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A comparison of obstetrical outcomes of the use of dinoprostone between pregnancies complicated by fetal growth restriction versus appropriate for gestational age

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Abstract

Objective: Our aim in this study was to compare the mode of delivery in pregnancies with fetal growth restriction(FGR) and with normal antenatal assesment udergoing induction of labor(IOL) with vaginal application of dinoprostone.

Methods: This was a retrospective cohort study of consecutive pregnancies undergoing IOL with vaginal dinoprostone between 2022 to 2023 at our hospital. Participants with a prenatal diagnosis of FGR were compared with those without FGR.

Results: We found that IOL with dinoprostone did not increase the cesarean section rate when compared with fetuses with FGR and APGAR scores at 1 and 5 minuted were similar in both groups.

Conclusion: In conclusion, IOL with dinoprostone in fetuses with FGR seems to be as safe as for non-FGR fetuses.

Keywords: Growth restriction, labor induction, dinoprostone, delivery

Introduction

Fetal growth restriction (FGR) is the impairement of fetal growth and failure of the fetus to achieve its genetic growth potential. This situation is a common pregnancy complication and a leading cause of perinatal mortality, and short- and long-term morbidity.[1-5] Although uterine height measurement can be used to diagnose FGR, ultrasonography is considered a better screening modality[6] Biometric ultrasonographic measurements of the fetus are combined to calculate an estimated fetal weight (EFW). FGR fetuses have an EFW or/and abdominal circumference (AC) below the 10th percentile for gestational age.[7,8]

Guidelines recommend arranging timing of delivery according to the severity of FGR and accompanying Doppler findings. However, it is still unknown the best method of induction of labor (IOL) if vaginal delivery is chosen for these fetuses . Few international societies have reported in their guidelines which method of IOL better for pregnancies with FGR.[8-10]

Uteroplacental insufficiency is the most common cause of FGR. These fetuses already have impaired uteroplacental blood flow, so uterine contractions caused by cervical ripening agents may further disrupt this flow.[11] This situation is associated with an increased risk of cesarean delivery (CD) for fetal distress, admission to the neonatal intensive care unit (NICU), and low Apgar scores.[12,13]

Our primary outcome in this study was to compare the modes of delivery in pregnancies with

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FGR and those with normal antenatal assessments undergoing IOL with vaginal dinoprostone. Our secondary outcome was to investigate maternal and perinatal outcomes.

Methods

This was a case-control study of consecutive pregnancies undergoing IOL with vaginal dinoprostone between 2022 to 2023 at our hospital. The inclusion criteria were singleton pregnancies without fetal anomalies with cephalic presentation whose Bishop scores were below 6 undergoing IOL after 34 weeks of gestation with vaginal application of dinoprostone. Patients with a history of CD, and those with abnormal fetal heart rate traces before IOL were excluded from the study. Participants with a prenatal diagnosis of fetal FGR were compared with those without FGR. FGR were considered with an estimated fetal weight below the 10th centile.[8] The study and control groups were matched for maternal age and parity. Ultrasound scans were performed by maternal-fetal medicine specialists with Samsung RS85 ultrasound machine (Samsung,South Korea) .EFW and centiles were calculated by using the Hadlock formula and fetal growth charts.[14-16] Descriptive data of the pregnant women such as age, gestational age at the time of delivery, mode of delivery, and maternal and perinatal outcomes were recorded from our hospital's electronic database.

In our institution, fetuses suspected of having FGR that have serious Doppler findings such as absent or reverse flow in the umbilical artery are delivered by cesarean section as stated by the International Federation of Gynaecology and Obstetrics (FIGO) in 2021.[17] We perform trials of labor for FGR fetuses with forward umbilical artery flow with reassuring non-stress tests (NST). If the cervix is unfavorable with a Bishop score of <6, a vaginal pessary containing 10 mg dinoprostone is placed in the posterior fornix. When cervical ripening occurs, we remove the dinoprostone and administer oxytocin if needed. Dinoprostone is maintained for a maximum 24 h. If the Bishop score did not change, another dinoprostone pessary is inserted. The dinoprostone is removed if uterine tachysystole (>5 uterine contractions in 10 min), or non-reassuring fetal heart rate occur. We use continuous electronic fetal heart monitoring to check fetal well-being. Failed induction was defined as the need of third application of dinoprostone and a Bishop score of <6 or active phase arrest or prolonged second stage not suitable for instrumental delivery. We do not prefer to use the third dose of dinoprostone except for patients in whom cesarean section is seriously contraindicated. Balloon dilation of the cervix is not routinely used in our hospital, the use of dinoprostone is preferred route of the IOL. We also perform trials of labor for non-FGR fetuses in the same way, when the cervix is not favorable and delivery is indicated because of maternal and/or fetal conditions such as premature rupture of membrane, post-term pregnancies, and maternal health issues.

