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Association of Prostaglandin Use for Cervical Ripening with Mode of Delivery in Small for Gestational Age versus Non–Small for Gestational Age Neonates

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Abstract

Objective Prostaglandins (PGs) use for cervical ripening with small for gestational age (SGA) fetuses is controversial since it remains uncertain if use increases the chance of cesarean delivery (CD). We aimed to assess the association between PG use for cervical ripening and mode of delivery between SGA and appropriate for gestational age (AGA) neonates.

Study Design Secondary analysis of the Nulliparous Pregnancy Outcomes Study: Monitoring Mothers-to-Be (nuMoM2b), a prospective observational cohort study of 10,038 nulliparas. We included women undergoing induction with nonanomalous fetuses in the cephalic presentation. Women with >2 cm cervical dilation or prior uterine scar were excluded. We assessed the association of PG use with CD among women with SGA and AGA neonates. SGA was defined as birth weight <10th percentile for gestational age and sex. Multivariable logistic regression was used to adjust for potential confounders and test for interaction. Secondary outcomes included adverse neonatal outcomes, indication for CD, maternal hemorrhage, and chorioamnionitis.

Results Among 2,353 women eligible, PGs were used in 54.8%, SGA occurred in 15.1%, and 35.0% had CD. The association between PG use and CD differed significantly (interaction $p = 0.018$) for SGA versus AGA neonates; CD occurred more often in SGA neonates exposed to PGs than not (35 vs. 22%, $p = 0.009$). PG use was not associated with CD among AGA neonates (36 vs. 36%, $p = 0.8$). This effect remained significant

Keywords
- labor Induction
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- small for gestational age
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when adjusting for body mass index, race/ethnicity, and cervical dilation. Among SGA neonates, CD for "nonreassuring fetal status" was similar between PG groups. Among SGA neonates, PG use was not associated with adverse neonatal outcomes or postpartum hemorrhage but had a higher rate of chorioamnionitis (7.0 vs. 2.1%, $p = 0.048$).

Conclusion PG use was associated with a higher rate of CD in SGA but not AGA neonates; however, further studies are needed before PG use is discouraged with SGA neonates.

Key Points

- PGs are commonly used for cervical ripening.
- PG use was associated with increased risk of cesarean delivery in SGA neonates.
- PG use was not associated with adverse neonatal outcomes.

Fetal growth restriction (FGR) is a leading cause of perinatal morbidity and mortality,[1,2] affecting 7 to 10% of all infants globally.[3] Historically, multiple terms have been used to describe a fetus that has not yet met its growth potential, including FGR and small for gestational age (SGA). FGR is commonly defined as an ultrasound-estimated fetal weight less than the 10th percentile for that gestational age, and SGA is defined as birth weight less than the 10th percentile for gestational age and sex.[4–7] The prevalence of SGA has been estimated to be 10% in the United States, and approximately 30% worldwide; in some countries it is as high as 47%.[3,8]

FGR is associated with neonatal morbidity due to complications of prematurity and perinatal mortality.[1,2,9–11] In order to mitigate the risk of stillbirth, delivery is often warranted once the fetal risks of continuing pregnancy are deemed to outweigh the risk of neonatal complications.[9–11] Although recent recommendations discuss consideration of cesarean delivery among those with FGR with severe placental insufficiency (e.g., absent or reversed end-diastolic umbilical arterial velocity), labor induction remains common practice in the setting of FGR.[7]

The ideal approach to labor induction in the context of suspected poor fetal growth remains uncertain. If the cervix is unfavorable, cervical ripening is often performed using prostaglandin (PG) analog or a cervical balloon. The two PG agents most widely utilized for cervical ripening are dinoprostone (PGE2) and misoprostol (PGE1). Dinoprostone is the only U.S. Food and Drug Administration-approved PG agent for cervical ripening, but because of higher cost and cold storage requirements, misoprostol is more widely used off-label.[12] Misoprostol has proven to be an effective method for cervical ripening in labor induction, but is associated with higher risk of tachysystole with associated fetal heart rate changes than dinoprostone.[13–15] This problem has not been associated with risk for cesarean delivery in normally grown fetuses.[14,15] However, in the setting of poor fetal growth especially when associated with placental insufficiency, fetuses may not tolerate tachysystole and may be more prone to unscheduled urgent or emergent cesarean delivery. The objective of this study was to determine if PG use, compared to other labor cervical ripening methods, is associated with differences in mode of delivery between SGA and appropriate for gestational age (AGA) neonates.

