, Liberati M, Rizzo G, et al. Pre- and postnatal brain hemodynamics in pregnancies at term: correlation with Doppler ultrasound, birthweight, and adverse perinatal outcome. *J Matern Fetal Neonatal Med*. 2020;9:1–7.
23. Di Mascio D, Rizzo G, Buca D, et al. Comparison between cerebroplacental ratio and umbilicocerebral ratio in predicting adverse perinatal outcome at term. *Eur J Obstet Gynecol Reprod Biol*. 2020;252:439–443.
24. Parisi S, Monzeglio C, Attini R, et al. Evidence of lower oxygen reserves during labour in the growth restricted human foetus: a retrospective study. *BMC Pregnancy Childbirth*. 2017;17:209.
25. de Vaan MDT, ten Eikelder MLG, Jozwiak M, et al. Mechanical methods for induction of labour. *Cochrane Database Syst Rev*. 2019;10:CD001233.

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APPENDIX 1

The complete *induCtion of labOr in Late fetaL Growth rEstriction* (COLLEGE) Study Group:

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