Statistical analysis

Descriptive statistics were used to summarize the data including mean, standard deviation, median, minimum, maximum, frequency, and ratio values. Kolmogorov-Smirnov and Shapiro–wilk tests were used to assess the distribution of variables. The Mann-Whitney U test was used to analyse quantitative independent data, and the Chi-square test and Fisher's exact test were used to analyse qualitative independent data. Statistical analyses of the data were carried out with the SPSS Statistics 27.0 statistical package program. The p-values of <0.05 were considered statistically significant. At 95% confidence interval and 80% power, the effect size was calculated 0.4. It was decided to include at least one hundred patients in the control group. Sample size of the study was determined based on previously published research using G Power 3.1 to compare the mode of delivery in pregnancies with FGR and those with normal antenatal assessments undergoing IOL with vaginal dinoprostone.[12] Statistical power (1-β) of 80% was deemed necessary at the 0.05 (α) significance level, and two-way analysis of variance test was utilized for the medium effect size. A minumum sample size of one hundred subjects was dee-

med necessary for the study.

Results

Of the 5489 deliveries that occurred during the study period. One hundred patients (1.8%) with suspected FGR met the study criteria and underwent IOL with dinoprostone during the study period. Two hundred nineteen patients with normal antenatal assessments were included in the control group. Figure 1 presents the flowchart of the study.

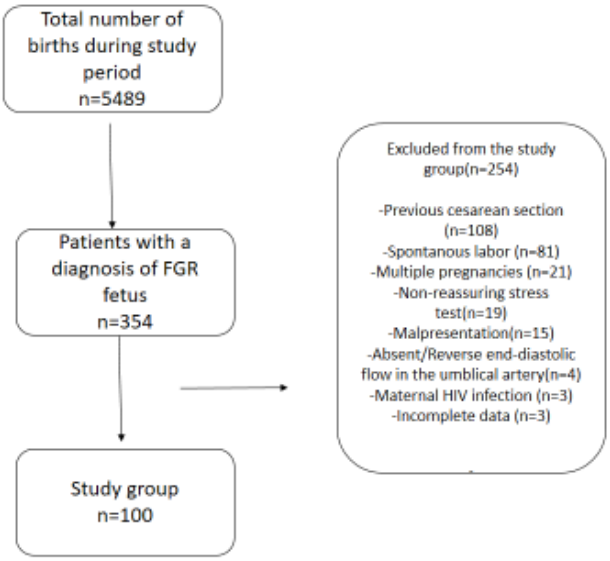

Fig 1. Flow chart of the study

Table 1 presents the antenatal and postnatal data in the study and control groups. Parity, gravidity, maternal age, nulliparity rate, Bishop scores before IOL, oligohydramnios (total amniotic fluid measured less than 5 cm or the absent of a single vertical pocket measured at least 2x1 cm) and meconium-stained fluid rates, time until delivery, maternal diabetes, maternal diabetes, maternal hypertensive disorders and maternal blood transfusion need were not significantly different between the two groups. Gestational age at delivery was significantly lower in fetuses with FGR ($p<0.05$). There was no difference between the groups in the rates of CD and Apgar scores at 1 minute and 5 minutes. Admission to the NICU was significantly higher in the FGR group ($p<0.05$).

Table 1. Antenatal and postnatal data in study and control groups

	Fetuses with FGR (n=100)	Fetuses without FGR (n=219)	p-value
Age (years)	27.6 ±5.9	27.4 ±5.4	0.980
Gravidity	1.98 ±1.27	2.07 ±1.37	0.594
Parity	1.53 ±0.63	1.55 ±0.79	0.678
Nulliparity rate (%)	55 (55.0)	126 (57.5)	0.672
Bishop score before IOL (median; min-max)	1 (0-4)	1 (1-4)	0.064
Oligohydramnios (%)	48 (48.0)	97 (44.3)	0.532
GA at delivery (week)	38.7 ±1.2	40.0 ±1.6	<0.001
Birthweight (g)	2722 ± 395	3408 ± 443	<0.001
C/S rate (%)	12 (12.0)	30 (13.7)	0.677
1 min Apgar	7.8 ±0.7	7.8 ±0.4	0.706
5 min Apgar	8.9 ±0.5	9.0 ±0.2	0.237
NICU	25 (25.0)	33 (15.1)	0.033
Meconium-stained fluid	7 (7.0)	24 (11.0)	0.268
Time until delivery (hour)	19.2 ± 16.6	16.9 ±13.1	0.429
Transfusion need	2 (2.0)	3 (1.4)	0.650
Diabetes	3 (3.0)	17 (7.7)	0,167
Hypertensive disorders	7 (7.0)	7 (3.1)	0,213

Table 2 presents indications for CD in the study and control groups. CD for non-reassuring fetal heart rate (FHR) or failed induction were not significantly different between the two groups.