Materials and Methods

Participants and Recruitment

We performed a secondary analysis of the Nulliparous Pregnancy Outcomes Study: Monitoring Mothers-to-Be (nuMoM2B). The prospective observational nuMoM2b cohort was funded by the Eunice Kennedy Shriver National Institute of Child Health and Human Development to identify risk factors predictive of adverse pregnancy outcomes. Full details on the methods of this study have been previously published.[16] Institutional review board approval was obtained prior to the study at each participating site and the data coordinating center and all participants gave written informed consent.

In nuMoM2B, 10,038 nulliparous women with singleton gestations were recruited from eight clinical centers in the U.S. study visits were conducted during three separate time periods over pregnancy ($6^{0/7}$–$13^{6/7}$, $16^{0/7}$–$21^{6/7}$, and $22^{0/7}$–$29^{6/7}$ weeks) where demographic, clinical, and biomarker data were collected. Outcomes were then abstracted from medical records following delivery.

In this secondary analysis, participants were included if they had a cephalic-presenting live fetus and underwent labor induction with a starting cervical examination consistent with a need for cervical ripening. For the purpose of this study, we defined the need for cervical ripening as cervical dilation of 2 cm or less. Data on other cervical examination parameters were not available. Participants were excluded if they had prenatally diagnosed fetal anomalies, defined as any malformation predisposing to adverse perinatal outcomes or neonatal surgical intervention. Women with any prior uterine scar were also excluded as this is a contraindication to PG use for labor induction. In cases where key variables such as initial cervical examination and birth weight classification were not available, participants were also excluded.

We chose to use birth weight–derived SGA diagnosis instead of prenatal FGR diagnosis to define our comparison groups for logistical reasons. Third trimester ultrasounds for nuMoM2B were performed earlier in gestation than most FGR cases would be expected to be detected. Also, clinically indicated ultrasound data were not universally available. Thus, to avoid missed diagnoses and systematic misclassification of FGR in this cohort, we chose to use the neonatal designation of SGA.

Outcomes, Measures, and Definitions

The primary outcome was mode of delivery. Vaginal deliveries included all successful operative vaginal deliveries, such as forceps or vacuum-assisted. Prespecified secondary outcomes included fetal acidemia (umbilical artery pH of <7.2), nonreassuring fetal status as an indication for cesarean delivery, neonatal intensive care unit admission, respiratory distress syndrome, intrapartum or neonatal death, 5-minute Apgar's score less than 7, maternal hemorrhage, and chorioamnionitis. Induction protocols were chosen at the discretion of the provider and included the PG agents, misoprostol or dinoprostone. Participants were included in the PG exposure group if they received a PG agent at any time during cervical ripening or labor induction. SGA was defined as a birth weight $<$10th percentile for gestational age and sex based on the Alexander birth weight standard.[17] AGA was defined as birth weight $\geq$ 10th percentile. While this group also includes large for gestational age infants, we refer to it as AGA in the article for simplicity. Gestational age was determined using standard and precise criteria at study eligibility screening, and birth weights were obtained by medical record abstraction.

Feasibility Assessment/Power Estimate

From the nuMoM2b cohort, we anticipated 2,365 deliveries would meet inclusion criteria for our analysis. Among these, rates of cesarean delivery, PG use, and SGA were 35, 55, and 15%, respectively. As such, this study was expected to achieve 80% power in a logistic regression model of cesarean delivery to detect a PG-SGA interaction with odds ratio (OR) 1.95 at alpha $= 0.05$ using a two-sided Wald's test.

Statistical Analysis

Right-skewed continuous variables are summarized with geometric mean and 95% confidence interval (CI), otherwise continuous measures are presented as mean and standard error, categorical measures are summarized as frequency and percentage. Patient demographic, socioeconomic, medical, and obstetrical characteristics were compared by SGA and non-SGA and PG and non-PG use status. A logistic regression model of cesarean delivery included an interaction between PGs and SGA; an adjusted model considered adjusting for demographic and clinical characteristics, with a parsimonious model achieved through backwards selection. A priori characteristics for inclusion in the model, determined by clinical relevance, included membrane rupture prior to cervical ripening, placental abruption, or nonreassuring fetal status as indications for delivery, gestational age at induction of labor, and hypertensive disorders of pregnancy. Among the subset of SGA deliveries, differences in secondary outcomes were assessed with Chi-square. A p-value of 0.05 was considered statistically significant. All analyses were conducted in SAS v9.4, with graphics created using GraphPad prism 8.3.

Results

Of the 10,038 women enrolled in the nuMoM2b study, 2,339 met study inclusion criteria for this secondary analysis (►Fig. 1). Cervical ripening and labor induction methods are summarized in ►Fig. 2. PGs were used in either cervical ripening or labor induction in the majority of deliveries, followed by oxytocin, amniotomy, and/or cervical balloon catheter. Many women received more than one agent. As seen in ►Table 1, the most common indications for labor induction included late-term or post-dates gestation, hypertensive disorders complicating pregnancy, and "other." For our study population, the overall proportions of SGA and cesarean delivery were 15 and 35%, respectively.

Characteristics of study participants included in this analysis are shown in ►Table 2. The average age of the participants was 26. Most participants were non-Hispanic white, of normal weight for height, completed a college degree, and had an annual income greater than 200% of the U.S. federal poverty level. There were no significant demographic or socioeconomic differences by PG use within the SGA subset. Women who received PGs had lower rates of chronic hypertension and were more likely to have a closed cervix on admission than women who did not receive PGs. Within the AGA subset, there were multiple demographic and socioeconomic differences by PG use. Women undergoing labor induction with PGs were younger, more often non-Hispanic white, more likely to have an education level below that of a high-school graduate, less likely to have household income above 200% of the federal poverty level, and had a higher body mass index (BMI). Additionally, within the AGA subset, women who received PGs delivered at an earlier gestational age, were more likely to have a closed cervix on admission, and less likely to have eclampsia.

The unadjusted results of our primary outcome, shown in ►Table 3, revealed a different relationship between PG use and cesarean delivery for SGA and AGA infants (p-value for interaction $= 0.02$). SGA neonates with PG exposure had a higher likelihood of cesarean delivery compared to SGA neonates without PG exposure (36 vs. 22%, $p = 0.007$; OR $= 1.9$, 95% CI: 1.19–3.16; ►Table 3). There was no difference in likelihood of cesarean delivery with PG use among AGA neonates (36 vs. 36%, $p = 0.8$, OR $= 1.0$, 95% CI: 0.85–1.23; ►Table 3). After adjusting for BMI, race/ethnicity, hypertensive disorders of pregnancy, gestational age at delivery, and cervical dilation prior to labor induction, the association among SGA neonates of PG exposure with cesarean delivery remained significant (►Fig. 3). PG use was neither associated with cesarean delivery for fetal intolerance of labor (►Table 4) nor with any other specific indication for cesarean delivery in SGA neonates (data not shown). To address possible bias arising from clinicians choosing to use PGs less often in pregnancies with suspected FGR, we