Table 2. Indications for cesarean section in the study and control groups

	Fetuses with FGR (n=100)	Fetuses without FGR (n=219)	p-value
Non-reassuring FHR	8 (8%)	17 (7.8%)	0,879
Failed induction	4 (4%)	13 (5.9)	0,637

Discussion

In our study, we found that IOL with dinoprostone did not increase the CD rate when compared with fetuses without FGR, and APGAR scores at 1 and 5 minutes were similar in both groups. Timing of delivery and optimal management remains a challenge in FGR fetuses in clinical practice. Another contro-

versial issue is which method to use if vaginal birth is to be induced.

In a systematic review including randomized controlled trials comparing vaginal dinoprostone, misoprostol and Foley's catheters for IOL, authors analyzed three goals to compare three IOL methods. These were to achieve vaginal delivery in 24 hours, and determine uterine hyperstimulation and CD rates. They concluded that neither method was superior to the others when considering all three clinical outcomes for IOL. However, most of the included trials excluded pregnancies with FGR so the findings cannot be applied to fetuses with FGR.[18]

In 2020, Familiari et al. performed a meta-analysis of observational studies of IOL with misoprostol, dinoprostone, or mechanical methods in FGR fetuses and found that mechanical methods appeared to be safer but they could not make a direct comparison between the three methods due to the clinical and statistical heterogenicity of the included studies.[12]

Al-Hafez et al. compared the rates of adverse outcomes among pregnancies with FGR undergoing IOL with and without prostaglandins. They found that there was a higher rate of CD when prostaglandins were used, compared with nonprostaglandin methods but there were no differences in the total of adverse perinatal outcomes between the two groups.[9]

In 2023, Rodriguez-Subaja et al. compared neonatal outcomes in pregnancies with FGR by intended delivery mode. They found that pregnancies with spontaneous onset labor and those that underwent IOL had higher neonatal morbidity than with elective CD. However, it should be noted that there was no standardized approach among obstetricians in the decision on the mode of delivery of FGR fetuses in the author's hospital, and more severe forms of FGR were also included in the study if they exceeded the 34th week of gestation.[19]

Fetuses with FGR are generally recommended to be induced at around 37–38 weeks of gestation.[8] FGR fetuses are already suffering from placental insufficiency, and as mentioned before, some authors suggested that elective cesarean delivery or mechanical IOL may be a reasonable option to avoid uterine tachysystole caused by IOL with dinoprostone , but there is currently no clear evidence to avoid dinoprostone or vaginal delivery.[19-20]

Another controversial issue is that a significant proportion of suspected FGR fetuses are constitutionally small (SGA), but healthy. In the present study, we demonstrated that the obstetrical outcomes of IOL with dinoprostone in fetuses with suspected FGR was as safe as in non-FGR fetuses, but this results should be interpreted with caution because some FGR fetuses may actually be constitutionally small. However SGA fetuses are also at a higher risk of adverse events, mainly CD and it is not possible to clearly differentiate a SGA fetus from a FGR one[21]

There are some strengths and limitations of our study. First, scans of FGR fetuses and the decision of timing of the delivery were made by maternal-fetal specialists. Second, our obstetric team has a standardized approach for the delivery of FGR fetuses. Unless there are serious Doppler findings such as absent or reverse umbilical artery Doppler flow, or an obstetric contradiction to vaginal delivery, all obstetricians attempt vaginal delivery. Third, the major maternal and pregnancy clinical characteristics that have potential to affect primary outcomes such as maternal age, nulliparity rate, presence of oligohydramnios and/or meconium-stained amniotic fluid were similar in both groups.

The main limitations of our study are its retrospective nature and the difficulty in comparing two different groups. We could not compare cord pH or long-term perinatal mortality because the results would be different due to the different nature of groups. Higher perinatal mortality and long term impairment are already expected for fetuses with FGR. Accordingly, we had to focus only on short-term perinatal problems that might be caused by the use of dinoprostone such as fetal distress, CD rates, NICU admissions, and APGAR scores. However, finding no differences in CD rates due to fetal distress and similar APGAR scores in FGR fetuses com-

pared with healthy pregnancies showed us that IOL with dinoprostone in FGR fetuses could be as safe as in non-FGR fetuses. Admission to NICU was higher in the FGR group. This may be due to the low gestational age and the disease itself. However, physicians should still be careful when evaluating the results of this study, as it is not possible to give the exact reason for this increase in the two disparate groups.

Conclusion

In conclusion, IOL with dinoprostone in FGR fetuses seems to be as safe as in non-FGR fetuses. The mode of delivery of each FGR fetus and the method to be applied if vaginal birth is planned should be decided on a patient-by-patient basis.

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