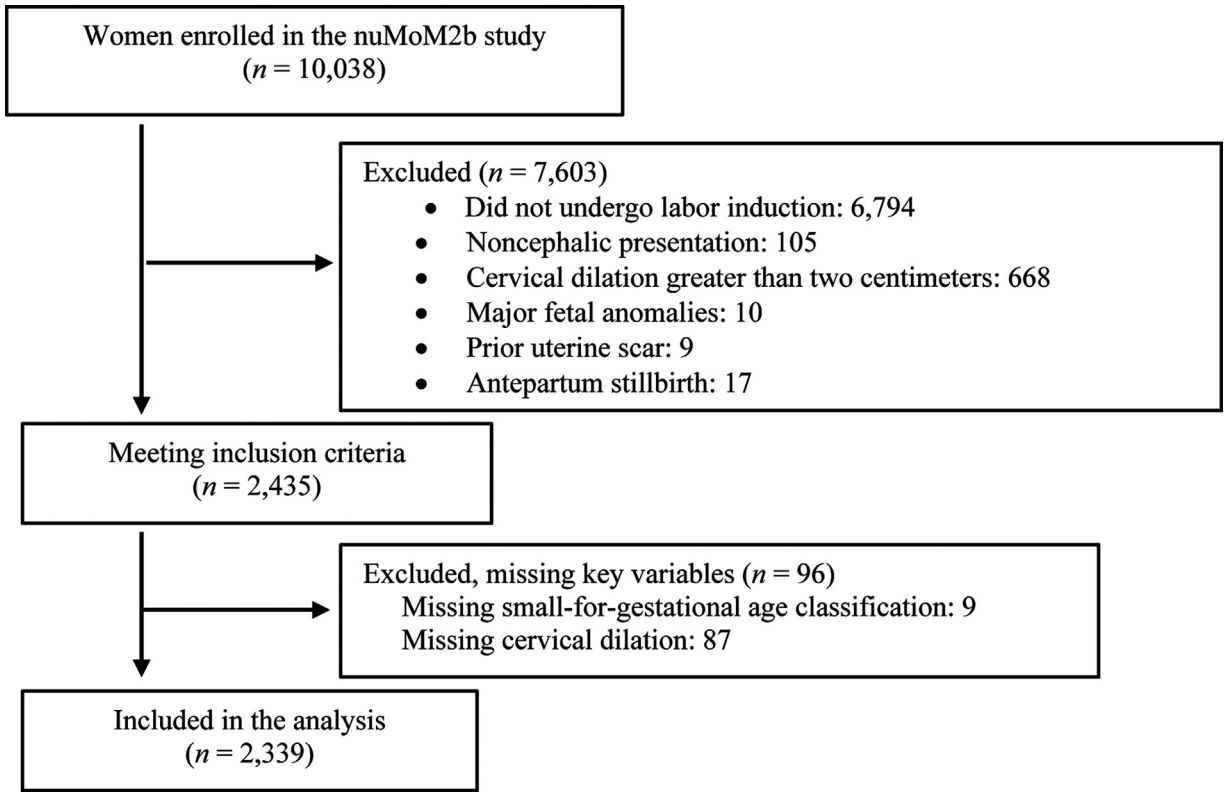

Fig. 1 Flowchart of participant exclusions. Note: Exclusion criteria listed as mutually exclusive frequencies among nested populations. nuMoM2B, nulliparous pregnancy outcomes study: monitoring mothers-to-be.

assessed the rate of PG use according to prenatal suspicion for FGR and found that PGs were actually used more often in cases of suspected FGR (data not shown).

Among SGA neonates, PG was not significantly associated with any adverse neonatal outcomes (►Table 4). Exposure to PG was not associated with significantly increased adverse maternal outcomes of postpartum hemorrhage or extrauterine infections but was associated with more frequent chorioamnionitis. This association appears to be driven by higher frequency of postpartum fever with PG use more so than other chorioamnionitis criteria, which were not significantly different between PG exposure groups (►Table 4).

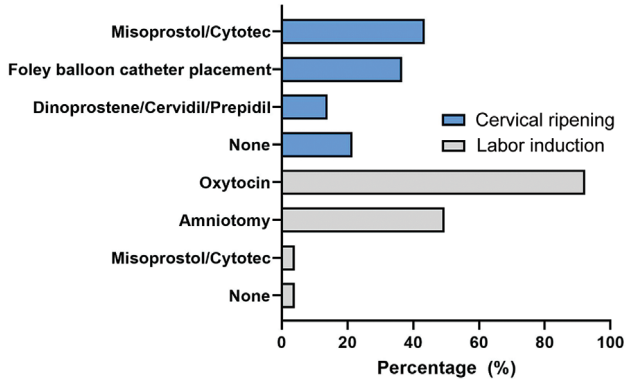

Fig. 2 Methods of cervical ripening and labor induction. Note: Methods are not graphically represented if utilized by <1% of cohort, but included "laminaria" and "other."

Discussion

In this secondary analysis of nuMoM2b study, our objective was to determine whether PG use for cervical ripening or labor induction was associated with differences in mode of delivery between SGA and AGA neonates. Nulliparous women with SGA infants who received PGs were at increased risk of cesarean delivery compared to those not receiving PGs, including after adjustment for multiple factors including cervical favorability on admission (OR = 1.77, $p = 0.011$).

Table 1 Indications for delivery

Primary indication for delivery	*n* (%)
Other maternal or fetal condition	806 (34.52)
Post due date	617 (26.42)
Rupture of membranes	192 (8.22)
Oligohydramnios/anhydramnios	187 (8.01)
Abnormal fetal testing	157 (6.72)
Scheduled, no reason found, other	129 (5.52)
Labor	114 (4.88)
Intrauterine fetal growth restriction	99 (4.24)
Polyhydramnios	15 (0.64)
Abruptio placenta	9 (0.39)
Intra-amniotic infection/chorioamnionitis	4 (0.17)
Intrauterine fetal demise	3 (0.13)
Placenta previa	3 (0.13)

Table 2 Participant characteristics

Characteristic at visit 1	Value	SGA		*p*	Not SGA		*p*
		PGs $n=211$	No PGs $n=140$		PGs $n=1,066$	No PGs $n=922$	
Age (y)	Gestational mean (95% GMCI)	24.6 (23.86, 25.43)	25.4 (24.44, 26.31)	0.244	26.1 (25.76, 26.44)	26.8 (26.40, 27.14)	**0.009**
Race/ethnicity	Non-Hispanic white	86 (40.95)	77 (55.00)	0.074	605 (56.75)	596 (64.64)	**<0.001**
	Non-Hispanic black	57 (27.14)	32 (22.86)		205 (19.23)	117 (12.69)	
	Hispanic	42 (20.00)	19 (13.57)		167 (15.67)	151 (16.38)	
	Asian	9 (4.29)	7 (5.00)		20 (1.88)	22 (2.39)	
	Other	16 (7.62)	5 (3.57)		69 (6.47)	36 (3.90)	
Education attained	Less than high school graduation	30 (14.29)	16 (11.43)	0.403	99 (9.29)	72 (7.82)	**0.048**
	High school graduation or GED	39 (18.57)	17 (12.14)		137 (12.85)	92 (9.99)	
	Some college	46 (21.90)	33 (23.57)		231 (21.67)	190 (20.63)	
	Associate/technical degree	18 (8.57)	19 (13.57)		121 (11.35)	90 (9.77)	
	Completed college	42 (20.00)	28 (20.00)		273 (25.61)	269 (29.21)	
	Degree beyond college	35 (16.67)	27 (19.29)		205 (19.23)	208 (22.58)	
Poverty category	>200%	90 (62.07)	70 (66.67)	0.517	534 (62.02)	549 (75.21)	**<0.001**
	100–200%	20 (13.79)	16 (15.24)		155 (18.00)	83 (11.37)	
	<100%	35 (24.14)	19 (18.10)		172 (19.98)	98 (13.42)	
BMI (kg/m^2)	Gestational mean (95% GMCI)	26.6 (25.68, 27.63)	26.0 (24.95, 27.04)	0.369	27.9 (27.54, 28.34)	26.7 (26.34, 27.13)	**<0.001**
Chronic hypertension	Yes	9 (4.29)	19 (13.57)	**0.002**	49 (4.60)	38 (4.13)	0.609
Diabetes	Pregestational diabetes	3 (1.42)	4 (2.86)	0.437	34 (3.19)	25 (2.71)	0.643
	Gestational diabetes	8 (3.79)	8 (5.71)		69 (6.47)	53 (5.75)	
	No diabetes	200 (94.79)	128 (91.43)		963 (90.34)	844 (91.54)	
At delivery							
Preeclampsia/gestation hypertension	Eclampsia	0 (0)	0 (0)	**0.049**	0 (0.00)	2 (0.22)	**0.008**
	Superimposed preeclampsia	4 (1.90)	6 (4.29)		9 (0.84)	8 (0.87)	
	Severe preeclampsia	34 (16.19)	11 (7.86)		58 (5.44)	52 (5.65)	
	Mild preeclampsia	9 (4.29)	5 (3.57)		62 (5.82)	31 (3.37)	
	Antepartum gestational hypertension	19 (9.05)	16 (11.43)		114 (10.69)	127 (13.79)	
	Intrapartum or postpartum hypertension	14 (6.67)	19 (13.57)		116 (10.88)	127 (13.79)	
	No hypertensive disorder	130 (61.90)	83 (59.29)		707 (66.32)	574 (62.32)	
Gestational age	Preterm delivery (<37 wk)	41 (19.43)	19 (13.57)	0.153	83 (7.79)	57 (6.18)	0.163

Table 2 (*Continued*)

Characteristic	Value	SGA		*p*	Not SGA		*p*
at visit 1		PGs $n = 211$	No PGs $n = 140$		PGs $n = 1,066$	No PGs $n = 922$	
	GA at delivery 37 wk+	170 (80.57)	121 (86.43)		983 (92.21)	865 (93.82)	
Gestational age	Mean (SE)	38.0 (0.14)	38.2 (0.18)	0.501	39.1 (0.06)	39.3 (0.06)	**0.003**
Cervical examination at admission	0	96 (45.50)	23 (16.43)	<**0.001**	349 (32.74)	138 (14.97)	<**0.001**
	.5	0 (0)	0 (0)		4 (0.38)	0 (0.00)	
	1	97 (45.97)	77 (55.00)		518 (48.59)	446 (48.37)	
	2	18 (8.53)	40 (28.57)		195 (18.29)	338 (36.66)	
Rupture of membranes	Premature	16 (7.58)	18 (12.86)	0.102	119 (11.16)	69 (7.48)	**0.005**
Indication for labor	Abruption or nonreassuring fetal status	10 (4.74)	8 (5.71)	0.685	41 (3.85)	24 (2.60)	0.12

Abbreviations: BMI, body mass index; GA, gestational age; GED, General Educational Development; GMCI, gestational mean confidence interval; PG, prostaglandin; SE, standard error; SGA, small for gestational age.
Note: Bold *p*-values are statistically significant.

This relationship differed substantially from that in the non-SGA group, wherein PG use was not significantly or substantially associated with cesarean delivery. In the SGA group, adverse neonatal outcomes and maternal hemorrhage were not significantly associated with PG use, while chorioamnionitis occurred more frequently in those exposed to PGs than in those not exposed.

In fetuses with compromised placental function, PG use is thought to predispose to cesarean delivery due to fetal intolerance of tachysystole, which is associated with PG use.[13–15] Although we found an association between PG use and cesarean delivery in SGA infants, PG use was not significantly associated with cesarean delivery for the indication of nonreassuring fetal status or any other specific indication for cesarean. However, our study was not adequately powered for these stratified comparisons. It is also notable that three of the groups (non-SGA with PG use, non-SGA without PG use, and SGA with PG use) had similar rates of cesarean delivery (36.1, 35.8, and 34.9%, respectively), whereas the SGA without PG use group had a lower rate of 22%. While the reason for the lower cesarean frequency in SGA infants is unclear, it may be that the smaller size of SGA infants makes for easier passage through the maternal pelvis, conferring a lower baseline cesarean risk due to labor abnormalities. We suspect the relationship of PG use and chorioamnionitis is driven by maternal fever, a well-known side effect of PG use.

Data on the safety of PG use in pregnancies affected by SGA neonates yield mixed results. A 2015 study assessing risk factors for cesarean delivery for nonreassuring fetal heart tracing in FGR found higher odds of cesarean with PG use versus no PG use (OR = 3.67, 95% CI: 1.07–12.6).[18] Additionally, a study of 20,000 Dutch women found PG use was associated with higher relative risk of emergency cesarean delivery in normotensive (relative risk [RR] = 2.3, 95% CI: 2.1–2.5) and hypertensive women (RR = 2.7, 95% CI: 2.3–3.1) undergoing labor induction.[19] In contrast, a 2015 analysis of the National Institute of Child Health and Human Development-sponsored Consortium on Safe Labor database found no difference in intrapartum fetal distress, cesarean delivery for fetal distress, or cesarean delivery for any reason among SGA neonates who received misoprostol and oxytocin compared to other agents.[20] This finding may be explained by the fact that dinoprostone was included in the "other agents" group, which could have obscured the assessment of any PG-mediated effect. Another retrospective analysis found an association between PG use and cesarean delivery in term SGA neonates that became null after propensity-score-weighted analysis, which found obesity and nulliparity to be the main confounders.[21] Our analysis was limited to nulliparous women and the association between PG use and cesarean delivery persisted after adjusting for multiple factors, including BMI. Finally, a randomized trial of 100 women with FGR found that 25 µg doses of misoprostol did not result in a higher cesarean delivery rate compared to cervical balloon catheter,[22] though the potential for tachysystole and resultant fetal heart rate changes may have been minimized since most women received only two doses of

Table 3 Unadjusted and adjusted multivariable model results for prostaglandin exposure and cesarean delivery among SGA and non-SGA neonates

	PG use	No PG	*p*-Value	OR of CS for PG vs. no-PG (95% CI)	
Non-SGA	*n* = 1,066	*n* = 922		Unadjusted	Adjusted[a]
Delivery by cesarean	388 (36.40)	330 (35.79)	0.779	1.03 (0.85, 1.23)	0.86 (0.71, 1.05)
SGA	*n* = 211	*n* = 140			
Delivery by cesarean	75 (35.55)	31 (22.14)	0.007	1.94 (1.19, 3.16)	1.77 (1.05, 2.97)
Interaction in modeling between PG use and SGA				*p* = 0.017	*p* = 0.011

Abbreviations: BMI, body mass index; CI, confidence interval; CS, cesarean section; OR, odds ratio; PG, prostaglandin; SGA, small for gestational age.
[a]Adjusted model includes maternal visit 1 BMI (continuous), any hypertensive disorder of pregnancy (yes/no), gestational age at delivery (continuous), maternal race (non-Hispanic white vs. other race/ethnicities), dilation at the time of admission (2 vs. <2 cm).

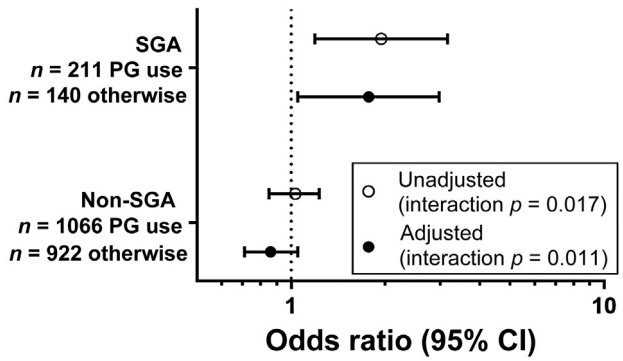

Fig. 3 Unadjusted and adjusted multivariable model results for prostaglandin exposure and cesarean delivery among small for gestational age (SGA) and non-SGA neonates. Note: Adjusted model includes maternal visit 1 BMI (continuous), any hypertensive disorder of pregnancy (yes/no), gestational age at delivery (continuous), maternal race (non-Hispanic white versus other race/ethnicities), dilation at the time of admission (2 vs. <2 cm). BMI, body mass index; CI, confidence interval.

misoprostol. Our finding that PG was not associated with adverse neonatal outcomes is consistent with previous studies.[19–22]

Strengths and Limitations

There are several strengths to our study. Data were collected prospectively from multiple centers using standardized methods without knowledge of specific hypotheses, which served to minimize bias. Our study included only nulliparous women. This is a strength as nulliparous women are more likely than multiparous women to require cesarean delivery after labor induction,[23] which is the reason that trials assessing labor induction approaches often focus on nulliparous women.[24–29] The definition of SGA was based on a common birth weight standard, which optimized the validity of our comparison groups. Finally, ours was one of the few SGA-labor induction studies to include preterm gestations,

Table 4 Secondary outcomes by prostaglandin exposure among SGA deliveries

Outcome	PGs *n* = 211	No PGs *n* = 140	*p*
Neonatal outcome			
Acidemia at birth: arterial cord blood gases pH <7.2 (missing among *n* = 1,404)	32 (31.07)	19 (27.94)	0.662
Indication for cesarean delivery: nonreassuring fetal status	37 (17.54)	18 (12.86)	0.238
NICU admission	65 (30.81)	34 (24.29)	0.184
Respiratory distress syndrome	14 (6.64)	4 (2.86)	0.142
Intrapartum stillbirth	0 (0)	0 (0)	–
Neonatal death	1 (0.47)	0 (0.00)	>0.99
Apgar's scores (5 minutes <7)	7 (3.32)	4 (2.88)	>0.99
Maternal outcome			
Postpartum hemorrhage	0 (0.00)	1 (0.71)	0.399
Chorioamnionitis prior to delivery	15 (7.11)	3 (2.14)	0.047
Temperature of 100.4°F without source of extrauterine infection	14 (6.67)	2 (1.43)	0.033
Fetal tachycardia (≥160 beats per minute)	7 (3.35)	3 (2.14)	0.542
Maternal tachycardia (≥100 beats per minute)	8 (3.85)	1 (0.71)	0.091
Maternal white blood cell count >16,000 cells/mm^3	1 (0.49)	0 (0.00)	> 0.99
Other infectious diagnosis (up to 14 days of postpartum)	4 (1.90)	6 (4.29)	0.206

Abbreviations: NICU, neonatal intensive care unit; PG, prostaglandin; SGA, small for gestational age.

specifically those less than 34 weeks, which have been excluded in most other studies.[19,21,22,30–32]

This study also has limitations. The principle limitation to clinical application is the use of birth weight rather than ultrasound assessments of fetal growth to define our comparison groups, since practicing clinicians do not know the birth weight classification when choosing a cervical ripening method. This approach has some advantages, however, such as minimizing the effect of clinician bias, since clinicians who are aware of poor fetal growth may have a lower threshold to recommend cesarean based on assumptions of diminished fetal reserve. Prior studies have also depended on this approach.[19–21,33] Though bias arising from clinician decision-making cannot be definitively mitigated in this study design, our finding that PGs were not used less often when FGR was suspected prenatally is reassuring. Furthermore, because most cases of FGR are not recognized clinically, the use of birth weight percentile may provide a better assessment of whether fetuses at the smallest end of the growth spectrum are actually at risk of cesarean during PG cervical ripening. Indeed, our objective was not to determine whether clinicians should use PGs when poor growth is suspected. That can only be determined by a randomized clinical trial. Rather, our purpose was to determine whether a true association exists between PG use and cesarean delivery in the setting of poor fetal growth. Finally, all cervical examination parameters were not available for a more refined assessment of the need for cervical ripening. While the nuMoM2b study noted labor induction as an indication for PG use, cervical dilation was the only parameter with which we could define an unfavorable cervix.

Conclusion

In conclusion, our study adds to the body of literature surrounding labor induction in SGA neonates. Although this study found an association between PG use and cesarean delivery in SGA neonates, the likelihood of vaginal delivery is high enough that PG use should not be contraindicated in this population. Further research should focus on optimizing the approach to cervical ripening in nulliparous women with suspected SGA, including whether the risks of PG use for labor induction outweigh the benefits when fetal compromise is suspected. This can best be addressed by studying cohorts where universal late third-trimester ultrasound data are available, as well as by randomized controlled trials of various cervical ripening methods in cases of suspected FGR.

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Conflict of Interest

B.D.E. received a one-time payment as an advisory board member for Medicem, manufacturer of cervical ripening device Dilapan-S. The other authors report no conflicts of interest.

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